Academic Research of
Graduate School of Veterinary Medicine

January – December
2024

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Tel.&Fax +81-11-388-4792
e-mail: yamasita@rakuno.ac.jp

2024年（1月～12月）の獣医学研究科英文業績の発刊にあたって

酪農学園大学大学院 獣医学研究科
研究科長 山下 和人

獣医学研究科では、2002年より、獣医学群教員が1年間に公表した英語論文を冊子体にまとめ、各教員の自己点検や研究の質保証、ならびに関係各位に獣医学群教員の研究状況を紹介する目的で業績集を刊行しています。

2024年の筆頭著者（FA）および責任著者（CA）の論文合計は55報でした。過去10年間では、2023年51報、2022年68報、2021年83報、2020年72報、2019年54報、2018年54報、2017年48報、2016年45報、2015年44報、2014年51報となっており、2017～2021年には右肩上がりで増えていましたが、2022年以降減少傾向にあり、2024年の論文合計はほぼ横這いでした。本学獣医学群では、2024年12月にヨーロッパ獣医学教育機関協会（EAEVE: European Association of Establishments for Veterinary Education）の国際認証を取得しました。これまでに、6年間にわたって獣医学教育の質の保証と国際化に取り組み、学生が卒後1日目の能力（Day One Competencies）を身につけることを保証するために、3Rs（Replacement、Reduction、Refinement）の思想を反映したスキルスラボを整備し、少人数によるHands On実習やクリニカルローテーションに対応した新カリキュラムをスタートしました。前研究科長が憂慮されていたように、EAEVE対応の教育負担増が英文業績の公表に影響しているようです。

一方、本年度の本学全体の科学研究費助成事業（科研費）の採択件数は52件であり（2023年度56件、2022年度48件、2021年度37件、2020年度31件）、本年度の配分額（7,732万円）は、昨年度（8,164万円）より少し減りましたが、科研費が配分された私立大学では配分された590大学中112位であり（2023年度100位、2022年度119位、2021年度129位、2020年度133位）、教員個々の研究活動の高まりは持続的に確保されています。獣医学群の新カリキュラムは、獣医保健看護学類で2024年度、獣医学類で2026年度に完成し、これに対応する教員組織も2025年度までに確保される計画です。獣医学群教員のFA/CA論文数が2021年レベルを超えていくには、「EAEVE 対応の教育負担増」を教員組織の完成と教員個々の馴化によって切り抜けること、さらに何かしらの研究活動の活性化を図る方策が必要と考えます。

最後に、関係各位には本業績集をご高覧頂き、教員個々の研究内容などから共同研究、さらには広範な研究体制の構築等へとご高配を頂けることを願っております。今後とも、獣医学研究科の教育・研究活動がさらに発展するよう、ご指導ご鞭撻をよろしくお願い申し上げます。

English publications from the Graduate School of Veterinary Medicine for the academic year 2024 (January to December)

Since 2002, the Graduate School of Veterinary Medicine has compiled the English papers published by veterinary medicine faculty members over the past year into a booklet, which allows each faculty member to conduct self-inspections and ensure the quality of their research, as well as inform everyone concerned about the research status of veterinary faculty members.

The total number of first author (FA) and corresponding author (CA) papers in the School of Veterinary Medicine in 2024 was 55 reports. In the past 10 years, 56 reports in 2023, 68 reports in 2022, 83 reports in 2021, 72 reports in 2020, 54 reports in 2019, 54 reports in 2018, 48 reports in 2017, 45 reports in 2016, 44 reports in 2015, and 51 reports in 2014. It was increasing steadily from 2017 to 2021 but has been declining since 2022, and the total number of papers in 2024 remained almost flat. Our veterinary school received international accreditation from the European Association of Establishments for Veterinary Education (EAEVE) in December 2024. Over the past six years, we have worked to ensure the quality of veterinary education and internationalize it. To ensure that students acquire Day One Competencies, we have established a skills lab that reflects the 3Rs (Replacement, Reduction, Refinement) philosophy and started a new curriculum that supports small-group Hands-On training and clinical rotations. As the previous dean was concerned, the increased educational burden of EAEVE seems to be affecting the publication of academic achievements.

On the other hand, the number of projects selected for Grants-in-Aid for Scientific Research (KAKENHI) across the university this year increased to 52 (56 in 2023, 48 in 2022, 37 in 2021, and 31 in 2020) and the amount allocated this year (77.32 million yen) is slightly less than last year (81.64 million yen). However, among private universities that have received KAKENHI, we rank 112th out of 590 universities that have received KAKENHI (100th in 2023, 119th in 2022, 129th in 2021, and 133rd in 2020), and we are ensuring a sustained increase in the research activities of individual faculty members. The new curriculum for the School of Veterinary Medicine is scheduled to be completed in 2024 for the Department of Veterinary Science and in 2026 for the Department of Veterinary Medicine, with the corresponding faculty organization also planned to be secured by 2025. In order for the number of FA/CA papers by faculty members in the School of Veterinary Medicine to exceed the 2021 level, we believe that it will be necessary to overcome the "increased teaching burden in response to EAEVE" by completing the faculty organization and acclimatizing each faculty member, as well as to find some way to stimulate research activities.

Finally, we hope that all concerned parties will take a look at this collection of accomplishments, and that they will be interested in the research content of individual faculty members, joint research, and even the establishment of a broader research system. We look forward to your continued guidance and support so that the educational and research activities of the Graduate School of Veterinary Medicine can further develop.

Kazuto Yamashita DVM, MS, PhD, Charter Dipl. JCVS, Honorary Dipl. AiCVS. .
Dean, Rakuno Gakuen University Graduate School of Veterinary Medicine.

Contents（January – December 2024）

＊：大学院担当教員（Supervisor）

■ 獣医学類 **Department of Veterinary Medicine**

■ 獣医保健看護学類 **Department of Veterinary Science**

獣医細菌学（Veterinary Bacteriology）

Masato Akiba

Professor

教授　秋庭　正人

I. 筆頭または責任著者　＜First or Corresponding Author＞

II.　その他＜Others＞

1）ICEmST contributes to colonization of *Salmonella* in the intestine of piglets.
Arai N, Shibahara T, Nishiura R, Tamamura-Andoh Y, Nishiura H, Muneta Y, Sawada H, Watanabe-Yanai A, Iwata T, **Akiba M**, Kusumoto M.
Sci Rep 14:31407. 2024. doi: 10.1038/s41598-024-83039-6.

scientific reports

OPEN

ICEmST contributes to colonization of *Salmonella* in the intestine of piglets

Nobuo Arai[1], Tomoyuki Shibahara[2,3], Reina Nishiura[2,5], Yukino Tamamura-Andoh[1], Hayate Nishiura[1], Yoshihiro Muneta[2], Hiroshi Sawada[2], Ayako Watanabe-Yanai[1], Taketoshi Iwata[1], Masato Akiba[4] & Masahiro Kusumoto[1,3]

Salmonella enterica serovar 4,[5],12:i:- sequence type 34 (ST34) has recently become a global concern for public and animal health. The acquisition of mobile genetic element ICEmST, which contains two copper tolerance gene clusters, _cus_ and _pco_, influences the epidemic success of this clone. Copper is used as a feed additive in swine at levels that potentially lead to selection pressure for _Enterobacteriaceae_; however, it remains unclear whether the copper tolerance system of ICEmST functions in vivo. We performed competition assays with _Salmonella_ 4,[5],12:i:- ST34 wildtype (WT) and deletion mutants of ICEmST (ΔICEmST, Δ_cus_, and Δ_pco_) in groups of mice fed 0, 150, and 500 ppm $CuSO_4$. In the competition of WT against ΔICEmST and Δ_cus_, the competitive index of the 500 ppm-fed group was significantly lower than that of the 0 ppm-fed group. In the swine experiment, all individuals were fed 150 ppm $CuSO_4$. The number of ICEmST-positive strain in the feces was significantly greater than that of ICEmST-negative strain. The serum inflammatory markers were significantly increased in swine infected with the ICEmST-positive strain. These data suggest that ICEmST, especially _cus_, provides _Salmonella_ with the ability to colonize in the intestine, even at high copper concentrations, leading to swine salmonellosis.

Keywords Copper tolerance, Feed, ICEmST, *Salmonella* 4,[5],12:i:-, Swine

Salmonella enterica subsp. *enterica* serovar Typhimurium and its monophasic variant (*Salmonella* 4,[5],12:i:-) are the most common serovars that cause gastroenteritis in humans and animals worldwide[1,2]. Previous reports indicated that since 2010, *Salmonella* Typhimurium and 4,[5],12:i:- were among the top five serovars in cases of human salmonellosis in the United States and European Union (EU)[3–8]. To date, several globally spread clones of *Salmonella* Typhimurium and 4,[5],12:i:-, which were determined to be ST19 and ST34 by multilocus sequence typing, have been reported in both humans and animals[9,10]. Among these clones, ST34 *Salmonella* 4,[5],12:i:- has recently spread rapidly in Europe, North America, South America, Oceania, Asia, and Africa, and these strains have been isolated from various sources, including humans, swine, cattle, and poultry[9,11–17]. This clone has been widely disseminated into swine in the EU, the United States, and other regions, including Japan[14,18–20]. In addition, pork and its products are among the major sources of human salmonellosis caused by ST34 *Salmonella* 4,[5],12:i:- in the EU[13,21]. As the selection pressure for this clone in swine is unclear, some background information should be obtained on the mechanism leading to the success of the epidemic.

Most ST34 *Salmonella* 4,[5],12:i:- strains possess the integrative and conjugative element ICEmST, which was first reported as *Salmonella* genomic island 3 and subsequently redesigned as an ST34-specific element[12,20]; this element is found on one of two transfer RNA gene locations on the chromosome, *pheR* or *pheV*. ICEmST is approximately 81 kb in size and is composed of genes related to conjugal transfer, DNA partitioning, and heavy-metal tolerance to copper and arsenic compounds. Our previous study demonstrated that ICEmST was excised from the donor chromosome, formed a circular intermediate, transferred by conjugation, and integrated into the *pheR* or *pheV* locus on the recipient chromosome[22]. ICEmST contains the *cus* and *pco* gene clusters as copper

[1]Division of Zoonosis Research, National Institute of Animal Health, National Agriculture and Food Research Organization, Tsukuba, Ibaraki, Japan. [2]Division of Hygiene Management Research, National Institute of Animal Health, National Agriculture and Food Research Organization, Tsukuba, Ibaraki, Japan. [3]Graduate School of Veterinary Science, Osaka Metropolitan University, Izumisano, Osaka, Japan. [4]Laboratory of Veterinary Bacteriology, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan. [5]Present address: Department of Veterinary Clinical Sciences, College of Veterinary Medicine, Purdue University, West Lafayette, IN, USA. email: kusu555@affrc.go.jp

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最終責任者　Masahiro Kusumoto (Corresponding Author)

医動物学（Parasitology and Zoology）

Mitsuhiko Asakawa

Professor

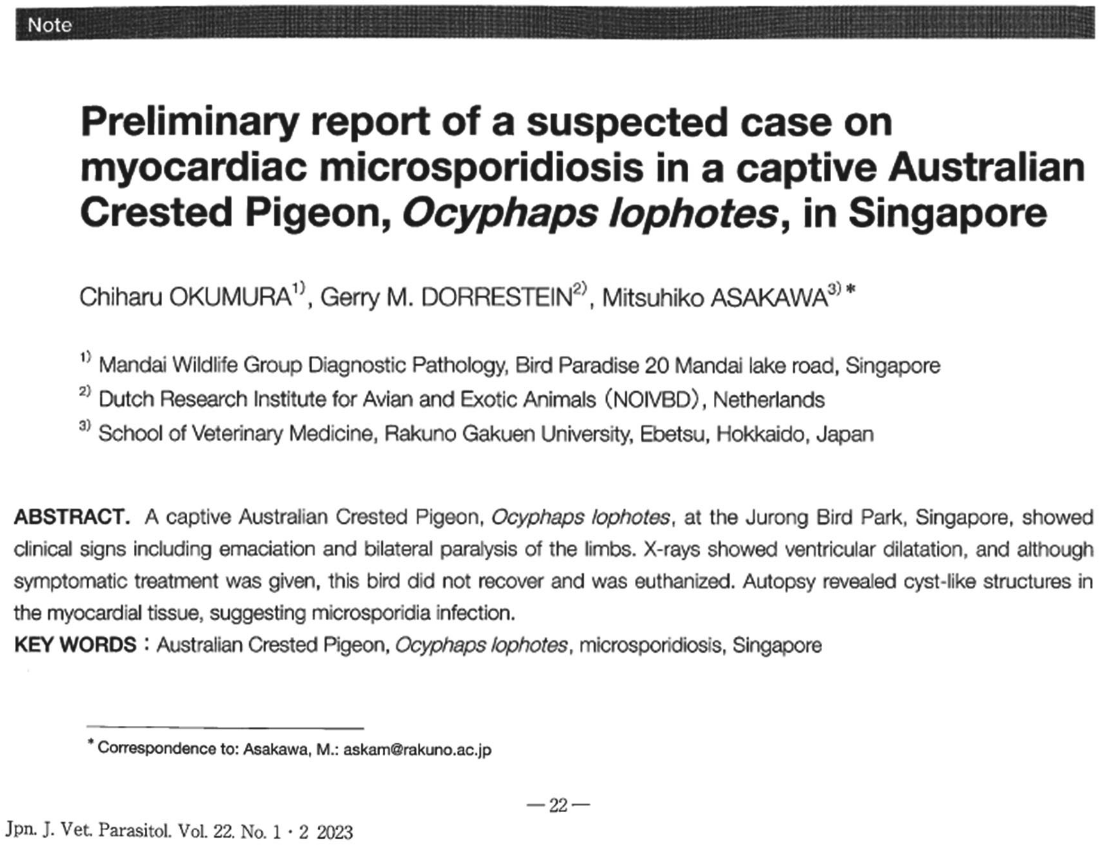
教授　浅川　満彦

I. 筆頭または責任著者　＜First or Corresponding Author＞

1）Preliminary report of a suspected case on myocardiac microsporidiosis in a captive Australian Crested Pigeon, *Ocyphaps lophotes*, in Singapore.
Okumura M, Dorrestein G M, **Asakawa M.**
J Jpn J Vet Parasitol 22: 2223. 2023

II.　その他＜Others＞

2) First report on mermithids (Enoplea: Mermithidae) parasitizing adult stable flies in Japan.
Shimizu K, Saito T, Takashima Y, Okada H, **Asakawa M,** Inoshima Y.
J Nematol 56:20240022. 2024. doi: 10.2478/jofnem-2024-0022.



Note

Preliminary report of a suspected case on myocardiac microsporidiosis in a captive Australian Crested Pigeon, *Ocyphaps lophotes*, in Singapore

Chiharu OKUMURA[1), Gerry M. DORRESTEIN[2), Mitsuhiko ASAKAWA[3)*

1) Mandai Wildlife Group Diagnostic Pathology, Bird Paradise 20 Mandai lake road, Singapore
2) Dutch Research Institute for Avian and Exotic Animals (NOIVBD), Netherlands
3) School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

ABSTRACT. A captive Australian Crested Pigeon, *Ocyphaps lophotes*, at the Jurong Bird Park, Singapore, showed clinical signs including emaciation and bilateral paralysis of the limbs. X-rays showed ventricular dilatation, and although symptomatic treatment was given, this bird did not recover and was euthanized. Autopsy revealed cyst-like structures in the myocardial tissue, suggesting microsporidia infection.

KEY WORDS：Australian Crested Pigeon, *Ocyphaps lophotes*, microsporidiosis, Singapore

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* Correspondence to: Asakawa, M.: askam@rakuno.ac.jp

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最終責任者 Mitsuhiko Asakawa (Corresponding Author)

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First Report of Mermithidae (Enoplea: Mermithida) Parasitizing Adult Stable Flies in Japan

Kaori Shimizu[1], Taizo Saito[1],
Yasuhiro Takashima[1,2,3,4],
Haruhiko Okada[5],
Mitsuhiko Asakawa[5] and
Yasuo Inoshima[1,2,3,*]

[1]Joint Department of Veterinary Medicine, Gifu University, Gifu, Gifu 501-1193, Japan

[2]Education and Research Center for Food Animal Health, Gifu University (GeFAH), Gifu, Gifu 501-1193, Japan

[3]Joint Graduate School of Veterinary Sciences, Gifu University, Gifu, Gifu 501-1193, Japan

[4]Center for One Medicine Innovative Translation Research (COMIT), Gifu University, Gifu, Gifu 501-1193, Japan

[5]School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan

*E-mail: inoshima.yasuo.b0@f.gifu-u.ac.jp

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Abstract

Mermithidae is a family of nematodes that parasitize a wide range of invertebrates worldwide. Herein, we report nematodes that were unexpectedly found in three of 486 adult stable flies (*Stomoxys calcitrans*) captured from three farms (F1, F2, and F3) in different regions of Gifu Prefecture, Japan. We aimed to characterize these nematodes both at the morphological and molecular level. Morphological studies revealed that the nematodes were juveniles of Mermithidae. Phylogenetic analysis based on 18S and 28S rDNA indicated that the mermithids from farms F1 and F2 could be categorized into the same cluster as *Ovomermis sinensis* and *Hexamermis* sp., whereas the mermithid from farm F3 clustered with *Amphimermis* sp. Additionally, these mermithids could be categorized within the same clusters as related mermithids detected in Japan that parasitize various arthropod orders. Our findings suggest that these stable flies may have been parasitized by mermithids already present in the region and that genetically distinct species of mermithids occur across Japan. To the best of our knowledge, this is the first report of mermithids parasitizing adult stable flies in Japan.

Keywords
blood-feeding pests, genetics, host–parasite relationship, insect parasitism, Mermithidae, stable fly

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最終責任者　Yasuo Inoshima (Corresponding Author)

獣医ウイルス学ユニット（Veterinary Virology）

Katsuro Hagiwara

Professor

教授　萩原　克郎

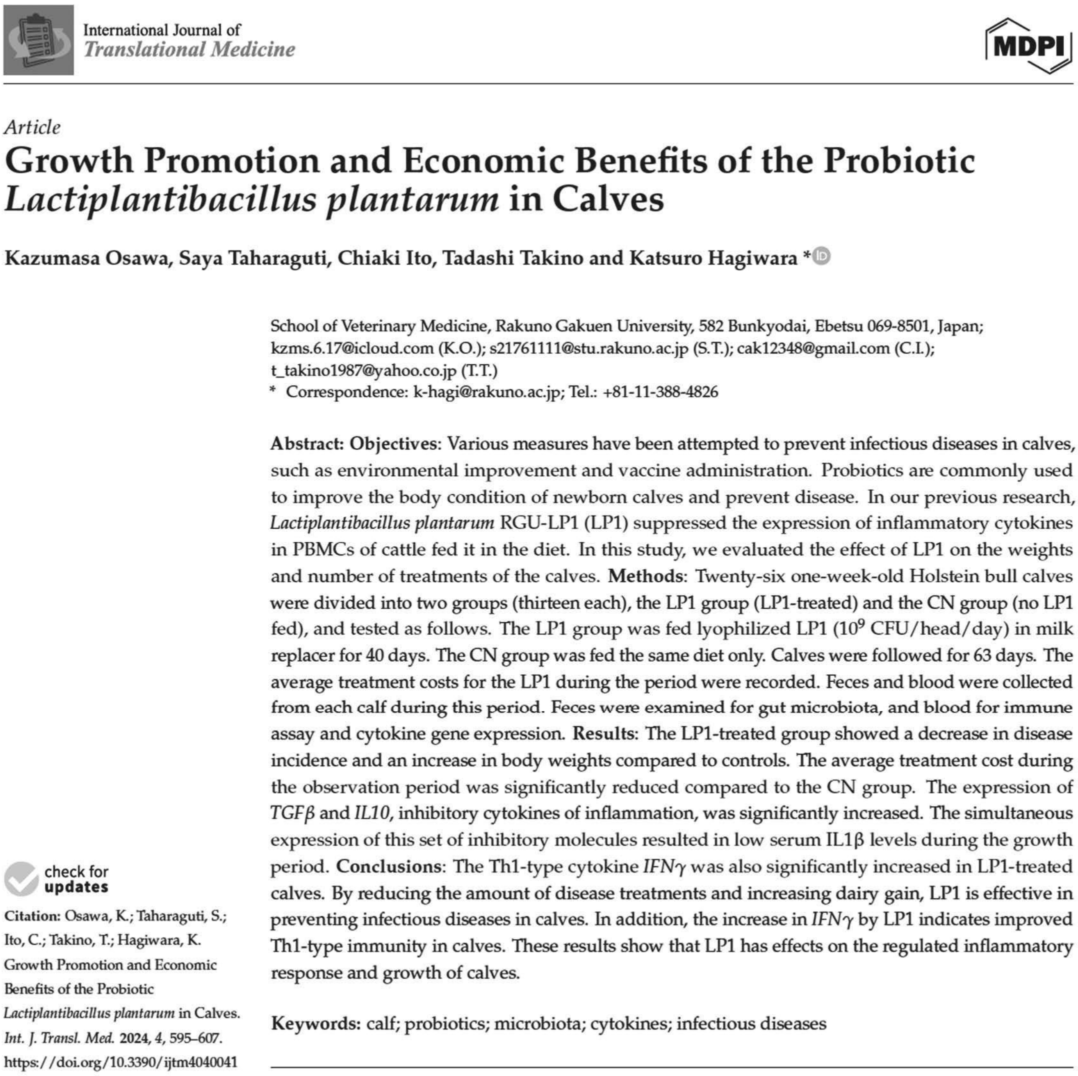
I. 筆頭または責任著者　＜First or Corresponding Author＞

1) Growth Promotion and Economic Benefits of the Probiotic Lactiplantibacillus plantarum in Calves.
Osawa K, Taharaguti S, Ito C. Takino T, **Hagiwara K.**
Int J Transl Med 4:595–607. 2024. https://doi.org/10.3390/ijtm4040041

II. その他　＜Others＞

1）Genetic investigation of glycosylphosphatidylinositol (GPI) anchored Bd37 orthologs in Babesia divergens group and potential use of recombinant protein for ecological survey in deer.
Zamoto-Niikura A, **Hagiwara K**, Imaoka K, Morikawa S, Hanaki KI.
J Vet Med Sci 86:1185–1197. 2024. doi:10.1292/jvms.24-0116.

2）Seasonal Dynamics of the Land-Surface Characteristics in Arid Regions Retrieved by Optical and Microwave Satellite Data.
Tian Y, Ackermann K, McCarthy C, Sternberg T, Purevtseren M, Limuge C, **Hagiwara K,** Ogawa K. Hobara S, Hoshino B.
Remote Sensing 16:3143. 2024. https://doi.org/10.3390/rs16173143



International Journal of
Translational Medicine

MDPI

Article

Growth Promotion and Economic Benefits of the Probiotic *Lactiplantibacillus plantarum* in Calves

Kazumasa Osawa, Saya Taharaguti, Chiaki Ito, Tadashi Takino and Katsuro Hagiwara *

School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyodai, Ebetsu 069-8501, Japan;
kzms.6.17@icloud.com (K.O.); s21761111@stu.rakuno.ac.jp (S.T.); cak12348@gmail.com (C.I.);
t_takino1987@yahoo.co.jp (T.T.)
* Correspondence: k-hagi@rakuno.ac.jp; Tel.: +81-11-388-4826

Abstract: Objectives: Various measures have been attempted to prevent infectious diseases in calves, such as environmental improvement and vaccine administration. Probiotics are commonly used to improve the body condition of newborn calves and prevent disease. In our previous research, *Lactiplantibacillus plantarum* RGU-LP1 (LP1) suppressed the expression of inflammatory cytokines in PBMCs of cattle fed it in the diet. In this study, we evaluated the effect of LP1 on the weights and number of treatments of the calves. **Methods**: Twenty-six one-week-old Holstein bull calves were divided into two groups (thirteen each), the LP1 group (LP1-treated) and the CN group (no LP1 fed), and tested as follows. The LP1 group was fed lyophilized LP1 (10^9 CFU/head/day) in milk replacer for 40 days. The CN group was fed the same diet only. Calves were followed for 63 days. The average treatment costs for the LP1 during the period were recorded. Feces and blood were collected from each calf during this period. Feces were examined for gut microbiota, and blood for immune assay and cytokine gene expression. **Results**: The LP1-treated group showed a decrease in disease incidence and an increase in body weights compared to controls. The average treatment cost during the observation period was significantly reduced compared to the CN group. The expression of *TGFβ* and *IL10*, inhibitory cytokines of inflammation, was significantly increased. The simultaneous expression of this set of inhibitory molecules resulted in low serum IL1β levels during the growth period. **Conclusions**: The Th1-type cytokine *IFNγ* was also significantly increased in LP1-treated calves. By reducing the amount of disease treatments and increasing dairy gain, LP1 is effective in preventing infectious diseases in calves. In addition, the increase in *IFNγ* by LP1 indicates improved Th1-type immunity in calves. These results show that LP1 has effects on the regulated inflammatory response and growth of calves.

Keywords: calf; probiotics; microbiota; cytokines; infectious diseases

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最終責任者　Katsuro Hagiwar (Corresponding Author)

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Science

FULL PAPER

Public Health

Genetic investigation of glycosylphosphatidylinositol (GPI) anchored *Bd37* orthologs in *Babesia divergens* group and potential use of recombinant protein for ecological survey in deer

Aya ZAMOTO-NIIKURA[1)]*, Katsuro HAGIWARA[2)], Koichi IMAOKA[3)], Shigeru MORIKAWA[3,4)], Ken-Ichi HANAKI[1)]

1)Research Center for Biosafety, Laboratory Animal and Pathogen Bank, National Institute of Infectious Diseases, Tokyo, Japan
2)School of Veterinary Medicine, Rakuno-Gakuen University, Hokkaido, Japan
3)Department of Veterinary Science, National Institute of Infectious Diseases, Tokyo, Japan
4)Department of Veterinary Medicine, Okayama University of Science, Okayama, Japan

ABSTRACT. The *Babesia divergens*/*B. capreoli* group includes parasites with confirmed or possible zoonotic potential to cause human babesiosis. Currently, diagnostic antigen of the group has not been established. In this study, we investigated the ortholog of *Bd37*, a glycosylphosphatidylinositol (GPI)-anchored major merozoite surface protein of *B. divergens* sensu stricto, in the Asia lineage of the group. From two genomic isolates from sporozoite/sporoblast stages, three *Bd37* gene variants, namely *Bd37* JP-A, JP-B, and JP-C, were isolated with 62.3–64.1% amino acid sequence identity. Discriminative blood direct PCR revealed that *Bd37* JP-A was encoded in all parasites infecting wild sika deer examined (n=22). While *Bd37* JP-B and JP-C genes were randomly detected in 12 and 11 specimens, respectively. Sequencing of all JP-A variants revealed that the gene was polymorphic, with a low ratio of non-synonymous to synonymous substitutions (dN/dS) and that a highly polymorphic region was not related to predicted B-cell epitopes. A recombinant JP-A-based ELISA showed an overall positive rate of 13.9% in sika deer in Japan from north (Hokkaido) to south (Kyushu island) across 24 prefectures (n=360). This positive rate was twice as high as that examined by *18S rRNA*-based PCR (6.6%). The geographical trends in infection rates were consistent. This study demonstrated that direct examination was informative for revealing genetic background and selecting antigen candidates. *Bd37* orthologs may serve diagnostic purposes in combination with indirect fluorescence assay, which requires biological isolates.

KEYWORDS: *Babesia divergens* Asia lineage, ecological survey, glycosylphosphatidylinositol (GPI), sika deer

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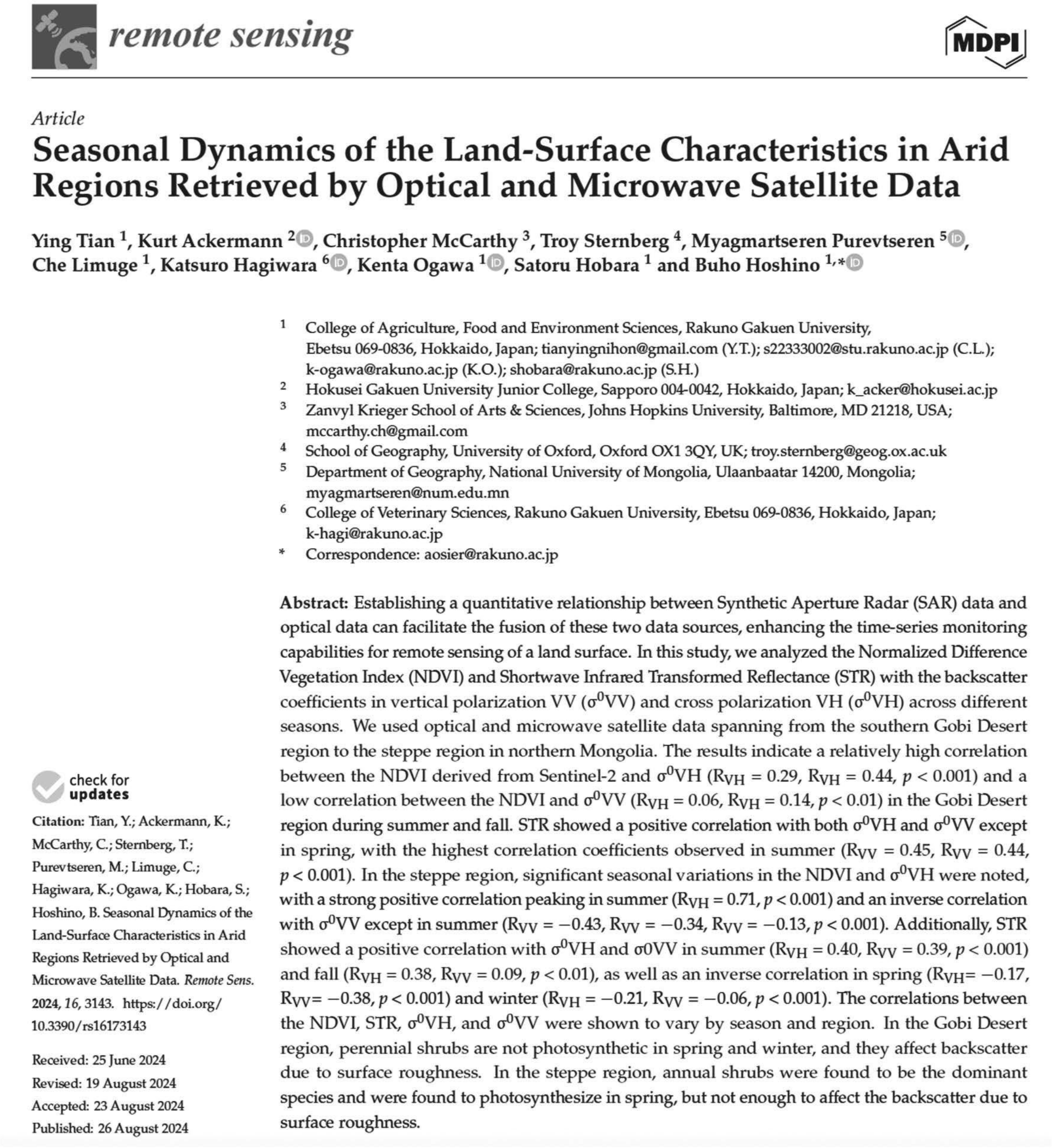
最終責任者　Aya Zamoto-Niikura (Corresponding Author)



remote sensing
MDPI

Article

Seasonal Dynamics of the Land-Surface Characteristics in Arid Regions Retrieved by Optical and Microwave Satellite Data

Ying Tian [1], Kurt Ackermann [2], Christopher McCarthy [3], Troy Sternberg [4], Myagmartseren Purevtseren [5], Che Limuge [1], Katsuro Hagiwara [6], Kenta Ogawa [1], Satoru Hobara [1] and Buho Hoshino [1,*]

[1] College of Agriculture, Food and Environment Sciences, Rakuno Gakuen University, Ebetsu 069-0836, Hokkaido, Japan; tianyingnihon@gmail.com (Y.T.); s22333002@stu.rakuno.ac.jp (C.L.); k-ogawa@rakuno.ac.jp (K.O.); shobara@rakuno.ac.jp (S.H.)
[2] Hokusei Gakuen University Junior College, Sapporo 004-0042, Hokkaido, Japan; k_acker@hokusei.ac.jp
[3] Zanvyl Krieger School of Arts & Sciences, Johns Hopkins University, Baltimore, MD 21218, USA; mccarthy.ch@gmail.com
[4] School of Geography, University of Oxford, Oxford OX1 3QY, UK; troy.sternberg@geog.ox.ac.uk
[5] Department of Geography, National University of Mongolia, Ulaanbaatar 14200, Mongolia; myagmartseren@num.edu.mn
[6] College of Veterinary Sciences, Rakuno Gakuen University, Ebetsu 069-0836, Hokkaido, Japan; k-hagi@rakuno.ac.jp
* Correspondence: aosier@rakuno.ac.jp

Abstract: Establishing a quantitative relationship between Synthetic Aperture Radar (SAR) data and optical data can facilitate the fusion of these two data sources, enhancing the time-series monitoring capabilities for remote sensing of a land surface. In this study, we analyzed the Normalized Difference Vegetation Index (NDVI) and Shortwave Infrared Transformed Reflectance (STR) with the backscatter coefficients in vertical polarization VV (σ^0VV) and cross polarization VH (σ^0VH) across different seasons. We used optical and microwave satellite data spanning from the southern Gobi Desert region to the steppe region in northern Mongolia. The results indicate a relatively high correlation between the NDVI derived from Sentinel-2 and σ^0VH ($R_{VH} = 0.29$, $R_{VH} = 0.44$, $p < 0.001$) and a low correlation between the NDVI and σ^0VV ($R_{VH} = 0.06$, $R_{VH} = 0.14$, $p < 0.01$) in the Gobi Desert region during summer and fall. STR showed a positive correlation with both σ^0VH and σ^0VV except in spring, with the highest correlation coefficients observed in summer ($R_{VV} = 0.45$, $R_{VV} = 0.44$, $p < 0.001$). In the steppe region, significant seasonal variations in the NDVI and σ^0VH were noted, with a strong positive correlation peaking in summer ($R_{VH} = 0.71$, $p < 0.001$) and an inverse correlation with σ^0VV except in summer ($R_{VV} = -0.43$, $R_{VV} = -0.34$, $R_{VV} = -0.13$, $p < 0.001$). Additionally, STR showed a positive correlation with σ^0VH and σ0VV in summer ($R_{VH} = 0.40$, $R_{VV} = 0.39$, $p < 0.001$) and fall ($R_{VH} = 0.38$, $R_{VV} = 0.09$, $p < 0.01$), as well as an inverse correlation in spring ($R_{VH}= -0.17$, $R_{VV}= -0.38$, $p < 0.001$) and winter ($R_{VH} = -0.21$, $R_{VV} = -0.06$, $p < 0.001$). The correlations between the NDVI, STR, σ^0VH, and σ^0VV were shown to vary by season and region. In the Gobi Desert region, perennial shrubs are not photosynthetic in spring and winter, and they affect backscatter due to surface roughness. In the steppe region, annual shrubs were found to be the dominant species and were found to photosynthesize in spring, but not enough to affect the backscatter due to surface roughness.

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Hidetoshi Higuchi

Professor

教授　樋口　豪紀

I. 筆頭または責任著者　＜First or Corresponding Author＞

1）Innate immune response of bovine mammary epithelial cells in *Mycoplasma bovis* mastitis using an *in vitro* model of bovine mammary gland infection. Imaizumi N, Gondaira S, Kamioka M, Sugiura T, Eguchi A, Nishi K, Fujiki J, Iwano H, **Higuchi H.**
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II. その他＜Others＞

1）Effects of amount of lactose in milk replacer on gastrointestinal function of dairy calves.
Fukumori R, Nakayama T, Hirose M, Norimura I, Izumi K, Shimada K, Mineo H, Steele MA, Gondaira S, **Higuchi H**, Watanabe T, Ueda H, Sano T, Chisato K, Oikawa S.
Anim Feed Sci Technol 116157. 2024. doi: 10.1016/j.anifeedsci.

2）Changes in mammary infection status in dairy cows during the dry period using dry cow therapy approaches on three farms.
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4）Characteristics of failure of passive transfer at the herd level using the serum immunoglobulin G concentration as an indicator on dairy farms in eastern Hokkaido, Japan.
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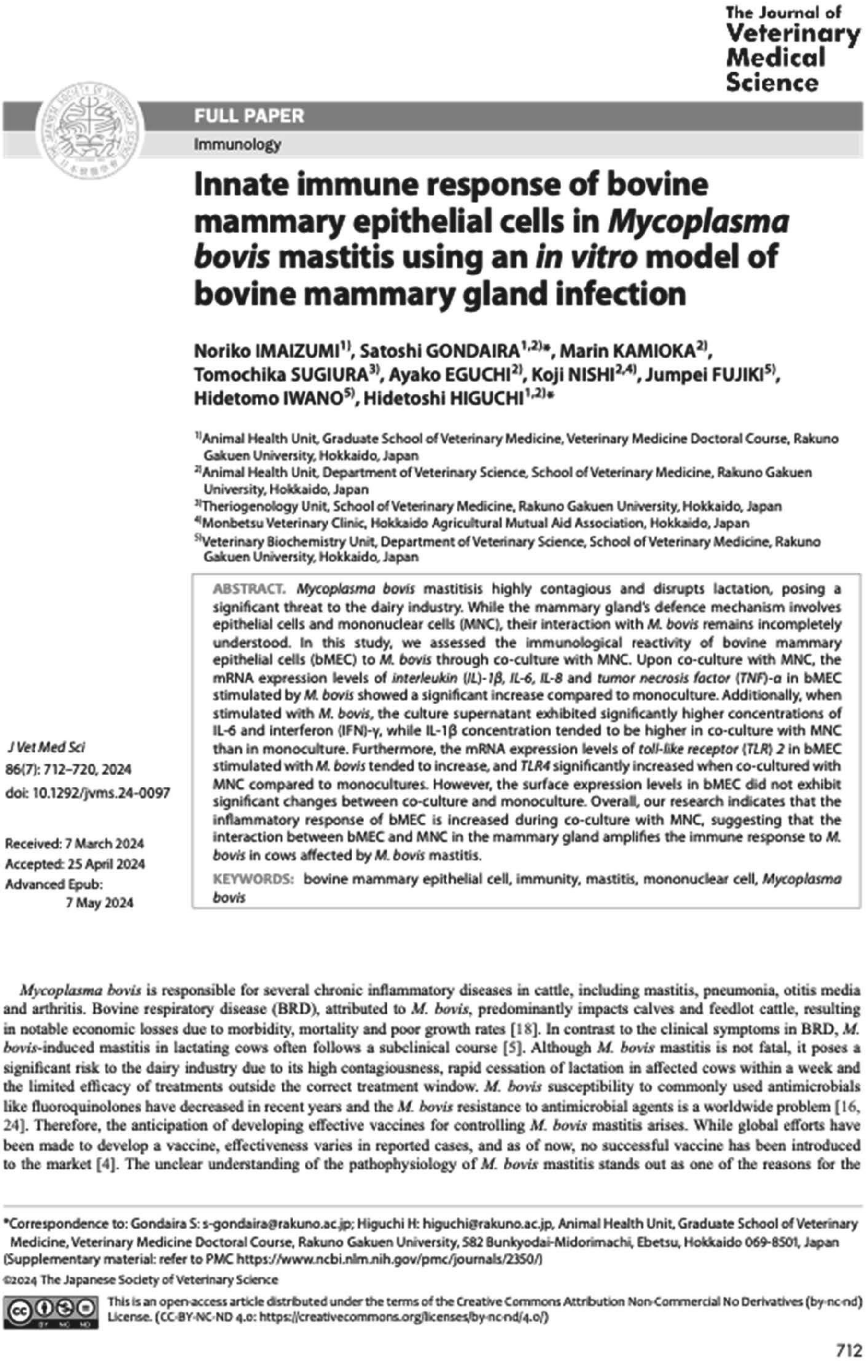

The Journal of
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FULL PAPER
Immunology

Innate immune response of bovine mammary epithelial cells in *Mycoplasma bovis* mastitis using an *in vitro* model of bovine mammary gland infection

Noriko IMAIZUMI[1], Satoshi GONDAIRA[1,2]*, Marin KAMIOKA[2], Tomochika SUGIURA[3], Ayako EGUCHI[2], Koji NISHI[2,4], Jumpei FUJIKI[5], Hidetomo IWANO[5], Hidetoshi HIGUCHI[1,2]*

[1]Animal Health Unit, Graduate School of Veterinary Medicine, Veterinary Medicine Doctoral Course, Rakuno Gakuen University, Hokkaido, Japan
[2]Animal Health Unit, Department of Veterinary Science, School of Veterinary Medicine, Rakuno Gakuen University, Hokkaido, Japan
[3]Theriogenology Unit, School of Veterinary Medicine, Rakuno Gakuen University, Hokkaido, Japan
[4]Monbetsu Veterinary Clinic, Hokkaido Agricultural Mutual Aid Association, Hokkaido, Japan
[5]Veterinary Biochemistry Unit, Department of Veterinary Science, School of Veterinary Medicine, Rakuno Gakuen University, Hokkaido, Japan

ABSTRACT. *Mycoplasma bovis* mastitisis highly contagious and disrupts lactation, posing a significant threat to the dairy industry. While the mammary gland's defence mechanism involves epithelial cells and mononuclear cells (MNC), their interaction with *M. bovis* remains incompletely understood. In this study, we assessed the immunological reactivity of bovine mammary epithelial cells (bMEC) to *M. bovis* through co-culture with MNC. Upon co-culture with MNC, the mRNA expression levels of *interleukin* (*IL*)*-1β, IL-6, IL-8* and *tumor necrosis factor* (*TNF*)*-α* in bMEC stimulated by *M. bovis* showed a significant increase compared to monoculture. Additionally, when stimulated with *M. bovis*, the culture supernatant exhibited significantly higher concentrations of IL-6 and interferon (IFN)-γ, while IL-1β concentration tended to be higher in co-culture with MNC than in monoculture. Furthermore, the mRNA expression levels of *toll-like receptor* (*TLR*) *2* in bMEC stimulated with *M. bovis* tended to increase, and *TLR4* significantly increased when co-cultured with MNC compared to monocultures. However, the surface expression levels in bMEC did not exhibit significant changes between co-culture and monoculture. Overall, our research indicates that the inflammatory response of bMEC is increased during co-culture with MNC, suggesting that the interaction between bMEC and MNC in the mammary gland amplifies the immune response to *M. bovis* in cows affected by *M. bovis* mastitis.

KEYWORDS: bovine mammary epithelial cell, immunity, mastitis, mononuclear cell, *Mycoplasma bovis*

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Mycoplasma bovis is responsible for several chronic inflammatory diseases in cattle, including mastitis, pneumonia, otitis media and arthritis. Bovine respiratory disease (BRD), attributed to *M. bovis*, predominantly impacts calves and feedlot cattle, resulting in notable economic losses due to morbidity, mortality and poor growth rates [18]. In contrast to the clinical symptoms in BRD, *M. bovis*-induced mastitis in lactating cows often follows a subclinical course [5]. Although *M. bovis* mastitis is not fatal, it poses a significant risk to the dairy industry due to its high contagiousness, rapid cessation of lactation in affected cows within a week and the limited efficacy of treatments outside the correct treatment window. *M. bovis* susceptibility to commonly used antimicrobials like fluoroquinolones have decreased in recent years and the *M. bovis* resistance to antimicrobial agents is a worldwide problem [16, 24]. Therefore, the anticipation of developing effective vaccines for controlling *M. bovis* mastitis arises. While global efforts have been made to develop a vaccine, effectiveness varies in reported cases, and as of now, no successful vaccine has been introduced to the market [4]. The unclear understanding of the pathophysiology of *M. bovis* mastitis stands out as one of the reasons for the

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*Correspondence to: Gondaira S: s-gondaira@rakuno.ac.jp; Higuchi H: higuchi@rakuno.ac.jp, Animal Health Unit, Graduate School of Veterinary Medicine, Veterinary Medicine Doctoral Course, Rakuno Gakuen University, 582 Bunkyodai-Midorimachi, Ebetsu, Hokkaido 069-8501, Japan
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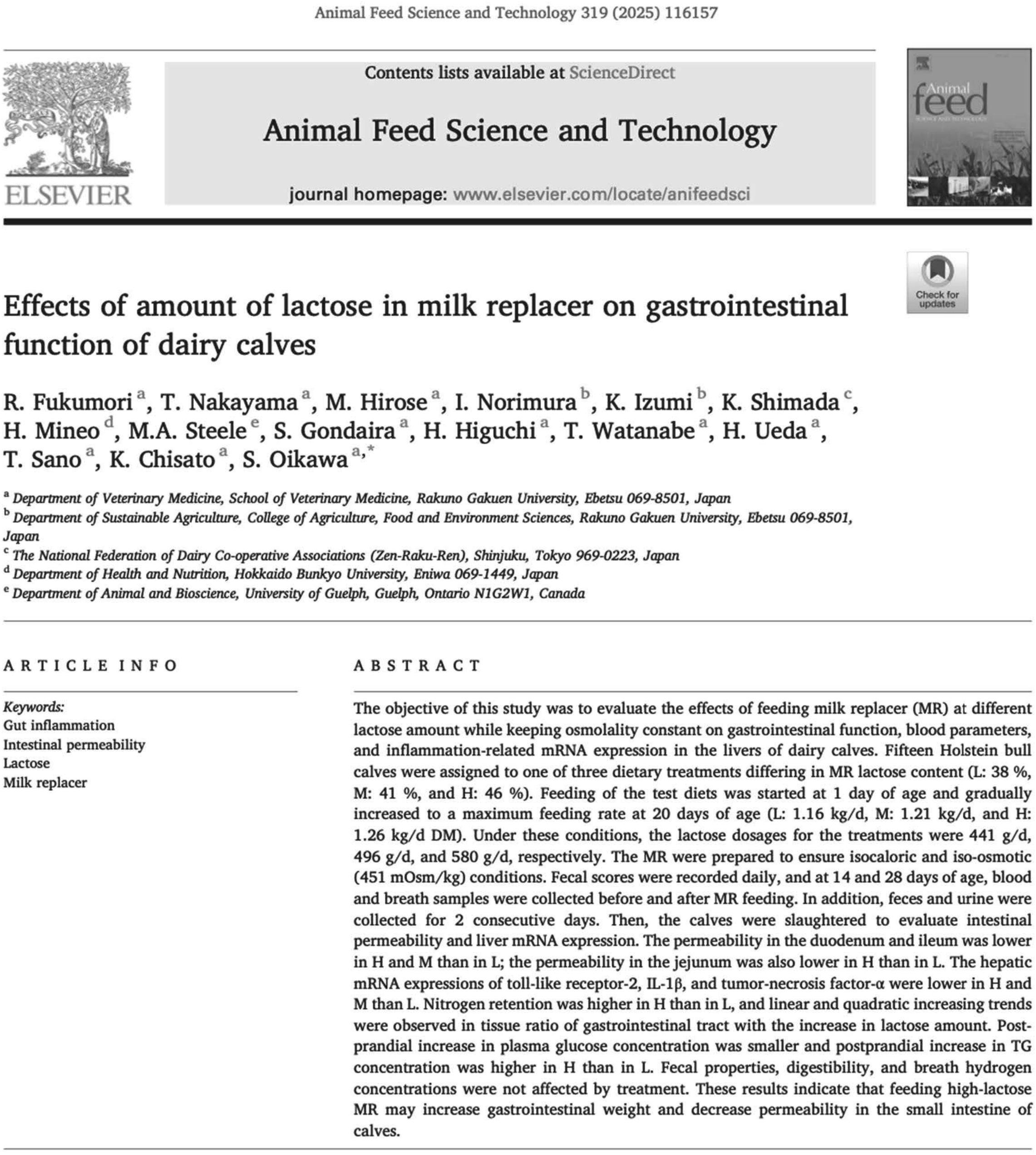

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Effects of amount of lactose in milk replacer on gastrointestinal function of dairy calves

R. Fukumori [a], T. Nakayama [a], M. Hirose [a], I. Norimura [b], K. Izumi [b], K. Shimada [c], H. Mineo [d], M.A. Steele [e], S. Gondaira [a], H. Higuchi [a], T. Watanabe [a], H. Ueda [a], T. Sano [a], K. Chisato [a], S. Oikawa [a,*]

[a] *Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu 069-8501, Japan*
[b] *Department of Sustainable Agriculture, College of Agriculture, Food and Environment Sciences, Rakuno Gakuen University, Ebetsu 069-8501, Japan*
[c] *The National Federation of Dairy Co-operative Associations (Zen-Raku-Ren), Shinjuku, Tokyo 969-0223, Japan*
[d] *Department of Health and Nutrition, Hokkaido Bunkyo University, Eniwa 069-1449, Japan*
[e] *Department of Animal and Bioscience, University of Guelph, Guelph, Ontario N1G2W1, Canada*

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Keywords:
Gut inflammation
Intestinal permeability
Lactose
Milk replacer

ABSTRACT

The objective of this study was to evaluate the effects of feeding milk replacer (MR) at different lactose amount while keeping osmolality constant on gastrointestinal function, blood parameters, and inflammation-related mRNA expression in the livers of dairy calves. Fifteen Holstein bull calves were assigned to one of three dietary treatments differing in MR lactose content (L: 38 %, M: 41 %, and H: 46 %). Feeding of the test diets was started at 1 day of age and gradually increased to a maximum feeding rate at 20 days of age (L: 1.16 kg/d, M: 1.21 kg/d, and H: 1.26 kg/d DM). Under these conditions, the lactose dosages for the treatments were 441 g/d, 496 g/d, and 580 g/d, respectively. The MR were prepared to ensure isocaloric and iso-osmotic (451 mOsm/kg) conditions. Fecal scores were recorded daily, and at 14 and 28 days of age, blood and breath samples were collected before and after MR feeding. In addition, feces and urine were collected for 2 consecutive days. Then, the calves were slaughtered to evaluate intestinal permeability and liver mRNA expression. The permeability in the duodenum and ileum was lower in H and M than in L; the permeability in the jejunum was also lower in H than in L. The hepatic mRNA expressions of toll-like receptor-2, IL-1β, and tumor-necrosis factor-α were lower in H and M than L. Nitrogen retention was higher in H than in L, and linear and quadratic increasing trends were observed in tissue ratio of gastrointestinal tract with the increase in lactose amount. Postprandial increase in plasma glucose concentration was smaller and postprandial increase in TG concentration was higher in H than in L. Fecal properties, digestibility, and breath hydrogen concentrations were not affected by treatment. These results indicate that feeding high-lactose MR may increase gastrointestinal weight and decrease permeability in the small intestine of calves.

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RESEARCH ARTICLE

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Changes in mammary infection status in dairy cows during the dry period using dry cow therapy approaches on three farms

Hajime Nagahata[1] | Nodoka Komori[2] | Mayu Fukutome[2] | Tomochika Sugiura[3] | Keiichi Hisaeda[1] | Satoshi Gondaira[4] | Hidetoshi Higuchi[4] | Tatsuya Ando[2] | Ken Nakada[3]

[1]Former Department of Veterinary Associated Studies, Okayama University of Sciences, Imabari, Ehime, Japan
[2]Farm Animal Internal Medicine Unit, Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan
[3]Theriogenology Unit, Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan
[4]Animal Health Unit, Department of Preventive Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

Correspondence
Satoshi Gondaira, Animal Health Unit, Department of Preventive Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan.
Email: s-gondaira@rakuno.ac.jp

Hajime Nagahata, Bunkyo-dai Minami 61-15, Ebetsu, Hokkaido 069-0835, Japan.
Email: nagahatahajime11@gmail.com

Abstract

This case study evaluated the mammary infection status of dairy cows during the dry periods and explored the associated problems in their quarters with dry cow therapy (DCT). This study assessed intramammary infections, antibiotic efficacy, and antimicrobial resistance of pathogens in 464-quarter milk samples from 59 dairy cows during the dry periods after applying blanket DCT, non-DCT, and selective DCT approaches on three farms. The recovery rates of intramammary infections were 95% (19/20 quarters) with blanket DCT on farm A, 70% (14/20) with non-DCT on farm B, and 19% (4/21) with selective DCT on farm C. Analysis of mammary infections in cows with DCT revealed that mammary infections were controlled by blanket DCT, well controlled by non-DCT, and substantial problems remained in selective DCT. Lower intramammary infection prevalence in the quarters at postpartum appeared to be associated with higher recovery of mammary infections, fewer new infections, and lower uncured mammary infections within the herds. Antibacterial resistance in 14 coagulase-negative staphylococci isolated to six antimicrobial drugs was suggested to be linked to antibiotic use on the farm. Follow-up studies on the quarter-based infection status with DCT will assist in improving mastitis control in cows during the dry period.

KEYWORDS
antibiotic resistance, blanket therapy, dry cow therapy, non-treated, selective therapy

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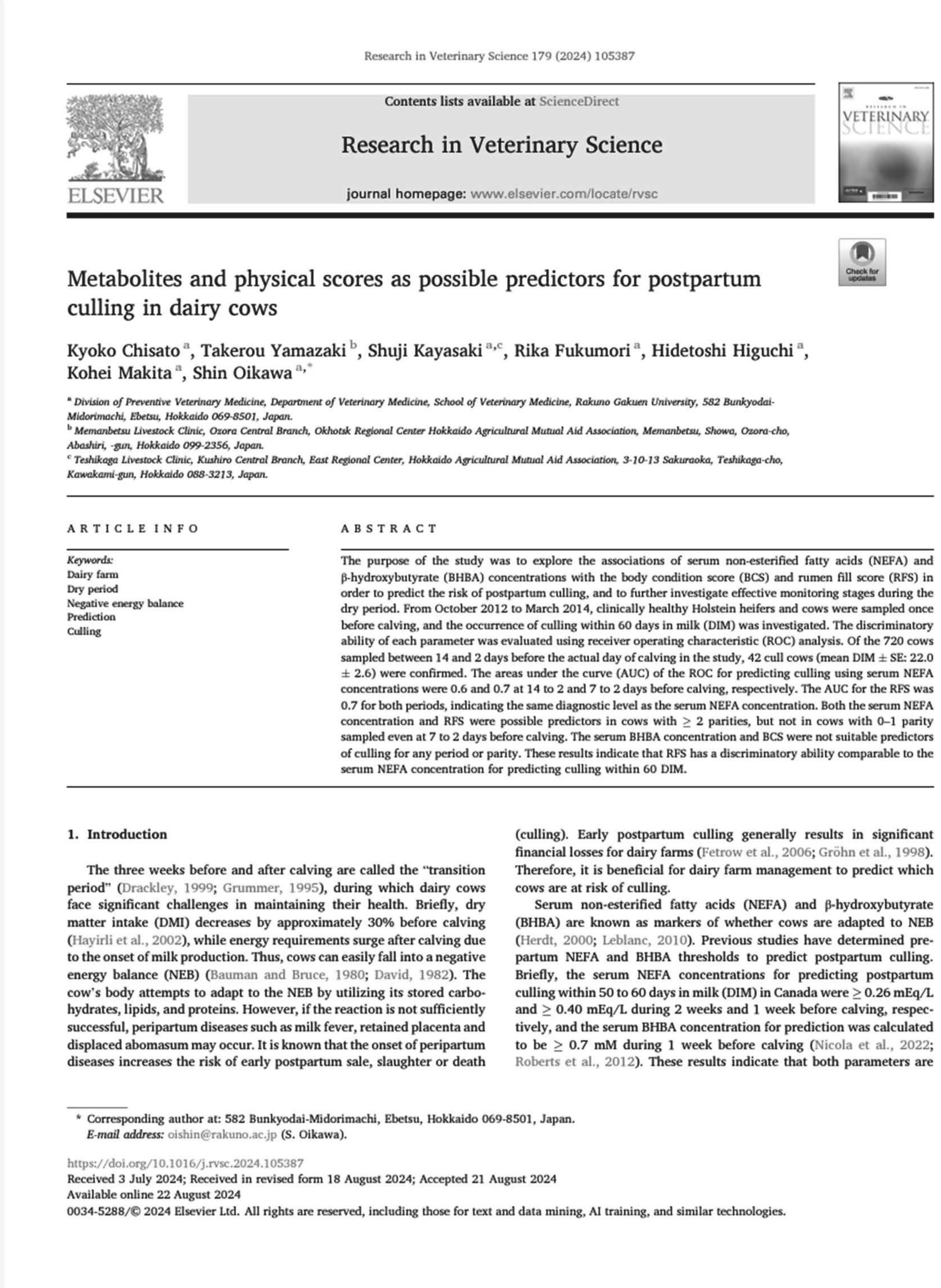

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Metabolites and physical scores as possible predictors for postpartum culling in dairy cows

Kyoko Chisato [a], Takerou Yamazaki [b], Shuji Kayasaki [a,c], Rika Fukumori [a], Hidetoshi Higuchi [a], Kohei Makita [a], Shin Oikawa [a,*]

[a] *Division of Preventive Veterinary Medicine, Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyodai-Midorimachi, Ebetsu, Hokkaido 069-8501, Japan.*

[b] *Memanbetsu Livestock Clinic, Ozora Central Branch, Okhotsk Regional Center Hokkaido Agricultural Mutual Aid Association, Memanbetsu, Showa, Ozora-cho, Abashiri, -gun, Hokkaido 099-2356, Japan.*

[c] *Teshikaga Livestock Clinic, Kushiro Central Branch, East Regional Center, Hokkaido Agricultural Mutual Aid Association, 3-10-13 Sakuraoka, Teshikaga-cho, Kawakami-gun, Hokkaido 088-3213, Japan.*

ARTICLE INFO

Keywords:
Dairy farm
Dry period
Negative energy balance
Prediction
Culling

ABSTRACT

The purpose of the study was to explore the associations of serum non-esterified fatty acids (NEFA) and β-hydroxybutyrate (BHBA) concentrations with the body condition score (BCS) and rumen fill score (RFS) in order to predict the risk of postpartum culling, and to further investigate effective monitoring stages during the dry period. From October 2012 to March 2014, clinically healthy Holstein heifers and cows were sampled once before calving, and the occurrence of culling within 60 days in milk (DIM) was investigated. The discriminatory ability of each parameter was evaluated using receiver operating characteristic (ROC) analysis. Of the 720 cows sampled between 14 and 2 days before the actual day of calving in the study, 42 cull cows (mean DIM ± SE: 22.0 ± 2.6) were confirmed. The areas under the curve (AUC) of the ROC for predicting culling using serum NEFA concentrations were 0.6 and 0.7 at 14 to 2 and 7 to 2 days before calving, respectively. The AUC for the RFS was 0.7 for both periods, indicating the same diagnostic level as the serum NEFA concentration. Both the serum NEFA concentration and RFS were possible predictors in cows with ≥ 2 parities, but not in cows with 0–1 parity sampled even at 7 to 2 days before calving. The serum BHBA concentration and BCS were not suitable predictors of culling for any period or parity. These results indicate that RFS has a discriminatory ability comparable to the serum NEFA concentration for predicting culling within 60 DIM.

1. Introduction

The three weeks before and after calving are called the "transition period" (Drackley, 1999; Grummer, 1995), during which dairy cows face significant challenges in maintaining their health. Briefly, dry matter intake (DMI) decreases by approximately 30% before calving (Hayirli et al., 2002), while energy requirements surge after calving due to the onset of milk production. Thus, cows can easily fall into a negative energy balance (NEB) (Bauman and Bruce, 1980; David, 1982). The cow's body attempts to adapt to the NEB by utilizing its stored carbohydrates, lipids, and proteins. However, if the reaction is not sufficiently successful, peripartum diseases such as milk fever, retained placenta and displaced abomasum may occur. It is known that the onset of peripartum diseases increases the risk of early postpartum sale, slaughter or death (culling). Early postpartum culling generally results in significant financial losses for dairy farms (Fetrow et al., 2006; Gröhn et al., 1998). Therefore, it is beneficial for dairy farm management to predict which cows are at risk of culling.

Serum non-esterified fatty acids (NEFA) and β-hydroxybutyrate (BHBA) are known as markers of whether cows are adapted to NEB (Herdt, 2000; Leblanc, 2010). Previous studies have determined prepartum NEFA and BHBA thresholds to predict postpartum culling. Briefly, the serum NEFA concentrations for predicting postpartum culling within 50 to 60 days in milk (DIM) in Canada were ≥ 0.26 mEq/L and ≥ 0.40 mEq/L during 2 weeks and 1 week before calving, respectively, and the serum BHBA concentration for prediction was calculated to be ≥ 0.7 mM during 1 week before calving (Nicola et al., 2022; Roberts et al., 2012). These results indicate that both parameters are

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* Corresponding author at: 582 Bunkyodai-Midorimachi, Ebetsu, Hokkaido 069-8501, Japan.
E-mail address: oishin@rakuno.ac.jp (S. Oikawa).

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FULL PAPER
Internal Medicine

Characteristics of failure of passive transfer at the herd level using the serum immunoglobulin G concentration as an indicator on dairy farms in eastern Hokkaido, Japan

Shuji KAYASAKI[1,2)], Hitomi SATOH[2)], Keitaro OGUCHI[2)], Kyoko CHISATO[2)],
Rika FUKUMORI[2)], Hidetoshi HIGUCHI[2)], Kazuyuki SUZUKI[2)], Shin OIKAWA[2)]*

[1)] Teshikaga Livestock Clinic, Kushiro Central Branch, East Regional Center, Hokkaido Agricultural Mutual Aid Association, Hokkaido, Japan
[2)] Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Hokkaido, Japan

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ABSTRACT. The objectives of this study were to conduct a survey of failure-of-passive-transfer (FPT) in eastern Hokkaido Japan, to evaluate the association between herd-level FPT and death and culling or treatment, and to test the effectiveness of monitoring using herd-level FPT. A total of 4,411 Holstein and Holstein-Wagyu crossbreds calves born from Holstein dams during the year beginning April 2, 2019 on 39 dairy farms were included in the study to investigate death-and-culling and the treatment rate during the first month of life, as well as rearing management up to 3 weeks of age. A subset of Holsteins ($n=381$) was included in the study for passive transfer and farms were diagnosed as having FPT if more than 20% of newborn calves had serum IgG levels below 10 g/L at the herd level. The prevalence of FPT (<IgG 10 g/L) on farms was significantly correlated ($r=0.27$, $P<0.05$) with the death-and-culling rate. Binomial logistic regression analysis showed that FPT farms had a significantly higher risk of being high death-and-culling farms than non-FPT farms (odds ratio: 5.20, $P<0.05$), emphasizing the importance of colostrum feeding. Farms not using frozen stored colostrum had a significantly higher risk of being FPT farms than those that did (odds ratio: 4.13, $P<0.05$), emphasizing the importance of feeding colostrum from the dam. Monitoring herd-level FPT was useful in assessing whether the problem of calf death and culling lies in passive transfer.

KEYWORDS: dairy, failure of passive transfer (FPT), herd level, immunoglobulin G (IgG)

Heifer deaths on dairy farms have been reported to be concentrated in the first month after birth [1, 2, 9, 12, 20, 21, 24, 30, 33, 37]. Similarly, in eastern Hokkaido, most preweaning deaths and culling occur during the first month of life, with concurrent digestive diseases being common causative diseases [10]. The health impact of colostrum feeding is emphasized in calf management. Agammaglobulinemic calves must ingest and absorb immunoglobulin from colostrum after birth. This is called passive transfer. Though failure of passive transfer (FPT) is not a disease, it is a condition that predisposes the neonate to the development of disease [38]. As a result, calves with FPT have an increased mortality risk [5, 12, 27, 28, 30, 32]. Because serum immunoglobulin G (IgG) concentrations of newborn calves are closely correlated to serum total protein (TP) concentrations, the status of passive transfer can be determined by determining serum TP concentrations, which can be easily measured [26]. At the individual level, a serum IgG concentration of 10 g/L or higher is considered to be an appropriate level of passive immune transfer. Serum TP concentrations of 5.0, 5.2 and 5.5 g/dL can be used to predict this IgG concentration [3, 26]. The recommended standards for passive transfer at the herd level are that 90% of sampled calves have serum TP concentrations of 5.2 g/dL or higher, or that 80% have serum TP concentrations of 5.5 g/dL or higher [14, 35]. It has been suggested that monitoring a herd using an indicator of the serum TP concentration and improving it when it is not achieved will lead to a reduction in the risk of mortality [27]. In addition to these mortality-risk standards, herd-level standards to reduce the risk of morbidity have also been reported [12]. The standards are based on four categories of serum IgG ≥25.0, 18.0–24.9, 10.0–17.9, and <10 g/L, with the proportion of calves in each category being >40, 30, 20, and <10%, respectively. It has

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*Correspondence to: Oikawa S: oishin@rakuno.ac.jp, Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyodai-Midorimachi, Ebetsu, Hokkaido 069-8501, Japan

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最終責任者　Shin Oikawa (Corresponding Author)

獣医生化学（Veterinary Biochemistry）

Hidetomo Iwano

Professor

教授　岩野　英知

I. 筆頭または責任著者　＜First or Corresponding Author＞

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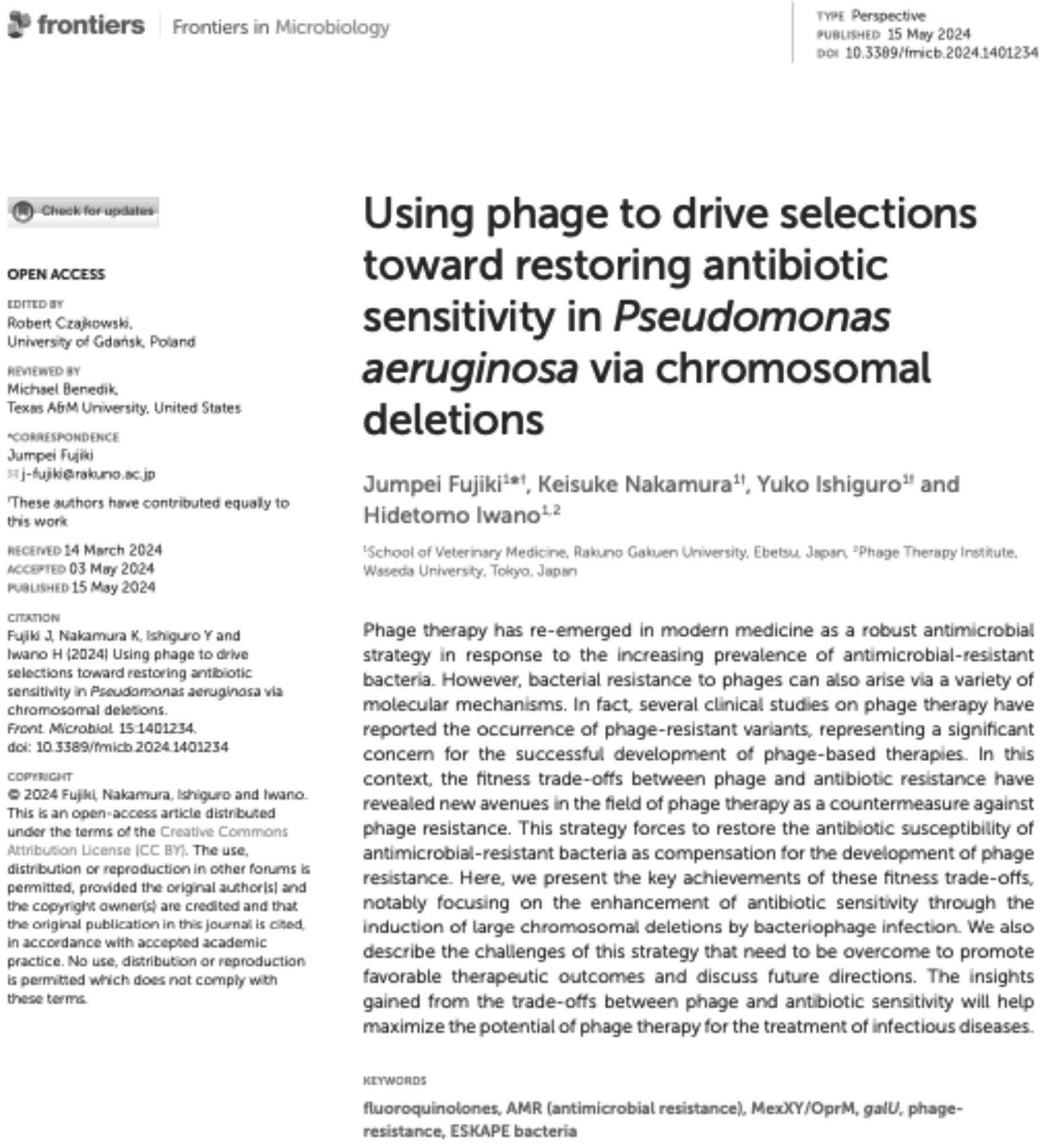

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Using phage to drive selections toward restoring antibiotic sensitivity in *Pseudomonas aeruginosa* via chromosomal deletions

Jumpei Fujiki[1*†], Keisuke Nakamura[1†], Yuko Ishiguro[1†] and Hidetomo Iwano[1,2]

[1]School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan, [2]Phage Therapy Institute, Waseda University, Tokyo, Japan

Phage therapy has re-emerged in modern medicine as a robust antimicrobial strategy in response to the increasing prevalence of antimicrobial-resistant bacteria. However, bacterial resistance to phages can also arise via a variety of molecular mechanisms. In fact, several clinical studies on phage therapy have reported the occurrence of phage-resistant variants, representing a significant concern for the successful development of phage-based therapies. In this context, the fitness trade-offs between phage and antibiotic resistance have revealed new avenues in the field of phage therapy as a countermeasure against phage resistance. This strategy forces to restore the antibiotic susceptibility of antimicrobial-resistant bacteria as compensation for the development of phage resistance. Here, we present the key achievements of these fitness trade-offs, notably focusing on the enhancement of antibiotic sensitivity through the induction of large chromosomal deletions by bacteriophage infection. We also describe the challenges of this strategy that need to be overcome to promote favorable therapeutic outcomes and discuss future directions. The insights gained from the trade-offs between phage and antibiotic sensitivity will help maximize the potential of phage therapy for the treatment of infectious diseases.

KEYWORDS

fluoroquinolones, AMR (antimicrobial resistance), MexXY/OprM, *galU*, phage-resistance, ESKAPE bacteria

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Robert Czajkowski,
University of Gdańsk, Poland

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Michael Benedik,
Texas A&M University, United States

*CORRESPONDENCE
Jumpei Fujiki
✉ j-fujiki@rakuno.ac.jp

†These authors have contributed equally to this work

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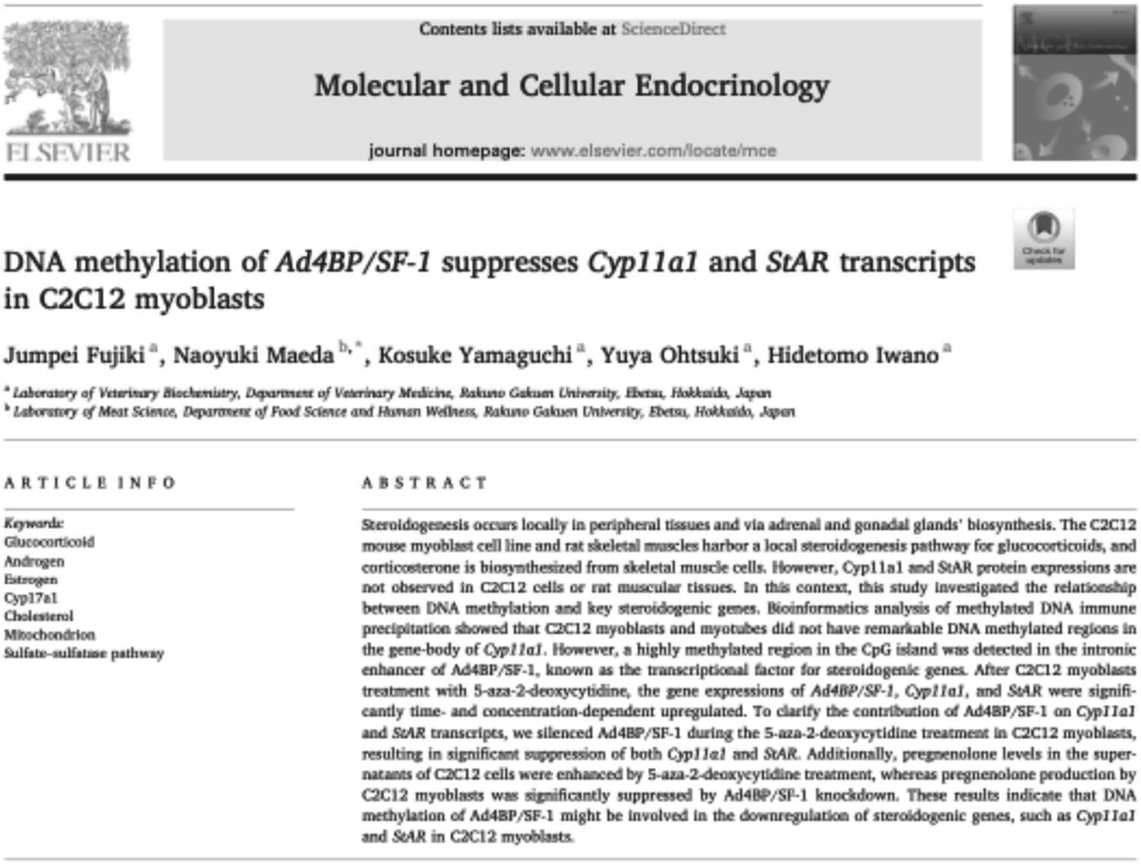

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DNA methylation of *Ad4BP/SF-1* suppresses *Cyp11a1* and *StAR* transcripts in C2C12 myoblasts

Jumpei Fujiki[a], Naoyuki Maeda[b,*], Kosuke Yamaguchi[a], Yuya Ohtsuki[a], Hidetomo Iwano[a]

[a] *Laboratory of Veterinary Biochemistry, Department of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan*
[b] *Laboratory of Meat Science, Department of Food Science and Human Wellness, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan*

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ABSTRACT

Steroidogenesis occurs locally in peripheral tissues and via adrenal and gonadal glands' biosynthesis. The C2C12 mouse myoblast cell line and rat skeletal muscles harbor a local steroidogenesis pathway for glucocorticoids, and corticosterone is biosynthesized from skeletal muscle cells. However, Cyp11a1 and StAR protein expressions are not observed in C2C12 cells or rat muscular tissues. In this context, this study investigated the relationship between DNA methylation and key steroidogenic genes. Bioinformatics analysis of methylated DNA immune precipitation showed that C2C12 myoblasts and myotubes did not have remarkable DNA methylated regions in the gene-body of *Cyp11a1*. However, a highly methylated region in the CpG island was detected in the intronic enhancer of Ad4BP/SF-1, known as the transcriptional factor for steroidogenic genes. After C2C12 myoblasts treatment with 5-aza-2-deoxycytidine, the gene expressions of *Ad4BP/SF-1*, *Cyp11a1*, and *StAR* were significantly time- and concentration-dependent upregulated. To clarify the contribution of Ad4BP/SF-1 on *Cyp11a1* and *StAR* transcripts, we silenced Ad4BP/SF-1 during the 5-aza-2-deoxycytidine treatment in C2C12 myoblasts, resulting in significant suppression of both *Cyp11a1* and *StAR*. Additionally, pregnenolone levels in the supernatants of C2C12 cells were enhanced by 5-aza-2-deoxycytidine treatment, whereas pregnenolone production by C2C12 myoblasts was significantly suppressed by Ad4BP/SF-1 knockdown. These results indicate that DNA methylation of Ad4BP/SF-1 might be involved in the downregulation of steroidogenic genes, such as *Cyp11a1* and *StAR* in C2C12 myoblasts.

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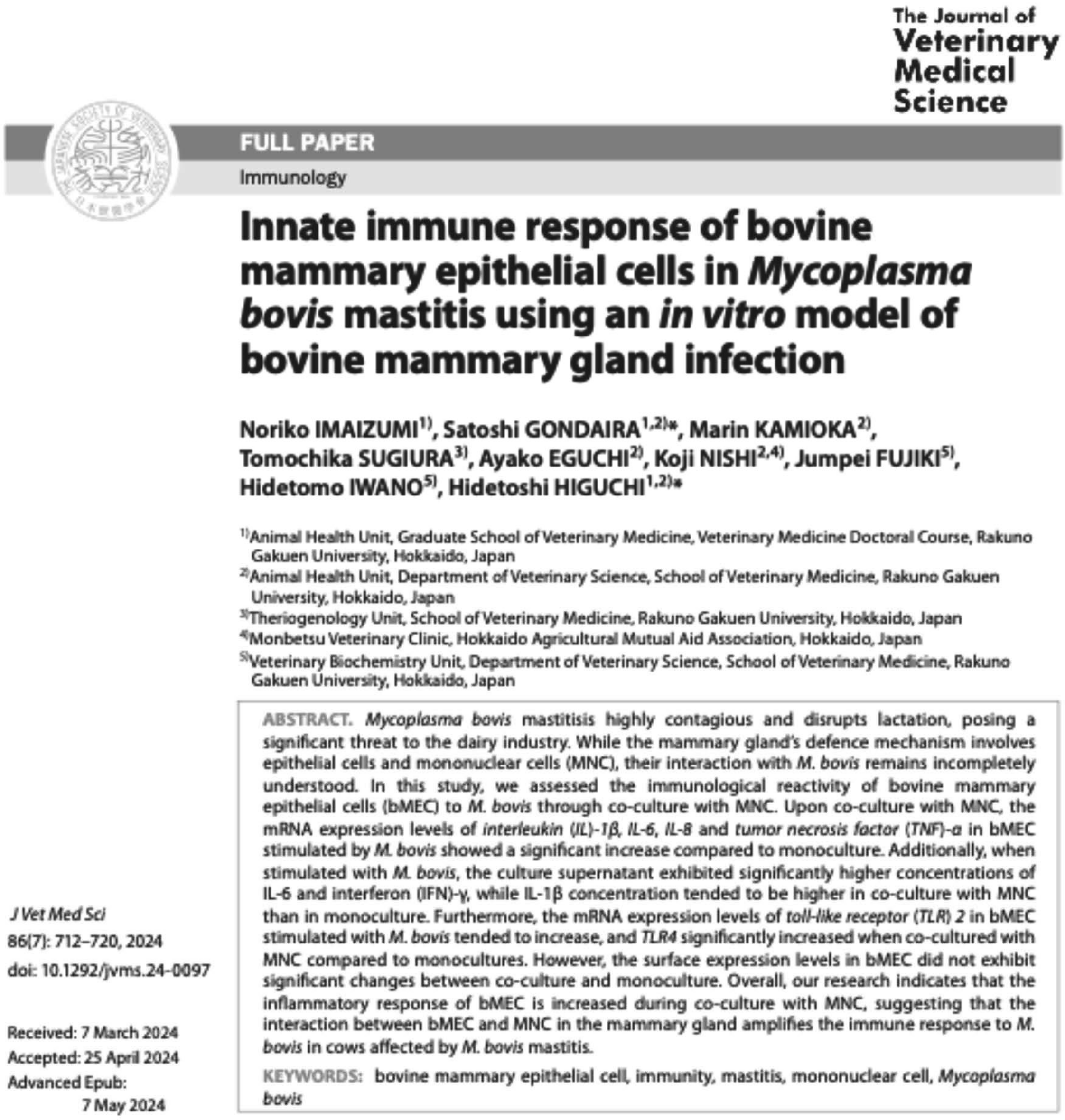

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FULL PAPER
Immunology

Innate immune response of bovine mammary epithelial cells in *Mycoplasma bovis* mastitis using an *in vitro* model of bovine mammary gland infection

Noriko IMAIZUMI[1)], Satoshi GONDAIRA[1,2)]*, Marin KAMIOKA[2)], Tomochika SUGIURA[3)], Ayako EGUCHI[2)], Koji NISHI[2,4)], Jumpei FUJIKI[5)], Hidetomo IWANO[5)], Hidetoshi HIGUCHI[1,2)]*

[1)]Animal Health Unit, Graduate School of Veterinary Medicine, Veterinary Medicine Doctoral Course, Rakuno Gakuen University, Hokkaido, Japan
[2)]Animal Health Unit, Department of Veterinary Science, School of Veterinary Medicine, Rakuno Gakuen University, Hokkaido, Japan
[3)]Theriogenology Unit, School of Veterinary Medicine, Rakuno Gakuen University, Hokkaido, Japan
[4)]Monbetsu Veterinary Clinic, Hokkaido Agricultural Mutual Aid Association, Hokkaido, Japan
[5)]Veterinary Biochemistry Unit, Department of Veterinary Science, School of Veterinary Medicine, Rakuno Gakuen University, Hokkaido, Japan

ABSTRACT. *Mycoplasma bovis* mastitisis highly contagious and disrupts lactation, posing a significant threat to the dairy industry. While the mammary gland's defence mechanism involves epithelial cells and mononuclear cells (MNC), their interaction with *M. bovis* remains incompletely understood. In this study, we assessed the immunological reactivity of bovine mammary epithelial cells (bMEC) to *M. bovis* through co-culture with MNC. Upon co-culture with MNC, the mRNA expression levels of *interleukin* (*IL*)*-1β*, *IL-6*, *IL-8* and *tumor necrosis factor* (*TNF*)*-α* in bMEC stimulated by *M. bovis* showed a significant increase compared to monoculture. Additionally, when stimulated with *M. bovis*, the culture supernatant exhibited significantly higher concentrations of IL-6 and interferon (IFN)-γ, while IL-1β concentration tended to be higher in co-culture with MNC than in monoculture. Furthermore, the mRNA expression levels of *toll-like receptor* (*TLR*) *2* in bMEC stimulated with *M. bovis* tended to increase, and *TLR4* significantly increased when co-cultured with MNC compared to monocultures. However, the surface expression levels in bMEC did not exhibit significant changes between co-culture and monoculture. Overall, our research indicates that the inflammatory response of bMEC is increased during co-culture with MNC, suggesting that the interaction between bMEC and MNC in the mammary gland amplifies the immune response to *M. bovis* in cows affected by *M. bovis* mastitis.

KEYWORDS: bovine mammary epithelial cell, immunity, mastitis, mononuclear cell, *Mycoplasma bovis*

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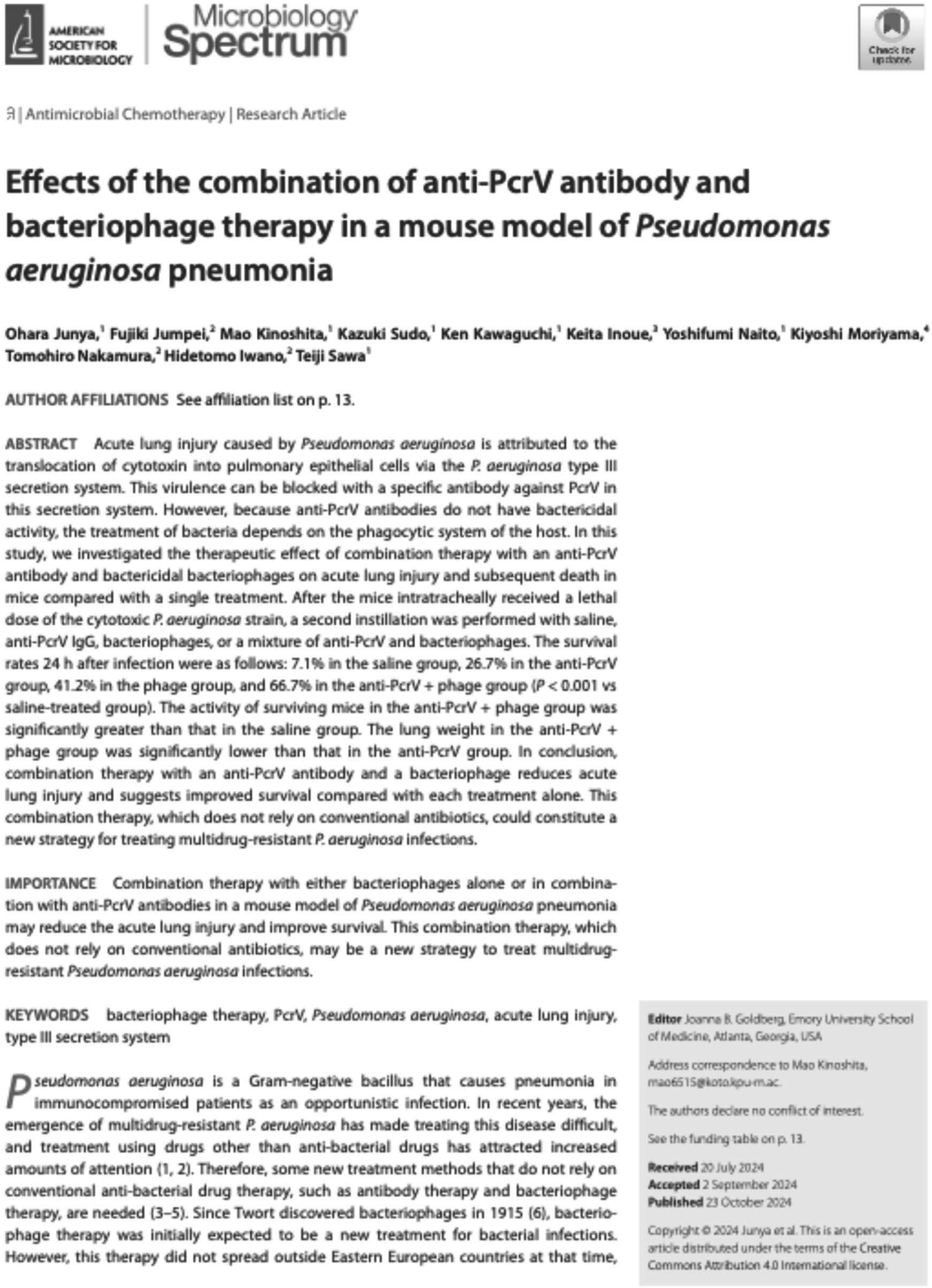

AMERICAN SOCIETY FOR MICROBIOLOGY | Microbiology Spectrum

Antimicrobial Chemotherapy | Research Article

Effects of the combination of anti-PcrV antibody and bacteriophage therapy in a mouse model of *Pseudomonas aeruginosa* pneumonia

Ohara Junya,[1] Fujiki Jumpei,[2] Mao Kinoshita,[1] Kazuki Sudo,[1] Ken Kawaguchi,[1] Keita Inoue,[3] Yoshifumi Naito,[1] Kiyoshi Moriyama,[4] Tomohiro Nakamura,[2] Hidetomo Iwano,[2] Teiji Sawa[1]

AUTHOR AFFILIATIONS See affiliation list on p. 13.

ABSTRACT Acute lung injury caused by *Pseudomonas aeruginosa* is attributed to the translocation of cytotoxin into pulmonary epithelial cells via the *P. aeruginosa* type III secretion system. This virulence can be blocked with a specific antibody against PcrV in this secretion system. However, because anti-PcrV antibodies do not have bactericidal activity, the treatment of bacteria depends on the phagocytic system of the host. In this study, we investigated the therapeutic effect of combination therapy with an anti-PcrV antibody and bactericidal bacteriophages on acute lung injury and subsequent death in mice compared with a single treatment. After the mice intratracheally received a lethal dose of the cytotoxic *P. aeruginosa* strain, a second instillation was performed with saline, anti-PcrV IgG, bacteriophages, or a mixture of anti-PcrV and bacteriophages. The survival rates 24 h after infection were as follows: 7.1% in the saline group, 26.7% in the anti-PcrV group, 41.2% in the phage group, and 66.7% in the anti-PcrV + phage group ($P < 0.001$ vs saline-treated group). The activity of surviving mice in the anti-PcrV + phage group was significantly greater than that in the saline group. The lung weight in the anti-PcrV + phage group was significantly lower than that in the anti-PcrV group. In conclusion, combination therapy with an anti-PcrV antibody and a bacteriophage reduces acute lung injury and suggests improved survival compared with each treatment alone. This combination therapy, which does not rely on conventional antibiotics, could constitute a new strategy for treating multidrug-resistant *P. aeruginosa* infections.

IMPORTANCE Combination therapy with either bacteriophages alone or in combination with anti-PcrV antibodies in a mouse model of *Pseudomonas aeruginosa* pneumonia may reduce the acute lung injury and improve survival. This combination therapy, which does not rely on conventional antibiotics, may be a new strategy to treat multidrug-resistant *Pseudomonas aeruginosa* infections.

KEYWORDS bacteriophage therapy, PcrV, *Pseudomonas aeruginosa*, acute lung injury, type III secretion system

Pseudomonas aeruginosa is a Gram-negative bacillus that causes pneumonia in immunocompromised patients as an opportunistic infection. In recent years, the emergence of multidrug-resistant *P. aeruginosa* has made treating this disease difficult, and treatment using drugs other than anti-bacterial drugs has attracted increased amounts of attention (1, 2). Therefore, some new treatment methods that do not rely on conventional anti-bacterial drug therapy, such as antibody therapy and bacteriophage therapy, are needed (3–5). Since Twort discovered bacteriophages in 1915 (6), bacteriophage therapy was initially expected to be a new treatment for bacterial infections. However, this therapy did not spread outside Eastern European countries at that time,

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Address correspondence to Mao Kinoshita, mao6515@koto.kpu-m.ac.

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最終責任者　Teiji Sawa (Corresponding Author)

疾患モデル学（Disease Models）

Hiroshi Kitamura

Professor

教授　北村　浩

Ⅰ. 筆頭または責任著者　＜First or Corresponding Author＞

1）USP2 mitigates reactive oxygen species-induced mitochondrial damage via UCP2 expression in myoblasts.
Kitamura H, Fujimoto M, Hashimoto M, Yasui H, Inanami O
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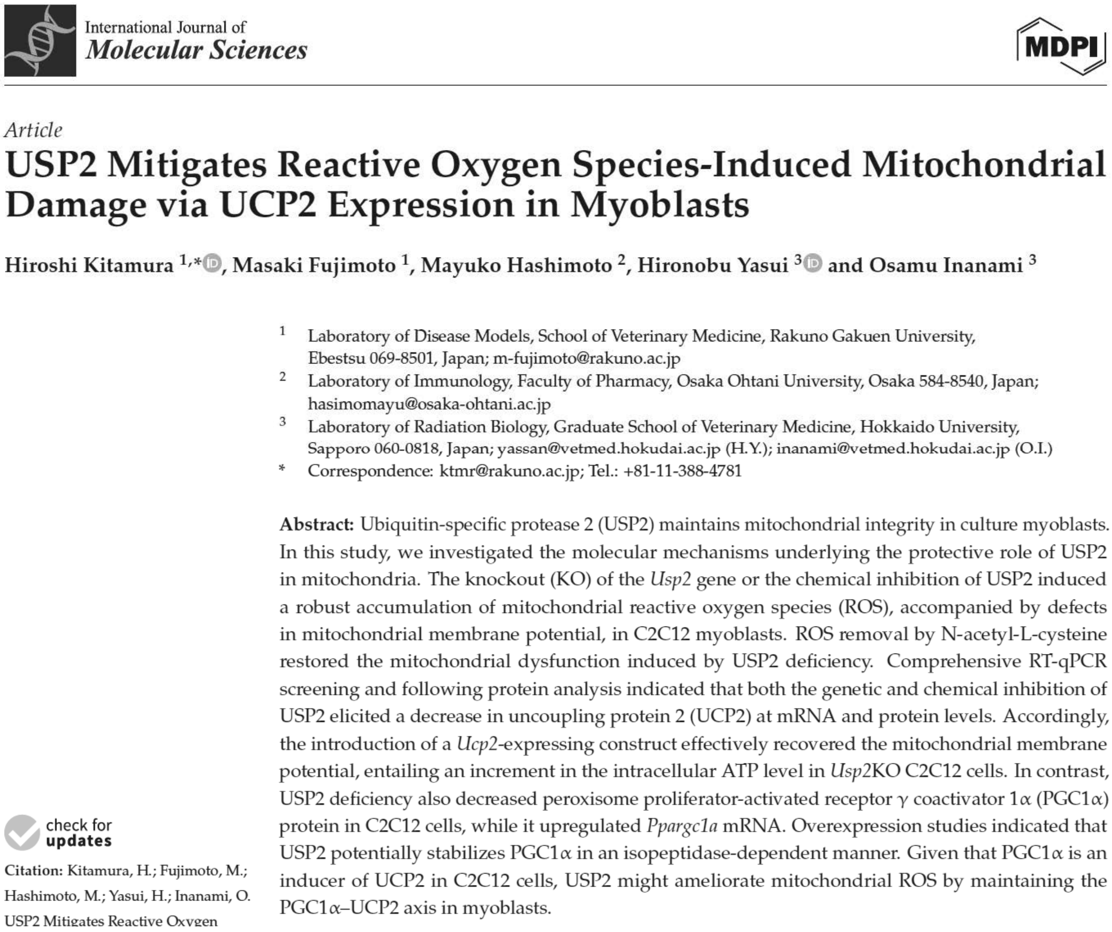

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Article

USP2 Mitigates Reactive Oxygen Species-Induced Mitochondrial Damage via UCP2 Expression in Myoblasts

Hiroshi Kitamura [1,*], Masaki Fujimoto [1], Mayuko Hashimoto [2], Hironobu Yasui [3] and Osamu Inanami [3]

[1] Laboratory of Disease Models, School of Veterinary Medicine, Rakuno Gakuen University, Ebestsu 069-8501, Japan; m-fujimoto@rakuno.ac.jp
[2] Laboratory of Immunology, Faculty of Pharmacy, Osaka Ohtani University, Osaka 584-8540, Japan; hasimomayu@osaka-ohtani.ac.jp
[3] Laboratory of Radiation Biology, Graduate School of Veterinary Medicine, Hokkaido University, Sapporo 060-0818, Japan; yassan@vetmed.hokudai.ac.jp (H.Y.); inanami@vetmed.hokudai.ac.jp (O.I.)
* Correspondence: ktmr@rakuno.ac.jp; Tel.: +81-11-388-4781

Abstract: Ubiquitin-specific protease 2 (USP2) maintains mitochondrial integrity in culture myoblasts. In this study, we investigated the molecular mechanisms underlying the protective role of USP2 in mitochondria. The knockout (KO) of the *Usp2* gene or the chemical inhibition of USP2 induced a robust accumulation of mitochondrial reactive oxygen species (ROS), accompanied by defects in mitochondrial membrane potential, in C2C12 myoblasts. ROS removal by N-acetyl-L-cysteine restored the mitochondrial dysfunction induced by USP2 deficiency. Comprehensive RT-qPCR screening and following protein analysis indicated that both the genetic and chemical inhibition of USP2 elicited a decrease in uncoupling protein 2 (UCP2) at mRNA and protein levels. Accordingly, the introduction of a *Ucp2*-expressing construct effectively recovered the mitochondrial membrane potential, entailing an increment in the intracellular ATP level in *Usp2*KO C2C12 cells. In contrast, USP2 deficiency also decreased peroxisome proliferator-activated receptor γ coactivator 1α (PGC1α) protein in C2C12 cells, while it upregulated *Ppargc1a* mRNA. Overexpression studies indicated that USP2 potentially stabilizes PGC1α in an isopeptidase-dependent manner. Given that PGC1α is an inducer of UCP2 in C2C12 cells, USP2 might ameliorate mitochondrial ROS by maintaining the PGC1α–UCP2 axis in myoblasts.

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最終責任者　Hiroshi Kitamura (First Author/Corresponding Author)

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Kohei Makita

Professor

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1） Quantitative release assessment for beta-lactamase–producing *Escherichia coli* of dairy origin into vegetables.
Makita K, Zhang D, Okamura A, Fukuda A, Tokunaga N, Asai T, Shimazaki Y, Usui M.
CABI One Health 3:1. 2024. doi: 10.1079/cabionehealth.2024.0021

2) Identifying effective biosecurity measures for preventing the introduction of classical swine fever in pig farms in Japan: under the condition of absence/presence of observable infected wild boar.
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Fukui M, Uraguchi K, Numa H, Suzuki T, Karasawa M, Maita K, Yokozawa T, Hayama Y, **Makita K.**
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II. その他＜Others＞

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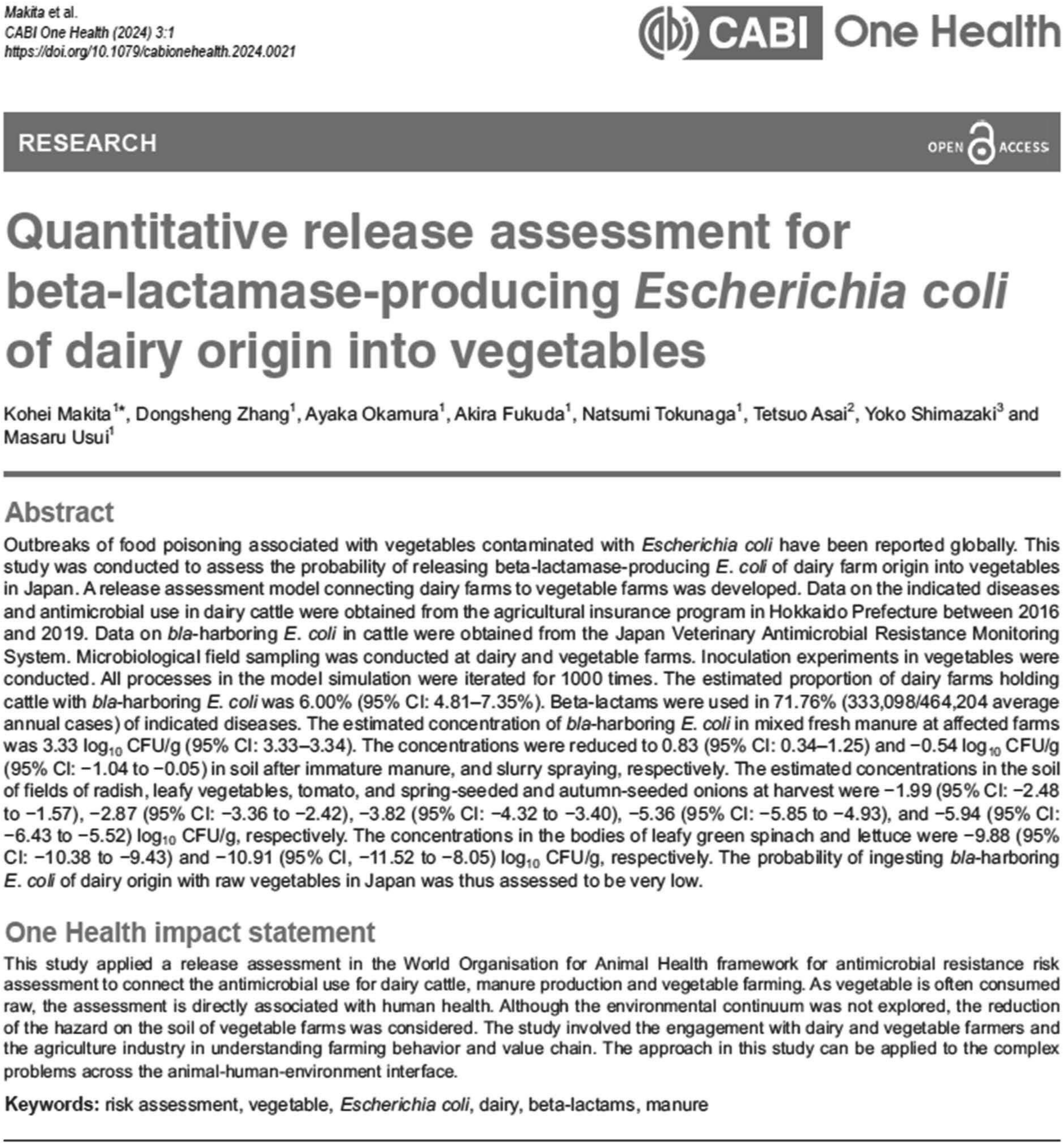

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RESEARCH

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Quantitative release assessment for beta-lactamase-producing *Escherichia coli* of dairy origin into vegetables

Kohei Makita[1*], Dongsheng Zhang[1], Ayaka Okamura[1], Akira Fukuda[1], Natsumi Tokunaga[1], Tetsuo Asai[2], Yoko Shimazaki[3] and Masaru Usui[1]

Abstract

Outbreaks of food poisoning associated with vegetables contaminated with *Escherichia coli* have been reported globally. This study was conducted to assess the probability of releasing beta-lactamase-producing *E. coli* of dairy farm origin into vegetables in Japan. A release assessment model connecting dairy farms to vegetable farms was developed. Data on the indicated diseases and antimicrobial use in dairy cattle were obtained from the agricultural insurance program in Hokkaido Prefecture between 2016 and 2019. Data on *bla*-harboring *E. coli* in cattle were obtained from the Japan Veterinary Antimicrobial Resistance Monitoring System. Microbiological field sampling was conducted at dairy and vegetable farms. Inoculation experiments in vegetables were conducted. All processes in the model simulation were iterated for 1000 times. The estimated proportion of dairy farms holding cattle with *bla*-harboring *E. coli* was 6.00% (95% CI: 4.81–7.35%). Beta-lactams were used in 71.76% (333,098/464,204 average annual cases) of indicated diseases. The estimated concentration of *bla*-harboring *E. coli* in mixed fresh manure at affected farms was 3.33 $\log_{10}$ CFU/g (95% CI: 3.33–3.34). The concentrations were reduced to 0.83 (95% CI: 0.34–1.25) and −0.54 $\log_{10}$ CFU/g (95% CI: −1.04 to −0.05) in soil after immature manure, and slurry spraying, respectively. The estimated concentrations in the soil of fields of radish, leafy vegetables, tomato, and spring-seeded and autumn-seeded onions at harvest were −1.99 (95% CI: −2.48 to −1.57), −2.87 (95% CI: −3.36 to −2.42), −3.82 (95% CI: −4.32 to −3.40), −5.36 (95% CI: −5.85 to −4.93), and −5.94 (95% CI: −6.43 to −5.52) $\log_{10}$ CFU/g, respectively. The concentrations in the bodies of leafy green spinach and lettuce were −9.88 (95% CI: −10.38 to −9.43) and −10.91 (95% CI, −11.52 to −8.05) $\log_{10}$ CFU/g, respectively. The probability of ingesting *bla*-harboring *E. coli* of dairy origin with raw vegetables in Japan was thus assessed to be very low.

One Health impact statement

This study applied a release assessment in the World Organisation for Animal Health framework for antimicrobial resistance risk assessment to connect the antimicrobial use for dairy cattle, manure production and vegetable farming. As vegetable is often consumed raw, the assessment is directly associated with human health. Although the environmental continuum was not explored, the reduction of the hazard on the soil of vegetable farms was considered. The study involved the engagement with dairy and vegetable farmers and the agriculture industry in understanding farming behavior and value chain. The approach in this study can be applied to the complex problems across the animal-human-environment interface.

Keywords: risk assessment, vegetable, *Escherichia coli*, dairy, beta-lactams, manure

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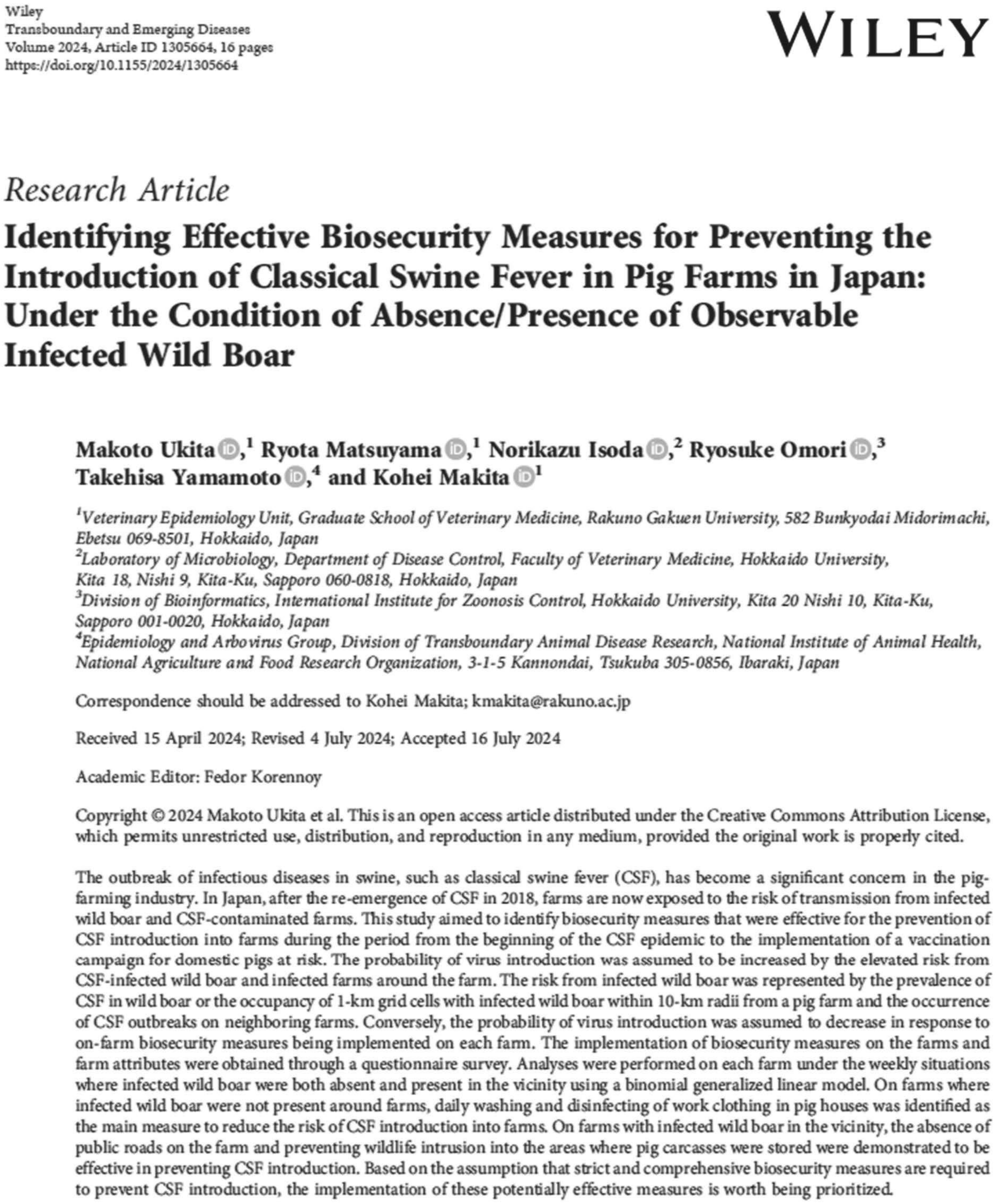

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Research Article

Identifying Effective Biosecurity Measures for Preventing the Introduction of Classical Swine Fever in Pig Farms in Japan: Under the Condition of Absence/Presence of Observable Infected Wild Boar

Makoto Ukita,[1] **Ryota Matsuyama**,[1] **Norikazu Isoda**,[2] **Ryosuke Omori**,[3] **Takehisa Yamamoto**,[4] **and Kohei Makita**[1]

[1] *Veterinary Epidemiology Unit, Graduate School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyodai Midorimachi, Ebetsu 069-8501, Hokkaido, Japan*
[2] *Laboratory of Microbiology, Department of Disease Control, Faculty of Veterinary Medicine, Hokkaido University, Kita 18, Nishi 9, Kita-Ku, Sapporo 060-0818, Hokkaido, Japan*
[3] *Division of Bioinformatics, International Institute for Zoonosis Control, Hokkaido University, Kita 20 Nishi 10, Kita-Ku, Sapporo 001-0020, Hokkaido, Japan*
[4] *Epidemiology and Arbovirus Group, Division of Transboundary Animal Disease Research, National Institute of Animal Health, National Agriculture and Food Research Organization, 3-1-5 Kannondai, Tsukuba 305-0856, Ibaraki, Japan*

Correspondence should be addressed to Kohei Makita; kmakita@rakuno.ac.jp

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The outbreak of infectious diseases in swine, such as classical swine fever (CSF), has become a significant concern in the pig-farming industry. In Japan, after the re-emergence of CSF in 2018, farms are now exposed to the risk of transmission from infected wild boar and CSF-contaminated farms. This study aimed to identify biosecurity measures that were effective for the prevention of CSF introduction into farms during the period from the beginning of the CSF epidemic to the implementation of a vaccination campaign for domestic pigs at risk. The probability of virus introduction was assumed to be increased by the elevated risk from CSF-infected wild boar and infected farms around the farm. The risk from infected wild boar was represented by the prevalence of CSF in wild boar or the occupancy of 1-km grid cells with infected wild boar within 10-km radii from a pig farm and the occurrence of CSF outbreaks on neighboring farms. Conversely, the probability of virus introduction was assumed to decrease in response to on-farm biosecurity measures being implemented on each farm. The implementation of biosecurity measures on the farms and farm attributes were obtained through a questionnaire survey. Analyses were performed on each farm under the weekly situations where infected wild boar were both absent and present in the vicinity using a binomial generalized linear model. On farms where infected wild boar were not present around farms, daily washing and disinfecting of work clothing in pig houses was identified as the main measure to reduce the risk of CSF introduction into farms. On farms with infected wild boar in the vicinity, the absence of public roads on the farm and preventing wildlife intrusion into the areas where pig carcasses were stored were demonstrated to be effective in preventing CSF introduction. Based on the assumption that strict and comprehensive biosecurity measures are required to prevent CSF introduction, the implementation of these potentially effective measures is worth being prioritized.

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Ecological factors associated with fox feces density in an *Echinococcus multilocularis* endemic zone in Japan

Megumi Fukui[1], Kohji Uraguchi[2], Himika Numa[1], Toru Suzuki[3], Michiko Karasawa[1], Kaoruko Maita[1], Terumi Yokozawa[1], Yoko Hayama[4] and Kohei Makita[1]*

[1]Veterinary Epidemiology Unit, Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan, [2]Hokkaido Institute of Public Health, Sapporo, Hokkaido, Japan, [3]Department of Environmental and Symbiotic Sciences, College of Agriculture, Food and Environmental Sciences, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan, [4]Division of Transboundary Animal Disease Research, National Institute of Animal Health, National Agriculture and Food Research Organization, Tsukuba, Ibaraki, Japan

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EDITED BY
Sirikachorn Tangkawattana,
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Mughees Aizaz Alvi,
University of Agriculture, Faisalabad, Pakistan

*CORRESPONDENCE
Kohei Makita
✉ kmakita@rakuno.ac.jp

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Introduction: Human alveolar echinococcosis caused by *Echinococcus multilocularis* is an important zoonotic disease in the northern hemisphere. The life cycle of *E. multilocularis* is maintained primarily in wild animals and requires an intermediate host (mainly small mammals). Human can become an intermediate host through accidental ingestion of *E. multilocularis* eggs. Hokkaido Prefecture is the only area of Japan in which human alveolar echinococcosis is endemic. The purposes of this study were to elucidate the land use ecological factors associated with the density of red fox feces along paved roads and the relationship between the distributions of red fox (*Vulpes vulpes*) populations and fox feces, which determine the level of hazard from eggs.

Methods: A series of surveys was conducted in the central part of the Nemuro Peninsula of Hokkaido, excluding urban areas, over a total of 4 years in May–June in 2014 and 2016–2018 when red foxes remain with their cubs around the dens. Transects of 500 m were set up on paved roads, and feces within the transects were counted. Univariable and multivariable analyses were performed to examine ecological factors including the principal components (PCs) of five land use–type occupancy proportions within 500 m and 1 km, respectively, as explanatory fixed-effect variables. The number of feces in each transect was examined as the response variable using integrated nested Laplace approximation with negative binomial errors with a spatio-temporal autocorrelations structure to separate the effects of similarities of neighboring locations and annual variation. The multivariable models with the lowest widely applicable information criterion values were selected.

Results: The feces density was explained by the PC of the 500- m buffer (−0.27, 2.5th and 97.5th percentiles: −0.44, −0.10) characterized by mixed forests (−0.82) and scarcity of residential areas (0.29) and the proximity to the nearest livestock farm house (−0.35, 2.5th and 97.5th percentiles: −0.53, −0.17). This suggested that foxes defecate in the areas where prey is abundant, avoiding humans.

Discussion: Policy discussions regarding bait distribution design targeting these conditions should be initiated.

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最終責任者　Kohei Makita (Corresponding Author)

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ANIMAL BIOSCIENCE

Association of farmers' knowledge, attitude and practices with bovine brucellosis seroprevalence in Myanmar

Su Su Hlaing[1,a], Satoko Kubota[2], Kohei Makita[3], Ye Tun Win[4], Hnin Thidar Myint[4], and Hiroichi Kono[2,a,*]

*** Corresponding Author:** Hiroichi Kono
Tel: +81-90-7052-3012,
E-mail: kono@obihiro.ac.jp

[1] Graduate School of Animal and Veterinary Sciences and Agriculture, Obihiro University of Agriculture and Veterinary Medicine, Obihiro 080-8555, Japan
[2] Department of Agro-environmental Science, Obihiro University of Agriculture and Veterinary Medicine, Obihiro 080-8555, Japan
[3] Department of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyodai Midorimachi, Ebetsu 069-8501, Japan
[4] Ministry of Agriculture, Livestock and Irrigation, Livestock Breeding and Veterinary Department, ZabuThiri 15011, Myanmar

[a] These authors contributed equally to this work.

ORCID
Su Su Hlaing
https://orcid.org/0000-0001-6399-4143
Satoko Kubota
https://orcid.org/0000-0002-7428-8663
Kohei Makita
https://orcid.org/0000-0002-0181-0246
Ye Tun Win
https://orcid.org/0000-0002-6122-8952
Hnin Thidar Myint
https://orcid.org/0009-0005-4213-1759
Hiroichi Kono
https://orcid.org/0000-0002-5660-3148

Objective: This study aimed to identify the relationship between bovine brucellosis prevalence, farmers' knowledge, attitude, practice (KAP), and social factors on migratory draft cattle and smallholder dairy farms in the central dry zone of Myanmar.
Methods: This cross-sectional study was conducted on 54 migratory and 38 dairy cattle farms between August 2020 and February 2021. A structured questionnaire was used to identify farmers' behaviors. Bulk milk was sampled and tested using indirect enzyme-linked immunosorbent assay (I-ELISA). STATA 17 was used for all the analyses.
Results: Migratory cattle farms had a higher farm level brucellosis prevalence (14.8%) than dairy farms (2.6%; $\chi^2 = 3.75$; df = 1; p = 0.05). Only 2.8% of the farmers had knowledge about brucellosis, while 39.1% and 41.6% had attitudes and farm practices with respect to brucellosis, respectively in the study area. Socio-economic attribute of training in animal husbandry ($p<0.01$), raising system ($p<0.01$), practice of separating the aborted cow ($p<0.01$) were negatively associated to brucellosis. The overall farm level brucellosis prevalence was strongly associated with cattle herd size (p = 0.01), free movement grazing practices ($p<0.01$), practice of self-removal of placental debris without using personal protective equipment ($p<0.01$) and farmers' attitudes towards eating cow placenta debris ($p<0.01$).
Conclusion: Farmers had little knowledge of brucellosis. Attitudes and practices differed significantly between migratory and dairy farmers. Training and extension programs are necessary to make farmers aware of their KAP situation since livestock migration and the custom of eating cow placental debris contribute to the spread of brucellosis. Persistent efforts are required to reduce the adverse effects of brucellosis. Therefore, the study suggests that a feasible control intervention and public awareness campaigns need to be conducted regarding methods of preventing human exposure to brucellosis.

Keywords: Bovine Brucellosis, Knowledge, Attitude, Practice, Custom, Myanmar

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Tropical Medicine and Infectious Disease

MDPI

Article

Patterns of Animal Rabies Prevalence in Northern South Africa between 1998 and 2022

Kgaogelo Mogano [1,2,*], Claude Taurai Sabeta [3,4], Toru Suzuki [5], Kohei Makita [6] and George Johannes Chirima [1,2]

[1] Agricultural Research Council, GeoInformatics Division, Natural Resources and Engineering, 600 Belvedere St., Pretoria 0083, South Africa
[2] Department of Geography, Geoinformatics and Meteorology, University of Pretoria, Pretoria 0028, South Africa
[3] Veterinary Tropical Diseases Department, University of Pretoria, Pretoria 0110, South Africa
[4] World Organisation for Animal Health (WOAH) Rabies Reference Laboratory, Agricultural Research Council (Onderstepoort Veterinary Research), Onderstepoort, Pretoria 0110, South Africa
[5] Department of Environmental and Symbiotic Sciences, Rakuno Gakuen University, Ebetsu 069-8501, Japan
[6] Department of Veterinary Medicine, Rakuno Gakuen University, Ebetsu 069-8501, Japan
* Correspondence: kgaogelo111@gmail.com or moganon@arc.agric.za

Abstract: Rabies is endemic in South Africa and rabies cycles are maintained in both domestic and wildlife species. The significant number of canine rabies cases reported by the World Organization for Animal Health Reference Laboratory for Rabies at Onderstepoort suggests the need for increased research and mass dog vaccinations on specific targeted foci in the country. This study aimed to investigate the spatiotemporal distribution of animal rabies cases from 1998 to 2017 in northern South Africa and environmental factors associated with highly enzootic municipalities. A descriptive analysis was used to investigate temporal patterns. The Getis-Ord Gi statistical tool was used to exhibit low and high clusters. Logistic regression was used to examine the association between the predictor variables and highly enzootic municipalities. A total of 9580 specimens were submitted for rabies diagnosis between 1998 and 2022. The highest positive case rates were from companion animals (1733 cases, 59.71%), followed by livestock (635 cases, 21.88%) and wildlife (621 cases, 21.39%). Rabies cases were reported throughout the year, with the majority occurring in the mid-dry season. Hot spots were frequently in the northern and eastern parts of Limpopo and Mpumalanga. Thicket bush and grassland were associated with rabies between 1998 and 2002. However, between 2008 and 2012, cultivated commercial crops and waterbodies were associated with rabies occurrence. In the last period, plantations and woodlands were associated with animal rabies. Of the total number of municipalities, five consistently and repeatedly had the highest rabies prevalence rates. These findings suggest that authorities should prioritize resources for those municipalities for rabies elimination and management.

check for updates

Citation: Mogano, K.; Sabeta, C.T.; Suzuki, T.; Makita, K.; Chirima, G.J. Patterns of Animal Rabies Prevalence in Northern South Africa between 1998 and 2022. *Trop. Med. Infect. Dis.* **2024**, *9*, 27. https://doi.org/10.3390/tropicalmed9010027

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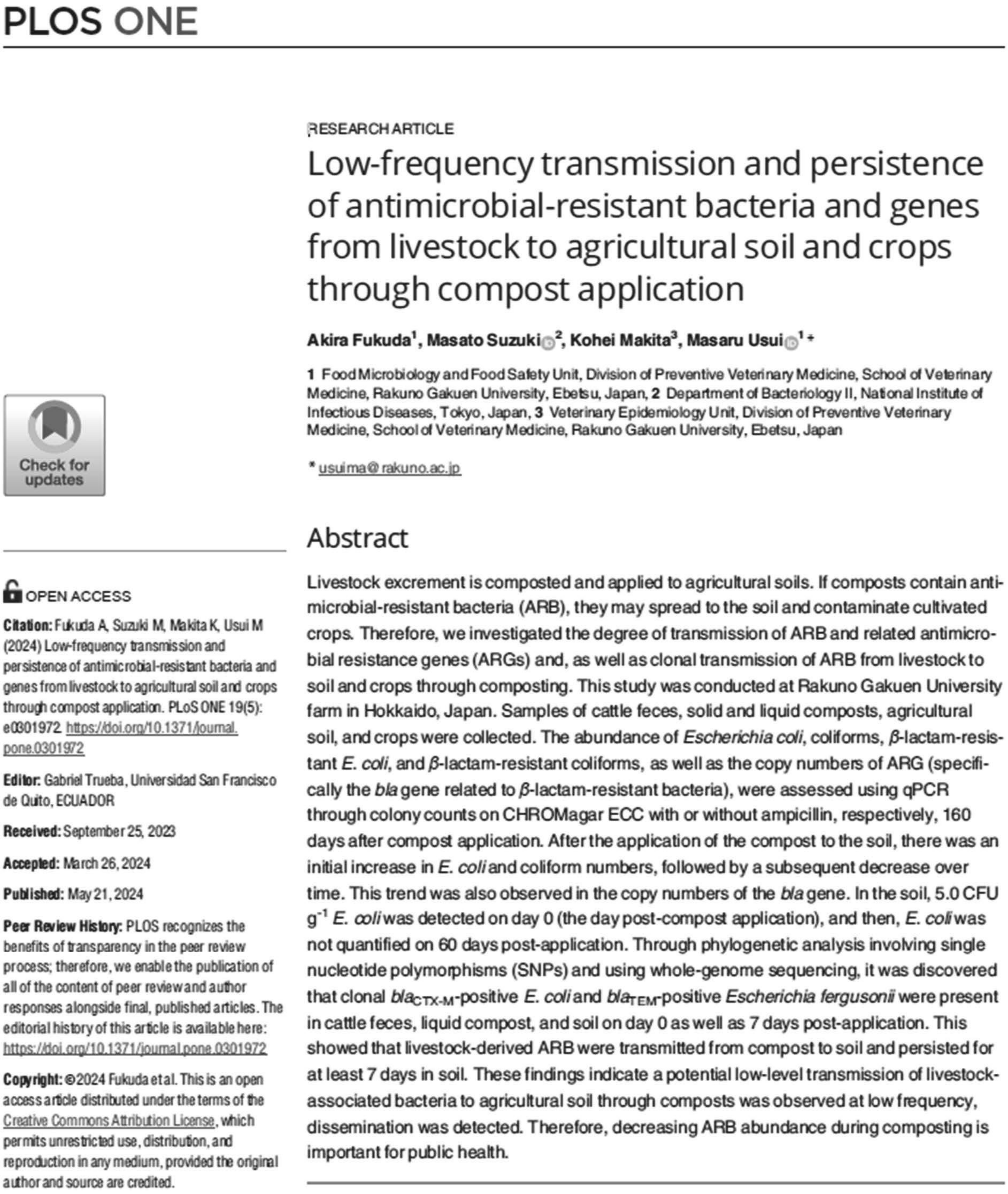
最終責任者　Kgaogelo Mogano (Corresponding Author)



PLOS ONE

RESEARCH ARTICLE

Low-frequency transmission and persistence of antimicrobial-resistant bacteria and genes from livestock to agricultural soil and crops through compost application

Akira Fukuda[1], **Masato Suzuki**[2], **Kohei Makita**[3], **Masaru Usui**[1]*

1 Food Microbiology and Food Safety Unit, Division of Preventive Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan, 2 Department of Bacteriology II, National Institute of Infectious Diseases, Tokyo, Japan, 3 Veterinary Epidemiology Unit, Division of Preventive Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan

* usuima@rakuno.ac.jp

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Abstract

Livestock excrement is composted and applied to agricultural soils. If composts contain antimicrobial-resistant bacteria (ARB), they may spread to the soil and contaminate cultivated crops. Therefore, we investigated the degree of transmission of ARB and related antimicrobial resistance genes (ARGs) and, as well as clonal transmission of ARB from livestock to soil and crops through composting. This study was conducted at Rakuno Gakuen University farm in Hokkaido, Japan. Samples of cattle feces, solid and liquid composts, agricultural soil, and crops were collected. The abundance of *Escherichia coli*, coliforms, β-lactam-resistant *E. coli*, and β-lactam-resistant coliforms, as well as the copy numbers of ARG (specifically the *bla* gene related to β-lactam-resistant bacteria), were assessed using qPCR through colony counts on CHROMagar ECC with or without ampicillin, respectively, 160 days after compost application. After the application of the compost to the soil, there was an initial increase in *E. coli* and coliform numbers, followed by a subsequent decrease over time. This trend was also observed in the copy numbers of the *bla* gene. In the soil, 5.0 CFU g^{-1} *E. coli* was detected on day 0 (the day post-compost application), and then, *E. coli* was not quantified on 60 days post-application. Through phylogenetic analysis involving single nucleotide polymorphisms (SNPs) and using whole-genome sequencing, it was discovered that clonal $bla_{\text{CTX-M}}$-positive *E. coli* and bla_{TEM}-positive *Escherichia fergusonii* were present in cattle feces, liquid compost, and soil on day 0 as well as 7 days post-application. This showed that livestock-derived ARB were transmitted from compost to soil and persisted for at least 7 days in soil. These findings indicate a potential low-level transmission of livestock-associated bacteria to agricultural soil through composts was observed at low frequency, dissemination was detected. Therefore, decreasing ARB abundance during composting is important for public health.

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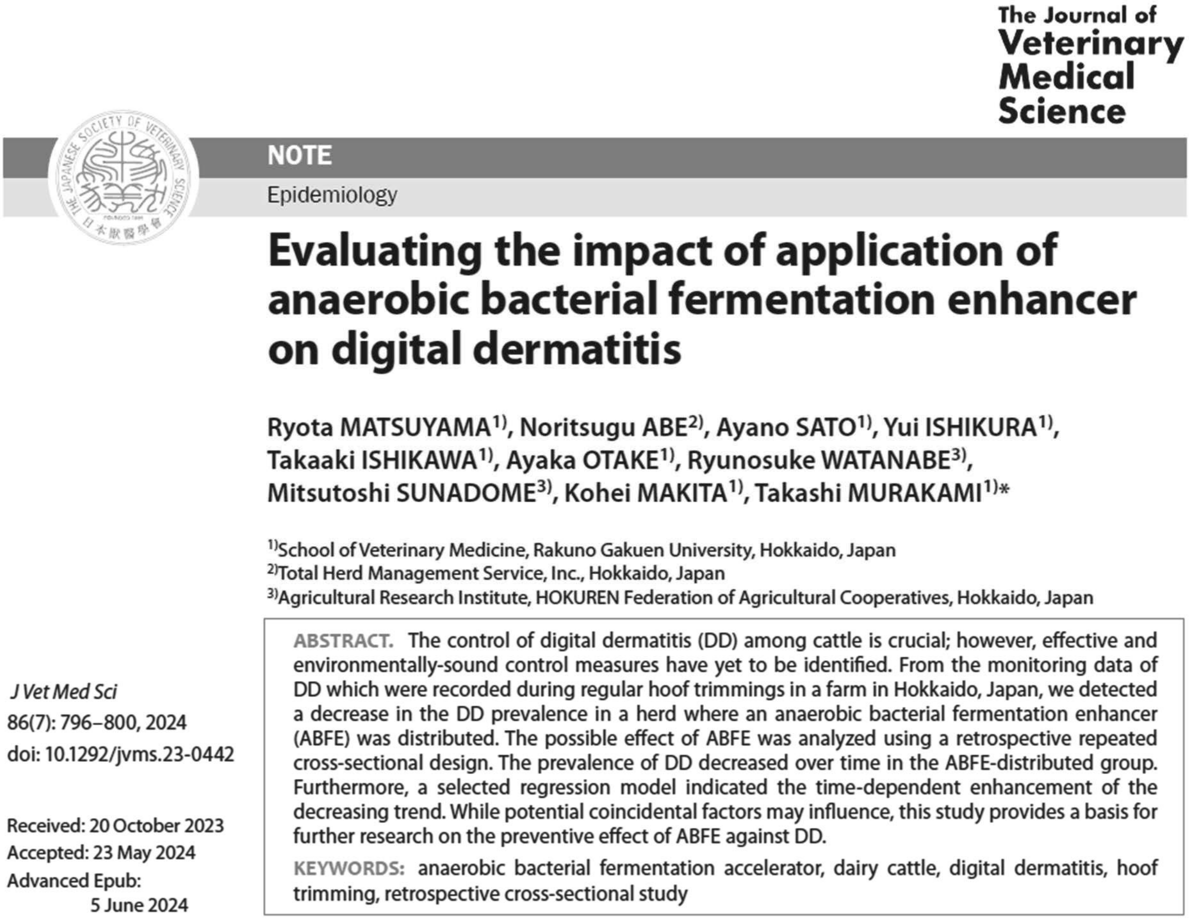
最終責任者　Masaru Usui (Corresponding Author)



The Journal of Veterinary Medical Science

NOTE

Epidemiology

Evaluating the impact of application of anaerobic bacterial fermentation enhancer on digital dermatitis

Ryota MATSUYAMA[1)], Noritsugu ABE[2)], Ayano SATO[1)], Yui ISHIKURA[1)], Takaaki ISHIKAWA[1)], Ayaka OTAKE[1)], Ryunosuke WATANABE[3)], Mitsutoshi SUNADOME[3)], Kohei MAKITA[1)], Takashi MURAKAMI[1)]*

[1)]School of Veterinary Medicine, Rakuno Gakuen University, Hokkaido, Japan
[2)]Total Herd Management Service, Inc., Hokkaido, Japan
[3)]Agricultural Research Institute, HOKUREN Federation of Agricultural Cooperatives, Hokkaido, Japan

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ABSTRACT. The control of digital dermatitis (DD) among cattle is crucial; however, effective and environmentally-sound control measures have yet to be identified. From the monitoring data of DD which were recorded during regular hoof trimmings in a farm in Hokkaido, Japan, we detected a decrease in the DD prevalence in a herd where an anaerobic bacterial fermentation enhancer (ABFE) was distributed. The possible effect of ABFE was analyzed using a retrospective repeated cross-sectional design. The prevalence of DD decreased over time in the ABFE-distributed group. Furthermore, a selected regression model indicated the time-dependent enhancement of the decreasing trend. While potential coincidental factors may influence, this study provides a basis for further research on the preventive effect of ABFE against DD.

KEYWORDS: anaerobic bacterial fermentation accelerator, dairy cattle, digital dermatitis, hoof trimming, retrospective cross-sectional study

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pathogens

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Article

Evaluation of Immune Status of Pigs against Classical Swine Fever for Three Years after the Initiation of Vaccination in Gifu Prefecture, Japan

Keisuke Kuwata [1], Naotoshi Kuninaga [1], Yoko Kimura [1], Kohei Makita [2], Norikazu Isoda [3,4,5,6], Yukio Shimizu [3] and Yoshihiro Sakoda [3,4,5,6,*]

[1] Gifu Central Livestock Hygiene Service Center, Gifu 501-1112, Japan
[2] Veterinary Epidemiology Unit, Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyodai Midori-machi, Ebetsu 069-8501, Japan; kmakita@rakuno.ac.jp
[3] Laboratory of Microbiology, Department of Disease Control, Faculty of Veterinary Medicine, Hokkaido University, Kita 18, Nishi 9, Kita-ku, Sapporo 060-0818, Japan; nisoda@vetmed.hokudai.ac.jp (N.I.)
[4] One Health Research Center, Hokkaido University, Sapporo 060-0818, Japan
[5] International Collaboration Unit, International Institute for Zoonosis Control, Hokkaido University, Kita 20, Nishi 10, Kita-ku, Sapporo 001-0020, Japan
[6] Hokkaido University Institute for Vaccine Research and Development (HU-IVReD), Hokkaido University, Sapporo 001-0021, Japan
* Correspondence: sakoda@vetmed.hokudai.ac.jp; Tel.: +81-11-706-5207

Abstract: In 2018, classical swine fever (CSF) reemerged in Gifu Prefecture, Japan, after 26 years of absence, and vaccination of domestic pigs using a live attenuated vaccine was initiated in 2019. Because the vaccine efficacy in piglets is influenced by the maternal antibody levels, vaccination should be administered at the optimal age by assuming the antibody level in sows. In this study, the shift in the antibody titer distribution in sows due to the initiation of vaccination to naïve herds and its influence on the vaccine-induced immunity rate in fattening pigs were investigated for 3 years. The results indicated that higher antibody titers were induced in first-generation sows after vaccine initiation because they were immunologically naïve, but the distribution of antibody titers shifted to lower levels along with their replacement with second-generation sows. The average vaccination age of fattening pigs became earlier year by year, and the vaccine-induced antibody rate was almost ≥80%. Based on the estimation of the optimal age for vaccination, it was found that vaccination at a younger age may reduce the risk of CSF infection. Taken together, the risk of CSF outbreaks can be reduced by administering vaccines at the optimal age based on the sequential monitoring of the sow's immune status.

Citation: Kuwata, K.; Kuninaga, N.; Kimura, Y.; Makita, K.; Isoda, N.; Shimizu, Y.; Sakoda, Y. Evaluation of Immune Status of Pigs against Classical Swine Fever for Three Years after the Initiation of Vaccination in Gifu Prefecture, Japan. *Pathogens* **2024**, *13*, 616. https://doi.org/10.3390

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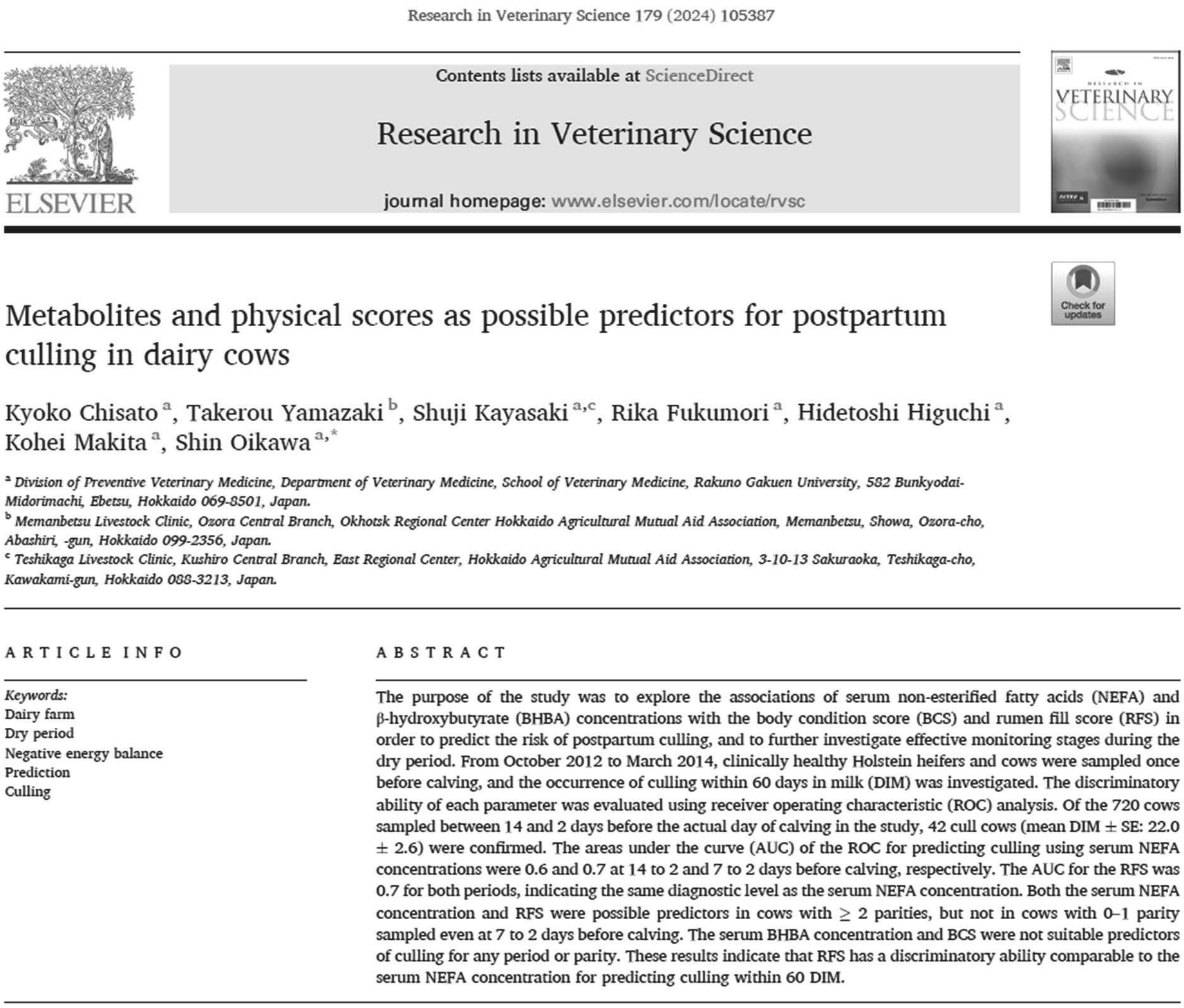

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Metabolites and physical scores as possible predictors for postpartum culling in dairy cows

Kyoko Chisato [a], Takerou Yamazaki [b], Shuji Kayasaki [a,c], Rika Fukumori [a], Hidetoshi Higuchi [a], Kohei Makita [a], Shin Oikawa [a,*]

[a] *Division of Preventive Veterinary Medicine, Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyodai-Midorimachi, Ebetsu, Hokkaido 069-8501, Japan.*
[b] *Memanbetsu Livestock Clinic, Ozora Central Branch, Okhotsk Regional Center Hokkaido Agricultural Mutual Aid Association, Memanbetsu, Showa, Ozora-cho, Abashiri, -gun, Hokkaido 099-2356, Japan.*
[c] *Teshikaga Livestock Clinic, Kushiro Central Branch, East Regional Center, Hokkaido Agricultural Mutual Aid Association, 3-10-13 Sakuraoka, Teshikaga-cho, Kawakami-gun, Hokkaido 088-3213, Japan.*

ARTICLE INFO

Keywords:
Dairy farm
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ABSTRACT

The purpose of the study was to explore the associations of serum non-esterified fatty acids (NEFA) and β-hydroxybutyrate (BHBA) concentrations with the body condition score (BCS) and rumen fill score (RFS) in order to predict the risk of postpartum culling, and to further investigate effective monitoring stages during the dry period. From October 2012 to March 2014, clinically healthy Holstein heifers and cows were sampled once before calving, and the occurrence of culling within 60 days in milk (DIM) was investigated. The discriminatory ability of each parameter was evaluated using receiver operating characteristic (ROC) analysis. Of the 720 cows sampled between 14 and 2 days before the actual day of calving in the study, 42 cull cows (mean DIM ± SE: 22.0 ± 2.6) were confirmed. The areas under the curve (AUC) of the ROC for predicting culling using serum NEFA concentrations were 0.6 and 0.7 at 14 to 2 and 7 to 2 days before calving, respectively. The AUC for the RFS was 0.7 for both periods, indicating the same diagnostic level as the serum NEFA concentration. Both the serum NEFA concentration and RFS were possible predictors in cows with ≥ 2 parities, but not in cows with 0–1 parity sampled even at 7 to 2 days before calving. The serum BHBA concentration and BCS were not suitable predictors of culling for any period or parity. These results indicate that RFS has a discriminatory ability comparable to the serum NEFA concentration for predicting culling within 60 DIM.

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最終責任者　Shin Oikawa (Corresponding Author)

獣医病理学（Veterinary Pathology）

Kazuya Matsuda

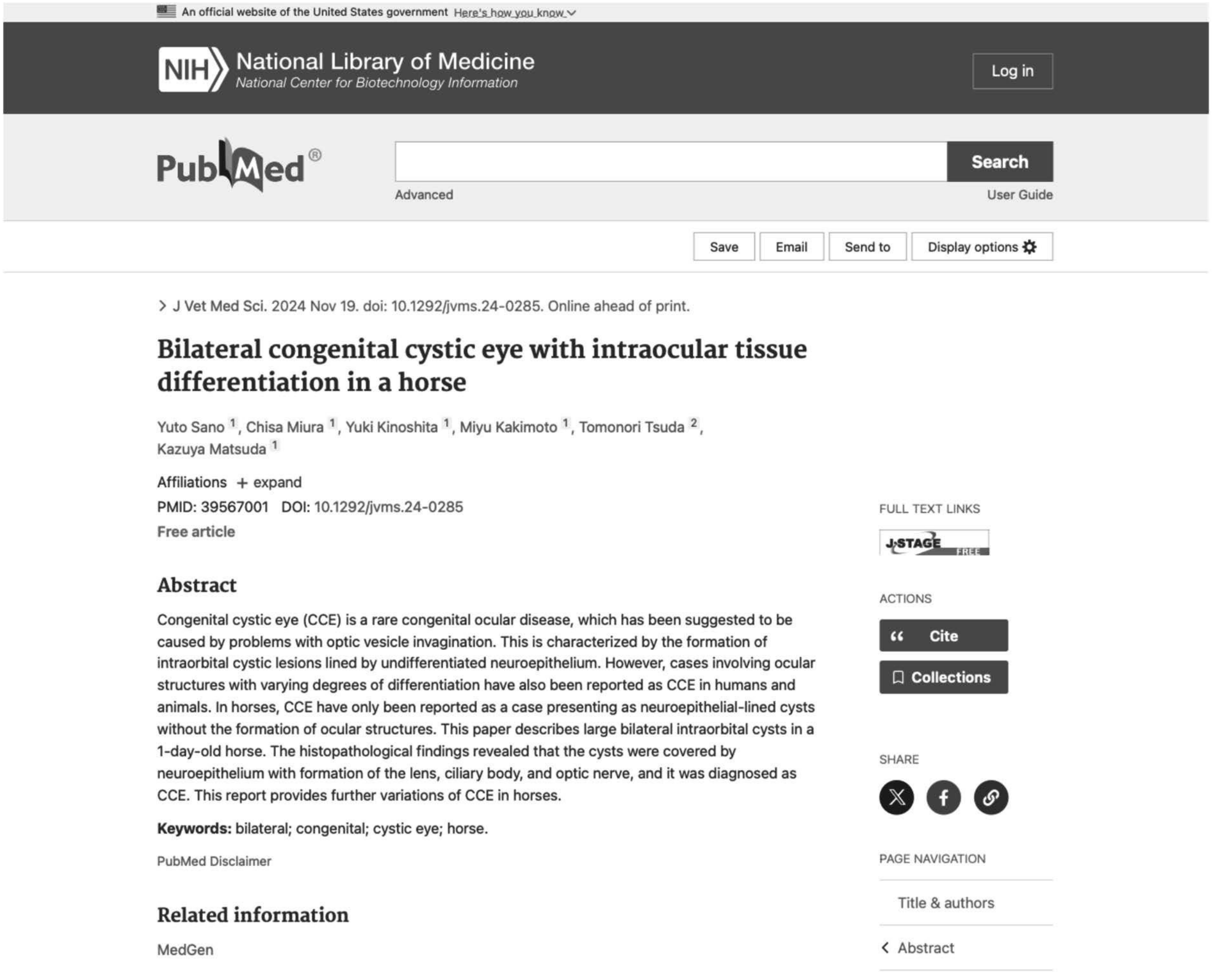
Professor

教授　松田　一哉

I. 筆頭または責任著者　＜First or Corresponding Author＞

II. その他　＜Others＞

1) Bilateral congenital cystic eye with intraocular tissue differentiation in a horse.
Sano Y, Miura C, Kinoshita Y, Kakimoto M, Tsuda T, **Matsuda K**.
J Vet Med Sci 86: *in press*. 2024. doi: 10.1292/jvms.24-0285. Online ahead of print.



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Bilateral congenital cystic eye with intraocular tissue differentiation in a horse

Yuto Sano [1], Chisa Miura [1], Yuki Kinoshita [1], Miyu Kakimoto [1], Tomonori Tsuda [2], Kazuya Matsuda [1]

Affiliations + expand

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Free article

Abstract

Congenital cystic eye (CCE) is a rare congenital ocular disease, which has been suggested to be caused by problems with optic vesicle invagination. This is characterized by the formation of intraorbital cystic lesions lined by undifferentiated neuroepithelium. However, cases involving ocular structures with varying degrees of differentiation have also been reported as CCE in humans and animals. In horses, CCE have only been reported as a case presenting as neuroepithelial-lined cysts without the formation of ocular structures. This paper describes large bilateral intraorbital cysts in a 1-day-old horse. The histopathological findings revealed that the cysts were covered by neuroepithelium with formation of the lens, ciliary body, and optic nerve, and it was diagnosed as CCE. This report provides further variations of CCE in horses.

Keywords: bilateral; congenital; cystic eye; horse.

PubMed Disclaimer

Related information

MedGen

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責任著者　Yuto Sano (First Author/Corresponding Author)

動物生殖学（Theriogenology）

Ken Nakada

Professor

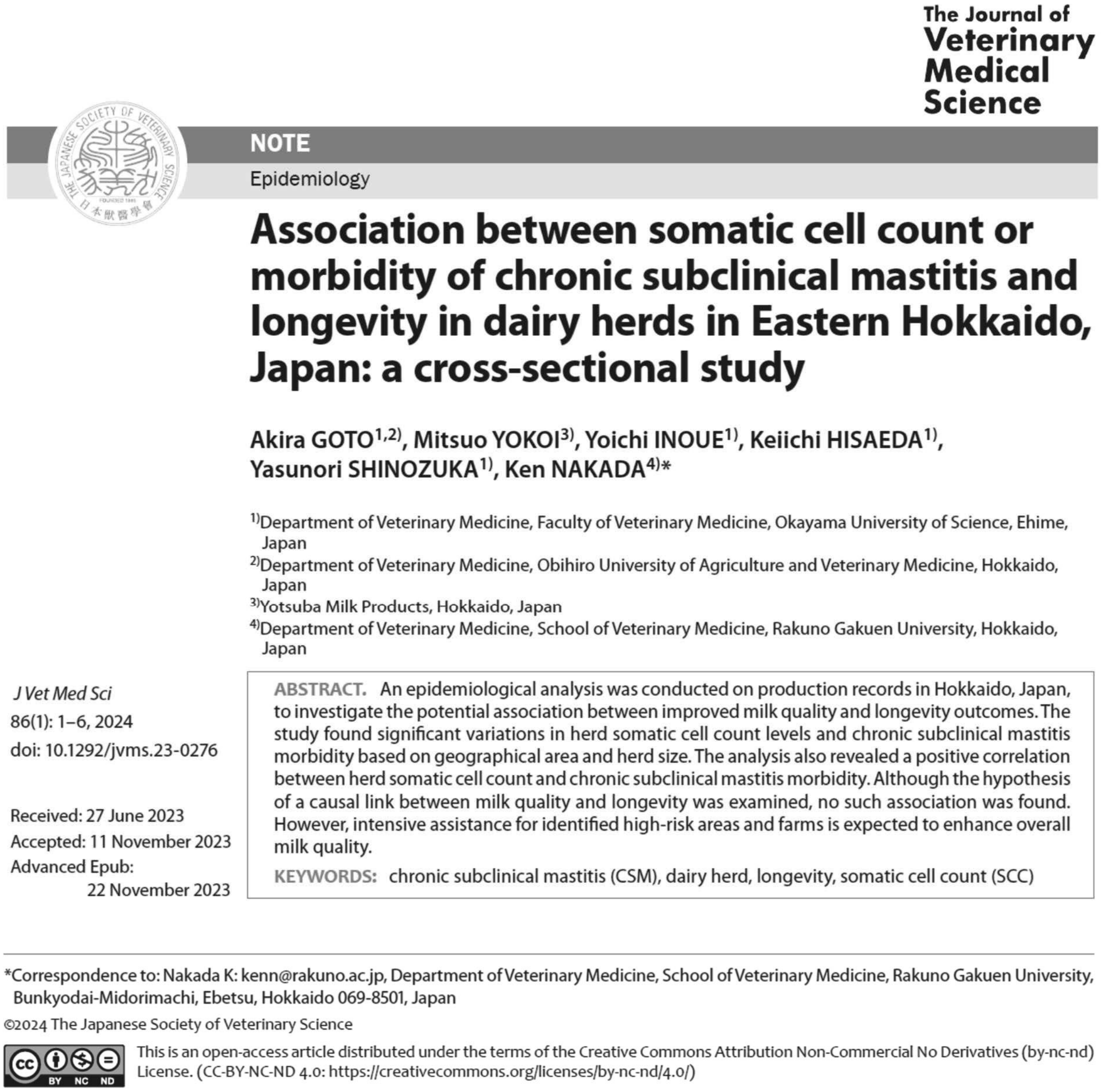
教授　中田　健

I. 筆頭または責任著者　＜First or Corresponding Author＞

1）Association between somatic cell count or morbidity of chronic subclinical mastitis and longevity in dairy herds in Eastern Hokkaido, Japan: a cross-sectional study.
Goto A, Yokoi M, Inoue Y, Hisaeda K. Shinozuka Y, **Nakada K.** 2024.
J Vet Med Sci 86:1–6. 2024. https://doi.org/10.1292/jvms.23-0276

II. **その他**＜Others＞

1）Changes in mammary infection status in dairy cows during the dry period using dry cow therapy approaches on three farms.
Nagahata H, Komori N, Fukutome M, Sugiura T, Hisaeda K, Gondaira S, Higuchi H, Ando T, **Nakada K.**
Anim Sci J 95:e13993. 2024. https://doi.org/10.1111/asj.13993



The Journal of
Veterinary
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Science

NOTE
Epidemiology

Association between somatic cell count or morbidity of chronic subclinical mastitis and longevity in dairy herds in Eastern Hokkaido, Japan: a cross-sectional study

Akira GOTO[1,2], Mitsuo YOKOI[3], Yoichi INOUE[1], Keiichi HISAEDA[1], Yasunori SHINOZUKA[1], Ken NAKADA[4]*

[1]Department of Veterinary Medicine, Faculty of Veterinary Medicine, Okayama University of Science, Ehime, Japan
[2]Department of Veterinary Medicine, Obihiro University of Agriculture and Veterinary Medicine, Hokkaido, Japan
[3]Yotsuba Milk Products, Hokkaido, Japan
[4]Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Hokkaido, Japan

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ABSTRACT. An epidemiological analysis was conducted on production records in Hokkaido, Japan, to investigate the potential association between improved milk quality and longevity outcomes. The study found significant variations in herd somatic cell count levels and chronic subclinical mastitis morbidity based on geographical area and herd size. The analysis also revealed a positive correlation between herd somatic cell count and chronic subclinical mastitis morbidity. Although the hypothesis of a causal link between milk quality and longevity was examined, no such association was found. However, intensive assistance for identified high-risk areas and farms is expected to enhance overall milk quality.

KEYWORDS: chronic subclinical mastitis (CSM), dairy herd, longevity, somatic cell count (SCC)

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*Correspondence to: Nakada K: kenn@rakuno.ac.jp, Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Bunkyodai-Midorimachi, Ebetsu, Hokkaido 069-8501, Japan

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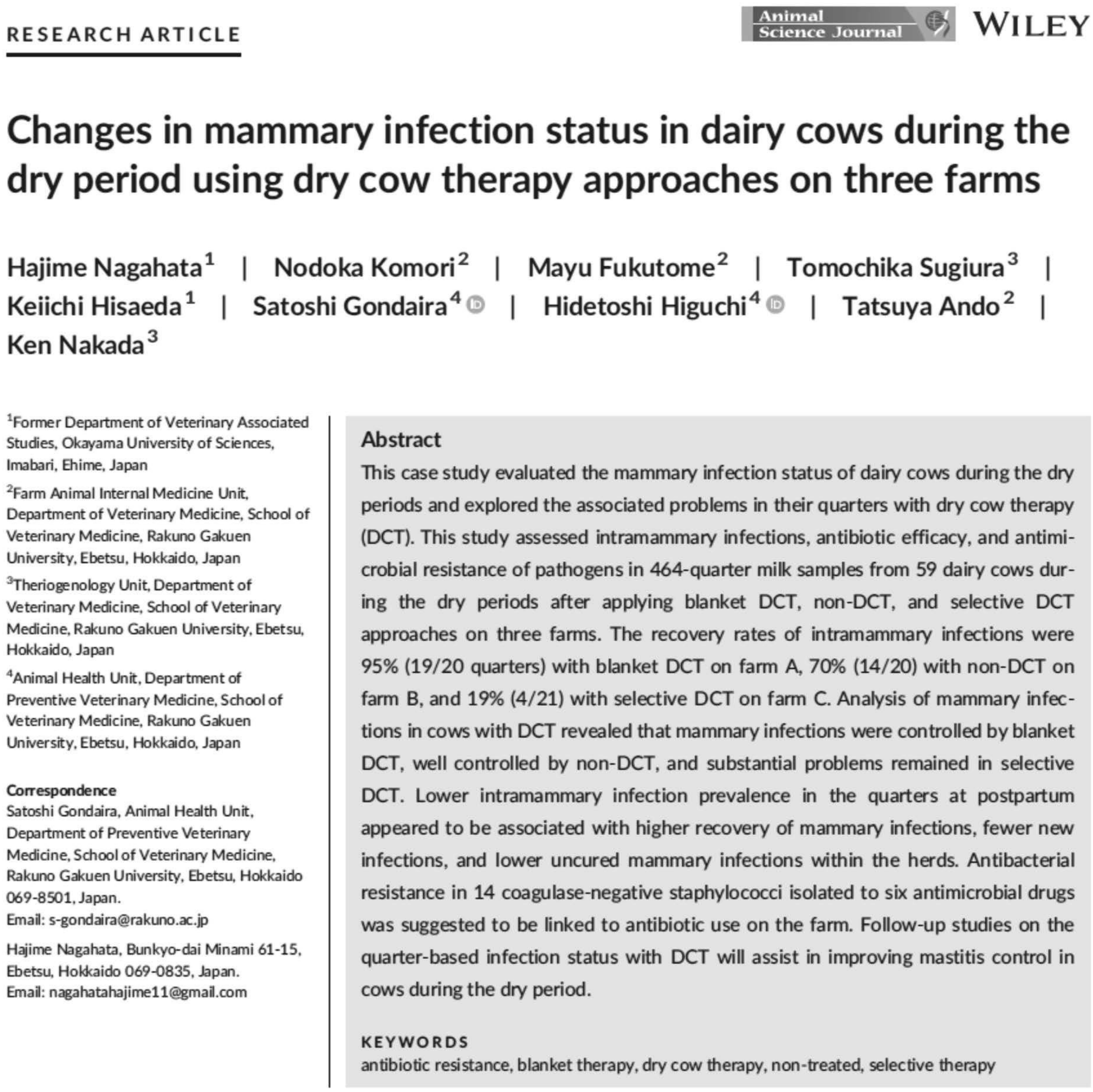

RESEARCH ARTICLE

Animal Science Journal WILEY

Changes in mammary infection status in dairy cows during the dry period using dry cow therapy approaches on three farms

Hajime Nagahata[1] | Nodoka Komori[2] | Mayu Fukutome[2] | Tomochika Sugiura[3] | Keiichi Hisaeda[1] | Satoshi Gondaira[4] | Hidetoshi Higuchi[4] | Tatsuya Ando[2] | Ken Nakada[3]

[1]Former Department of Veterinary Associated Studies, Okayama University of Sciences, Imabari, Ehime, Japan

[2]Farm Animal Internal Medicine Unit, Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

[3]Theriogenology Unit, Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

[4]Animal Health Unit, Department of Preventive Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

Correspondence
Satoshi Gondaira, Animal Health Unit, Department of Preventive Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan.
Email: s-gondaira@rakuno.ac.jp

Hajime Nagahata, Bunkyo-dai Minami 61-15, Ebetsu, Hokkaido 069-0835, Japan.
Email: nagahatahajime11@gmail.com

Abstract

This case study evaluated the mammary infection status of dairy cows during the dry periods and explored the associated problems in their quarters with dry cow therapy (DCT). This study assessed intramammary infections, antibiotic efficacy, and antimicrobial resistance of pathogens in 464-quarter milk samples from 59 dairy cows during the dry periods after applying blanket DCT, non-DCT, and selective DCT approaches on three farms. The recovery rates of intramammary infections were 95% (19/20 quarters) with blanket DCT on farm A, 70% (14/20) with non-DCT on farm B, and 19% (4/21) with selective DCT on farm C. Analysis of mammary infections in cows with DCT revealed that mammary infections were controlled by blanket DCT, well controlled by non-DCT, and substantial problems remained in selective DCT. Lower intramammary infection prevalence in the quarters at postpartum appeared to be associated with higher recovery of mammary infections, fewer new infections, and lower uncured mammary infections within the herds. Antibacterial resistance in 14 coagulase-negative staphylococci isolated to six antimicrobial drugs was suggested to be linked to antibiotic use on the farm. Follow-up studies on the quarter-based infection status with DCT will assist in improving mastitis control in cows during the dry period.

KEYWORDS
antibiotic resistance, blanket therapy, dry cow therapy, non-treated, selective therapy

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最終責任者　Satoshi Gondaira and Hajime Nagahata (Corresponding Authors)

Shin Oikawa

Professor

教授　及川　伸

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1) Epidemiological features of postpartum subclinical ketosis in dairy herds in Hokkaido, Japan.
Chisato K, Yamazaki T, Kayasaki S, Fukumori R, **Oikawa S**.
Animals 14:1–14. 2024. doi: 10.3390/ani14010144
2) Comparison of serum very low-density lipoprotein concentrations during transition in primiparous and multiparous cows.
Osada S, Chisato K, Fukumori R, **Oikawa S**.
J Vet Med Sci 86:358–362. 2024. doi: 10.1292/jvms.23-0454.
3) Characteristics of failure of passive transfer at the herd level using the serum immunoglobulin G concentration as an indicator on dairy farms in eastern Hokkaido, Japan.
Kayasaki S, Satoh H, Oguchi K, Chisato K, Fukumori R, Higuchi H, Suzuki K, **Oikawa S.**
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4) Metabolites and physical scores as possible predictors for postpartum culling in dairy cows.
Chisato K, Yamazaki T, Kayasaki S, Fukumori R, Higuchi H, Makita K, **Oikawa S**.
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5) Effects of amount of lactose in milk replacer on gastrointestinal function of dairy calves.
Fukumori R, Nakayama T, Hirose M, Norimura I, Izumi K, Shimada K, Mineo H, Steele M.A, Gondaira S, Higuchi H, Watanabe T, Ueda H, Sano T, Chisato K, **Oikawa S**.
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6) Lipoprotein composition of calves before and after weaning and comparison with adult cows.
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7) Effects of starch content of calf starter on rumen properties and blood concentrations of metabolites and hormones in dairy calves under a high plane of milk replacer feeding.
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Animals 14:3640. 2024. doi: 10.3390/ani14243640.

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JDS Communications 5:719–724. 2024. doi: 10.3168/jdsc.2023-0528.

animals

Article

Epidemiological Features of Postpartum Subclinical Ketosis in Dairy Herds in Hokkaido, Japan

Kyoko Chisato [1], Takerou Yamazaki [2], Shuji Kayasaki [3], Rika Fukumori [1] and Shin Oikawa [1,*]

[1] Veterinary Herd Health, Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyodai-Midorimachi, Ebetsu, Hokkaido 069-8501, Japan; k-chisato@rakuno.ac.jp (K.C.); fukumori@rakuno.ac.jp (R.F.)

[2] Memanbetsu Livestock Clinic, Ozora Central Branch, Okhotsk Regional Center, Hokkaido Agricultural Mutual Aid Association, 149-10 Memanbetsu Syouwa, Ozora-cho, Abashiri-gun, Hokkaido 099-2356, Japan; takerou_yamazaki_gb@nosai-do.or.jp

[3] Teshikaga Livestock Clinic, Kushiro Central Branch, East Regional Center, Hokkaido Agricultural Mutual Aid Association, 3-10-13 Sakuraoka, Teshikaga-cho, Kawakami-gun, Hokkaido 088-3213, Japan; s22041006@stu.rakuno.ac.jp

* Correspondence: oishin@rakuno.ac.jp; Tel.: +81-11-388-4825

Simple Summary: The aim of this study was to investigate the prevalence of subclinical ketosis (SCK) in Hokkaido, Japan, and to assess its characteristics epidemiologically at the individual and herd levels. Blood samples were taken from clinically healthy cows once within 3–88 days in milk (DIM) for blood tests. Cows with SCK were classified as SCK II within 2 weeks postpartum and SCK I from 15 DIM. The prevalence of SCK II (20.2%) tended to be higher than that of SCK I (16.5%, $p = 0.094$). The prevalence peaked around 2 weeks postpartum. The frequency of SCK I was higher at the fourth parity. The number of milking cows in herds with higher SCK ($\geq$25%) was significantly smaller than in herds with lower SCK ($p = 0.004$). The frequency of herds with higher SCK in tie stalls with component feeding was higher than for those in free stalls and free barns fed a total mixed ration ($p = 0.054$ and $p = 0.002$). This study reveals the prevalence of SCK in Hokkaido, Japan, and shows that SCK is associated with parity and the management system.

Abstract: This study was carried out as an observational study in order to determine the prevalence of postpartum subclinical ketosis (SCK) in dairy herds in Hokkaido, Japan. From April 2012 to March 2014, blood β-hydroxybutyrate (BHBA) concentration was measured once within 3–88 days in milk (DIM) in 1394 apparently healthy cows from 108 farms to diagnose SCK ($\geq$1.2 mM). In cows within 14 DIM, this was classified as SCK II, and from 15 DIM, this was classified as SCK I. Herds with a combined percentage of SCK I and SCK II of less than 10% were classified as SCK-negative herds, those with percentages of 10–25%, were classified as alert herds, and those with one of 25% or more, we classified as positive herds. The prevalence of SCK in the entire DIM was 17.6%. The prevalence of SCK II (20.2%) tended to occur more frequently than SCK I (16.5%, $p = 0.094$). The frequency of SCK I was higher at the fourth parity. The number of milking cows in SCK-positive herds was significantly smaller than those of the other two types of herds ($p = 0.004$). The frequency of SCK-positive herds in tie stalls and with component feeding was higher than for free stall or free barn and with total mixed ration ($p = 0.054$ and $p = 0.002$). This study reveals the prevalence of SCK in Hokkaido, Japan, and shows that SCK is associated with parity and the management system.

Keywords: dairy cow; subclinical ketosis; prevalence; risk factor; postpartum

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1. Introduction

The three weeks before and after calving are called the "transition period" [1,2], during which dramatic changes occur in the cows. This means that the fetus grows significantly in the three weeks before calving, and after calving, more energy is required for milk synthesis.

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The Journal of
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FULL PAPER

Internal Medicine

Comparison of serum very low-density lipoprotein concentrations during transition in primiparous and multiparous cows

Shinya OSADA[1], **Kyoko CHISATO**[1], **Rika FUKUMORI**[1], **Shin OIKAWA**[1]*

[1]Department of Veterinary Herd Health, School of Veterinary Medicine, Rakuno Gakuen University, Hokkaido, Japan

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ABSTRACT. This study was carried out as an observational study in order to examine the difference of change in serum very low-density lipoprotein (VLDL) between primiparous and multiparous cows. Twenty-one clinically healthy cows (10 primiparous and 11 multiparous) were selected at 21 days prior to expected calving. Blood samples were collected in the morning (before feeding) on days −21, −7, 7, 21 and 56 days in milk (DIM). At 7 and 21 DIM, the serum non-esterified fatty acid concentration of multiparous cows was significantly higher than that of primiparous cows. The serum β-hydroxybutyrate concentration was also markedly higher in multiparous cows than in primiparous cows at 21 DIM. These results suggested that the degree of negative energy balance was greater in multiparous cows than in primiparous cows during this period. In both, serum VLDL concentrations decreased at over 7 DIM, increased at 21 DIM, and then decreased at 56 DIM. On the other hand, triglyceride and total protein concentrations of VLDL in multiparous cows were significantly lower than in primiparous cows at 21 DIM. This suggests that multiparous cows have poor triglyceride secretion from the liver and that they become more susceptible to hepatic lipidosis.

KEYWORDS: cattle, parity, transition, very low-density lipoprotein (VLDL)

In dairy cows, the transition period before and after calving is a time when the outbreak of periparturient diseases is concentrated due to significant physiological changes associated with the drastic growth of the fetus, the preparation for calving and the start of lactation. Hepatic lipidosis is often induced prepartum and is known as the underlying pathogenesis or facilitator of typical perinatal diseases such as abomasum displacement, ketosis, milk fever, and retained placenta [14–16], key factors of death and culling from a dairy herd.

The main cause of hepatic lipidosis before parturition is a negative energy balance (NEB) due to various stresses or/and failures from the feeding environment and a resultant increase in non-esterified fatty acids (NEFA) in the blood [2, 11]. In reaction to NEB, body fat is mobilized to supplement energy production [16]. Briefly, triglyceride (TG) stored in adipose tissue is decomposed by hormone-sensitive lipase, and NEFA in blood increases. Upon entering the liver, NEFA is metabolized by two pathways. The first is the pathway that produces ATP through β-oxidation to acetyl CoA, which then enters the TCA cycle. However, when the degree of NEB is high in this pathway glucose is greatly depleted, making it difficult for the acetyl CoA produced to be incorporated into the TCA cycle, resulting in increased production of ketone bodies [9]. The second is the pathway where NEFA mobilized into the liver is re-esterified to become TG, which combines with apoproteins and lipid components to form very low-density lipoproteins (VLDL) that are supplied to extrahepatic tissues as an energy source [1, 3]. However, it is known that in dairy cattle, when a large amount of NEFA flows into the liver, VLDL assembly is not in time and, as a result, TG accumulation progresses to hepatic lipidosis [6, 8, 20]. Briefly, fatty liver is induced by an increase in blood NEFA concentrations associated with mobilization of body fat before and after parturition, an increase in lipid mobilization to the liver, and insufficient secretion of VLDLs, including TGs from the liver.

Perinatal disease is known to occur more often in multiparous cows than in primiparous cows [21], which may reflect differences in lipid metabolism. A previous study reported lower TG content in the postpartum liver in primiparous cows than in multiparous cows [22]. Oikawa *et al*. also reported that there was a positive correlation between blood VLDL and NEFA with TG in nulli/primiparous cows, but not in multiparous cows [17]. From these studies, it is speculated that primiparous cows are less likely to accumulate NEFA mobilized into the liver as TG than multiparous cows. In other words, it is possible that cows with perinatal disease have abnormal lipid metabolism and develop hepatic lipidosis before calving. An increased NEFA concentration during the dry period has been shown to be a risk factor for inducing diseases [19]. It is thought that comparing serum NEFA and VLDL in primiparous and multiparous

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*Correspondence to: Oikawa S: oishin@rakuno.ac.jp, Department of Veterinary Herd Health, School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyodai-Midorimachi, Ebetsu, Hokkaido 069-8501, Japan

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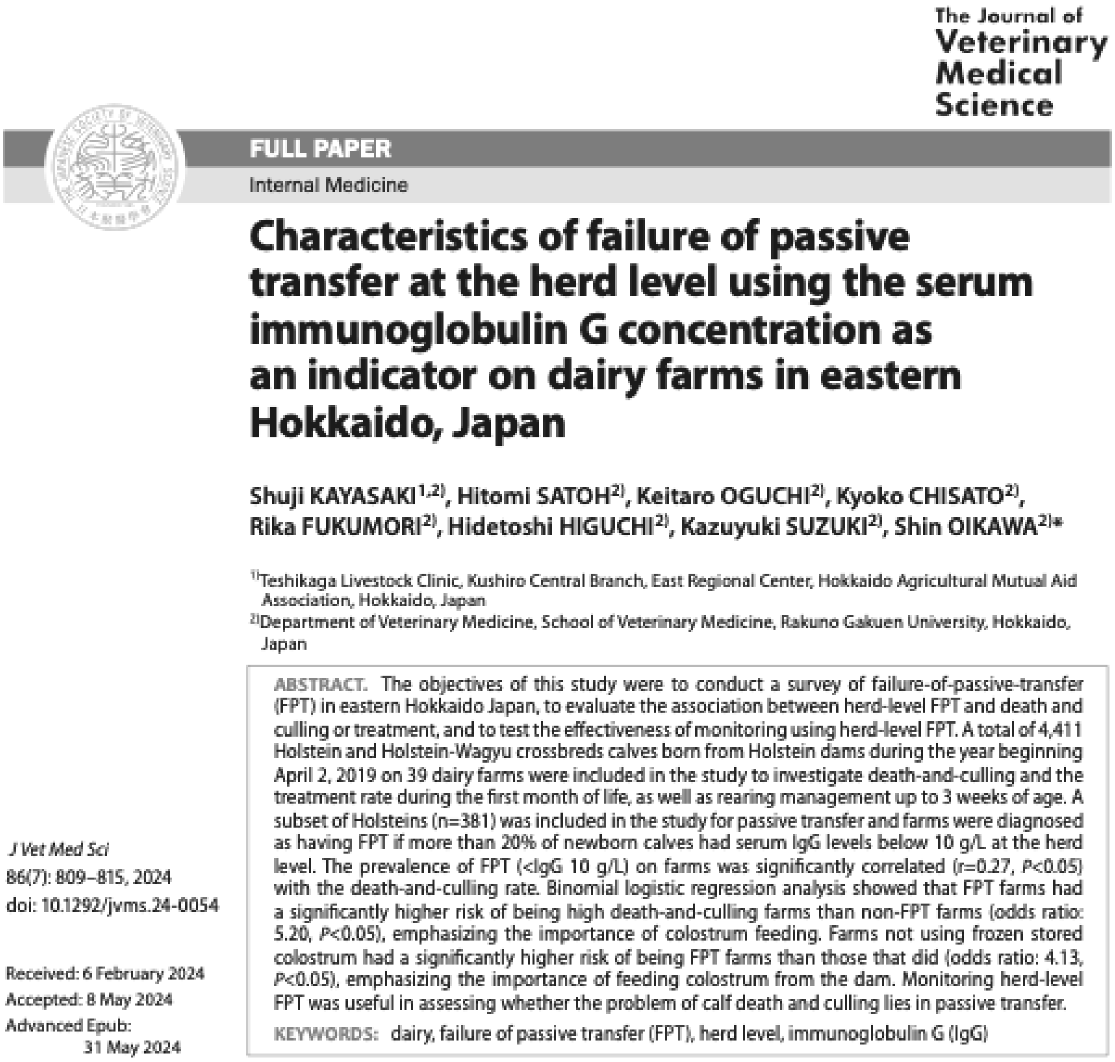
最終責任者　Shin Oikawa (Corresponding Author)



The Journal of Veterinary Medical Science

FULL PAPER

Internal Medicine

Characteristics of failure of passive transfer at the herd level using the serum immunoglobulin G concentration as an indicator on dairy farms in eastern Hokkaido, Japan

Shuji KAYASAKI[1,2], Hitomi SATOH[2], Keitaro OGUCHI[2], Kyoko CHISATO[2], Rika FUKUMORI[2], Hidetoshi HIGUCHI[2], Kazuyuki SUZUKI[2], Shin OIKAWA[2]*

[1]Teshikaga Livestock Clinic, Kushiro Central Branch, East Regional Center, Hokkaido Agricultural Mutual Aid Association, Hokkaido, Japan

[2]Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Hokkaido, Japan

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ABSTRACT. The objectives of this study were to conduct a survey of failure-of-passive-transfer (FPT) in eastern Hokkaido Japan, to evaluate the association between herd-level FPT and death and culling or treatment, and to test the effectiveness of monitoring using herd-level FPT. A total of 4,411 Holstein and Holstein-Wagyu crossbreds calves born from Holstein dams during the year beginning April 2, 2019 on 39 dairy farms were included in the study to investigate death-and-culling and the treatment rate during the first month of life, as well as rearing management up to 3 weeks of age. A subset of Holsteins ($n=381$) was included in the study for passive transfer and farms were diagnosed as having FPT if more than 20% of newborn calves had serum IgG levels below 10 g/L at the herd level. The prevalence of FPT (<IgG 10 g/L) on farms was significantly correlated ($r=0.27$, $P<0.05$) with the death-and-culling rate. Binomial logistic regression analysis showed that FPT farms had a significantly higher risk of being high death-and-culling farms than non-FPT farms (odds ratio: 5.20, $P<0.05$), emphasizing the importance of colostrum feeding. Farms not using frozen stored colostrum had a significantly higher risk of being FPT farms than those that did (odds ratio: 4.13, $P<0.05$), emphasizing the importance of feeding colostrum from the dam. Monitoring herd-level FPT was useful in assessing whether the problem of calf death and culling lies in passive transfer.

KEYWORDS: dairy, failure of passive transfer (FPT), herd level, immunoglobulin G (IgG)

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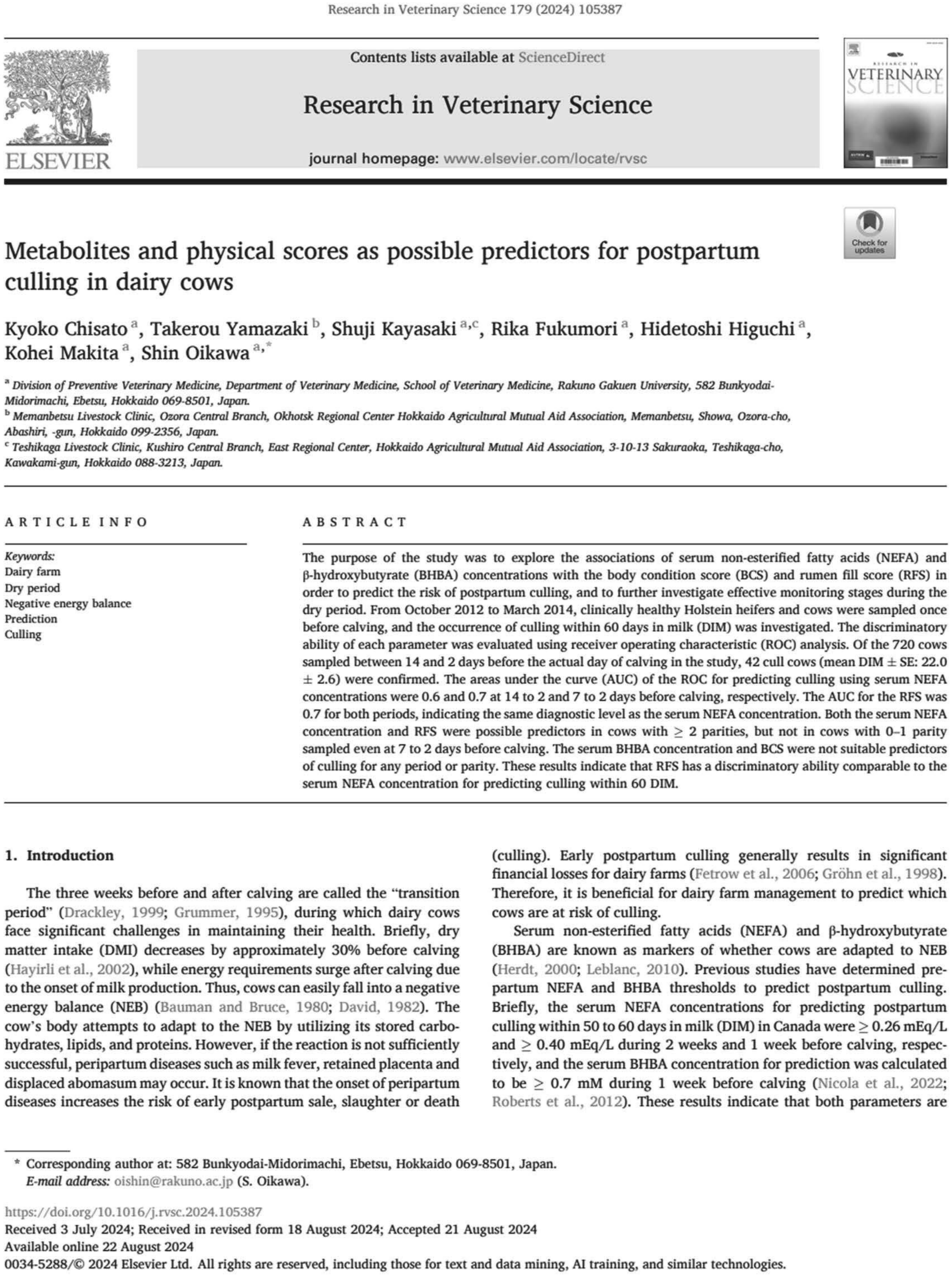

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Metabolites and physical scores as possible predictors for postpartum culling in dairy cows

Kyoko Chisato [a], Takerou Yamazaki [b], Shuji Kayasaki [a,c], Rika Fukumori [a], Hidetoshi Higuchi [a], Kohei Makita [a], Shin Oikawa [a,*]

[a] *Division of Preventive Veterinary Medicine, Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyodai-Midorimachi, Ebetsu, Hokkaido 069-8501, Japan.*

[b] *Memanbetsu Livestock Clinic, Ozora Central Branch, Okhotsk Regional Center Hokkaido Agricultural Mutual Aid Association, Memanbetsu, Showa, Ozora-cho, Abashiri, -gun, Hokkaido 099-2356, Japan.*

[c] *Teshikaga Livestock Clinic, Kushiro Central Branch, East Regional Center, Hokkaido Agricultural Mutual Aid Association, 3-10-13 Sakuraoka, Teshikaga-cho, Kawakami-gun, Hokkaido 088-3213, Japan.*

ARTICLE INFO

Keywords:
Dairy farm
Dry period
Negative energy balance
Prediction
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ABSTRACT

The purpose of the study was to explore the associations of serum non-esterified fatty acids (NEFA) and β-hydroxybutyrate (BHBA) concentrations with the body condition score (BCS) and rumen fill score (RFS) in order to predict the risk of postpartum culling, and to further investigate effective monitoring stages during the dry period. From October 2012 to March 2014, clinically healthy Holstein heifers and cows were sampled once before calving, and the occurrence of culling within 60 days in milk (DIM) was investigated. The discriminatory ability of each parameter was evaluated using receiver operating characteristic (ROC) analysis. Of the 720 cows sampled between 14 and 2 days before the actual day of calving in the study, 42 cull cows (mean DIM ± SE: 22.0 ± 2.6) were confirmed. The areas under the curve (AUC) of the ROC for predicting culling using serum NEFA concentrations were 0.6 and 0.7 at 14 to 2 and 7 to 2 days before calving, respectively. The AUC for the RFS was 0.7 for both periods, indicating the same diagnostic level as the serum NEFA concentration. Both the serum NEFA concentration and RFS were possible predictors in cows with ≥ 2 parities, but not in cows with 0–1 parity sampled even at 7 to 2 days before calving. The serum BHBA concentration and BCS were not suitable predictors of culling for any period or parity. These results indicate that RFS has a discriminatory ability comparable to the serum NEFA concentration for predicting culling within 60 DIM.

1. Introduction

The three weeks before and after calving are called the "transition period" (Drackley, 1999; Grummer, 1995), during which dairy cows face significant challenges in maintaining their health. Briefly, dry matter intake (DMI) decreases by approximately 30% before calving (Hayirli et al., 2002), while energy requirements surge after calving due to the onset of milk production. Thus, cows can easily fall into a negative energy balance (NEB) (Bauman and Bruce, 1980; David, 1982). The cow's body attempts to adapt to the NEB by utilizing its stored carbohydrates, lipids, and proteins. However, if the reaction is not sufficiently successful, peripartum diseases such as milk fever, retained placenta and displaced abomasum may occur. It is known that the onset of peripartum diseases increases the risk of early postpartum sale, slaughter or death (culling). Early postpartum culling generally results in significant financial losses for dairy farms (Fetrow et al., 2006; Gröhn et al., 1998). Therefore, it is beneficial for dairy farm management to predict which cows are at risk of culling.

Serum non-esterified fatty acids (NEFA) and β-hydroxybutyrate (BHBA) are known as markers of whether cows are adapted to NEB (Herdt, 2000; Leblanc, 2010). Previous studies have determined prepartum NEFA and BHBA thresholds to predict postpartum culling. Briefly, the serum NEFA concentrations for predicting postpartum culling within 50 to 60 days in milk (DIM) in Canada were ≥ 0.26 mEq/L and ≥ 0.40 mEq/L during 2 weeks and 1 week before calving, respectively, and the serum BHBA concentration for prediction was calculated to be ≥ 0.7 mM during 1 week before calving (Nicola et al., 2022; Roberts et al., 2012). These results indicate that both parameters are

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* Corresponding author at: 582 Bunkyodai-Midorimachi, Ebetsu, Hokkaido 069-8501, Japan.
E-mail address: oishin@rakuno.ac.jp (S. Oikawa).

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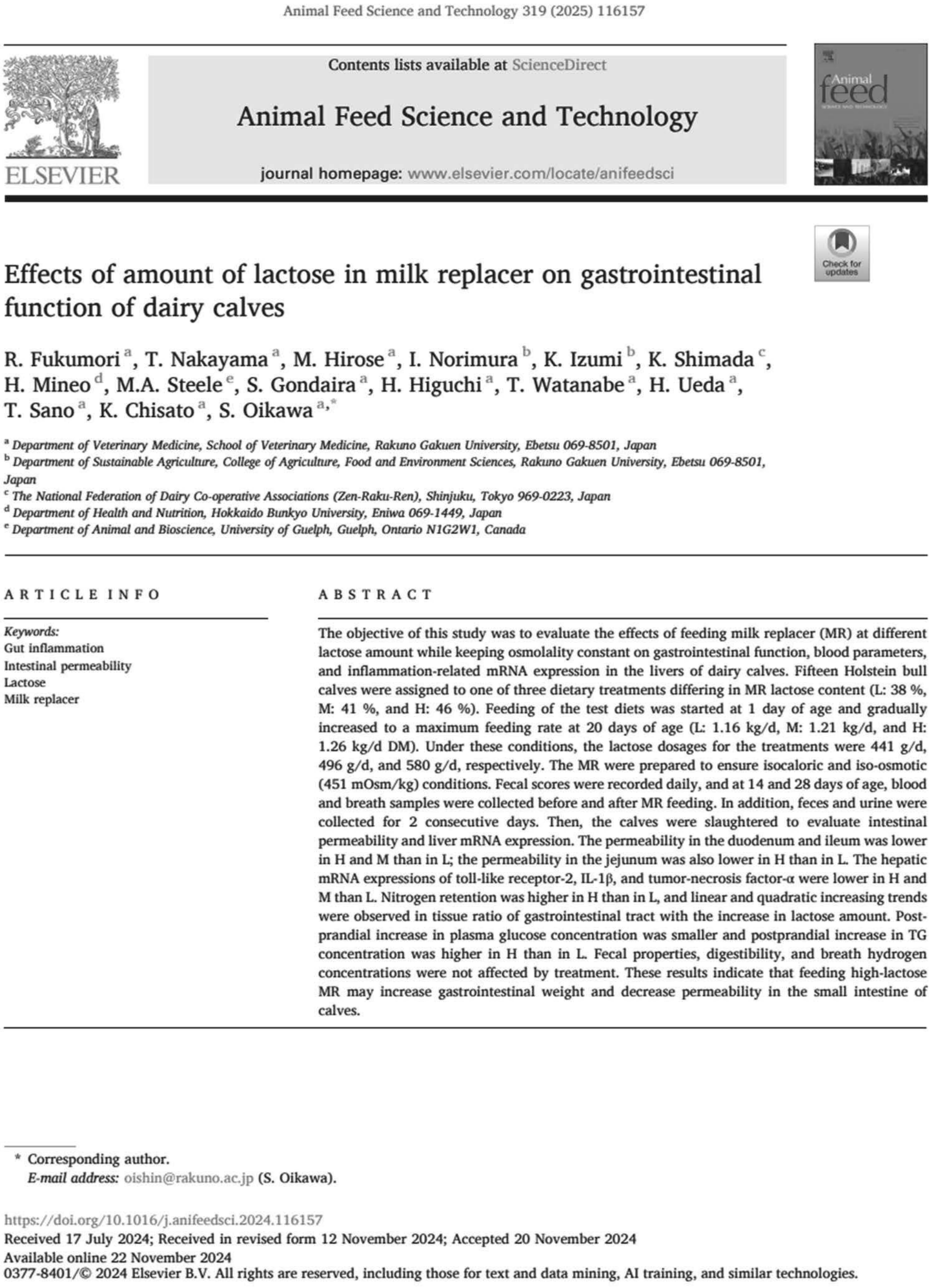

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Effects of amount of lactose in milk replacer on gastrointestinal function of dairy calves

R. Fukumori [a], T. Nakayama [a], M. Hirose [a], I. Norimura [b], K. Izumi [b], K. Shimada [c], H. Mineo [d], M.A. Steele [e], S. Gondaira [a], H. Higuchi [a], T. Watanabe [a], H. Ueda [a], T. Sano [a], K. Chisato [a], S. Oikawa [a,*]

[a] *Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu 069-8501, Japan*
[b] *Department of Sustainable Agriculture, College of Agriculture, Food and Environment Sciences, Rakuno Gakuen University, Ebetsu 069-8501, Japan*
[c] *The National Federation of Dairy Co-operative Associations (Zen-Raku-Ren), Shinjuku, Tokyo 969-0223, Japan*
[d] *Department of Health and Nutrition, Hokkaido Bunkyo University, Eniwa 069-1449, Japan*
[e] *Department of Animal and Bioscience, University of Guelph, Guelph, Ontario N1G2W1, Canada*

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Gut inflammation
Intestinal permeability
Lactose
Milk replacer

ABSTRACT

The objective of this study was to evaluate the effects of feeding milk replacer (MR) at different lactose amount while keeping osmolality constant on gastrointestinal function, blood parameters, and inflammation-related mRNA expression in the livers of dairy calves. Fifteen Holstein bull calves were assigned to one of three dietary treatments differing in MR lactose content (L: 38 %, M: 41 %, and H: 46 %). Feeding of the test diets was started at 1 day of age and gradually increased to a maximum feeding rate at 20 days of age (L: 1.16 kg/d, M: 1.21 kg/d, and H: 1.26 kg/d DM). Under these conditions, the lactose dosages for the treatments were 441 g/d, 496 g/d, and 580 g/d, respectively. The MR were prepared to ensure isocaloric and iso-osmotic (451 mOsm/kg) conditions. Fecal scores were recorded daily, and at 14 and 28 days of age, blood and breath samples were collected before and after MR feeding. In addition, feces and urine were collected for 2 consecutive days. Then, the calves were slaughtered to evaluate intestinal permeability and liver mRNA expression. The permeability in the duodenum and ileum was lower in H and M than in L; the permeability in the jejunum was also lower in H than in L. The hepatic mRNA expressions of toll-like receptor-2, IL-1β, and tumor-necrosis factor-α were lower in H and M than L. Nitrogen retention was higher in H than in L, and linear and quadratic increasing trends were observed in tissue ratio of gastrointestinal tract with the increase in lactose amount. Postprandial increase in plasma glucose concentration was smaller and postprandial increase in TG concentration was higher in H than in L. Fecal properties, digestibility, and breath hydrogen concentrations were not affected by treatment. These results indicate that feeding high-lactose MR may increase gastrointestinal weight and decrease permeability in the small intestine of calves.

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* Corresponding author.
E-mail address: oishin@rakuno.ac.jp (S. Oikawa).

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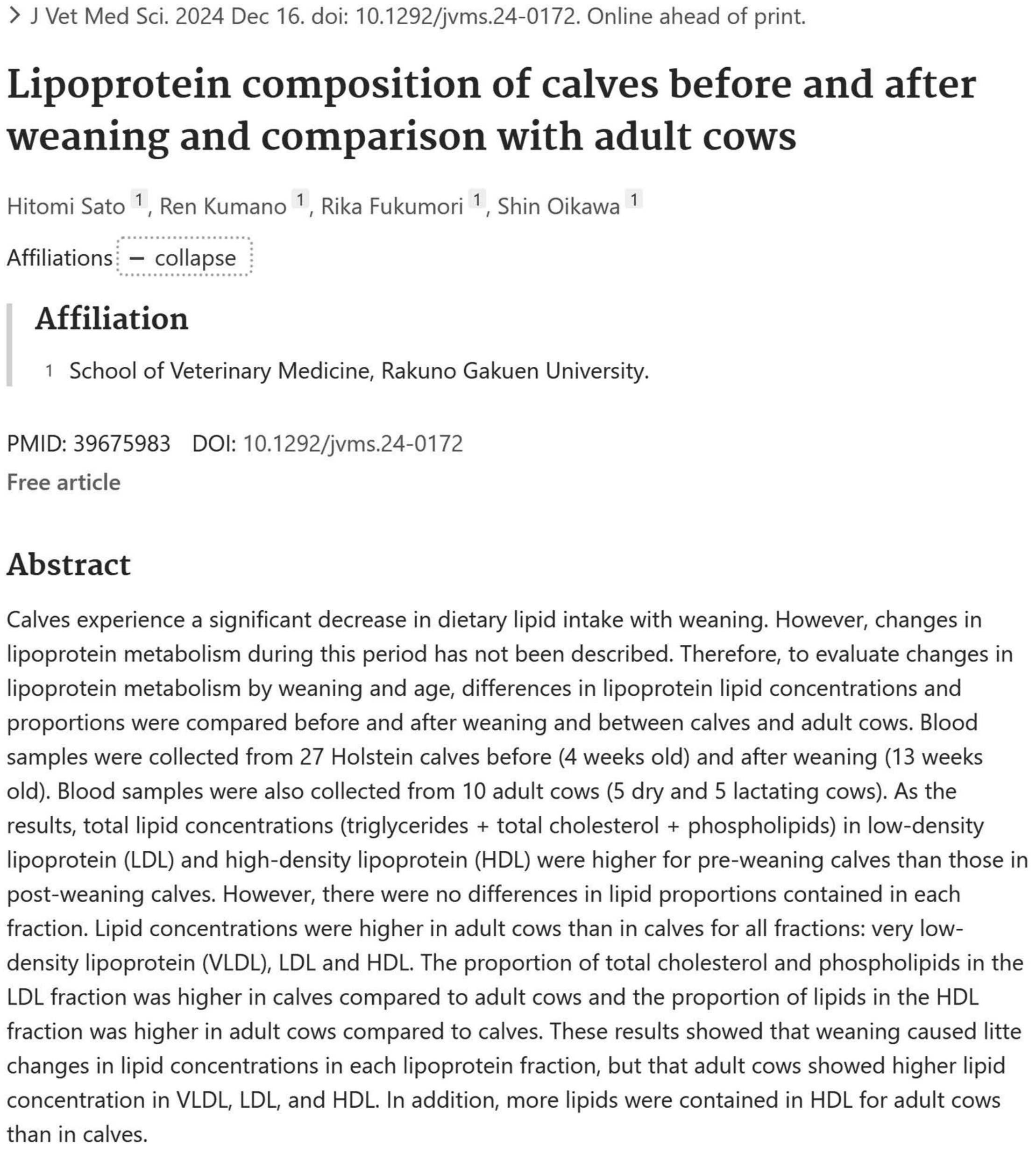

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Lipoprotein composition of calves before and after weaning and comparison with adult cows

Hitomi Sato [1], Ren Kumano [1], Rika Fukumori [1], Shin Oikawa [1]

Affiliations – collapse

Affiliation

1 School of Veterinary Medicine, Rakuno Gakuen University.

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Free article

Abstract

Calves experience a significant decrease in dietary lipid intake with weaning. However, changes in lipoprotein metabolism during this period has not been described. Therefore, to evaluate changes in lipoprotein metabolism by weaning and age, differences in lipoprotein lipid concentrations and proportions were compared before and after weaning and between calves and adult cows. Blood samples were collected from 27 Holstein calves before (4 weeks old) and after weaning (13 weeks old). Blood samples were also collected from 10 adult cows (5 dry and 5 lactating cows). As the results, total lipid concentrations (triglycerides + total cholesterol + phospholipids) in low-density lipoprotein (LDL) and high-density lipoprotein (HDL) were higher for pre-weaning calves than those in post-weaning calves. However, there were no differences in lipid proportions contained in each fraction. Lipid concentrations were higher in adult cows than in calves for all fractions: very low-density lipoprotein (VLDL), LDL and HDL. The proportion of total cholesterol and phospholipids in the LDL fraction was higher in calves compared to adult cows and the proportion of lipids in the HDL fraction was higher in adult cows compared to calves. These results showed that weaning caused litte changes in lipid concentrations in each lipoprotein fraction, but that adult cows showed higher lipid concentration in VLDL, LDL, and HDL. In addition, more lipids were contained in HDL for adult cows than in calves.

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RESEARCH ARTICLE

Animal Science Journal WILEY

Effects of starch content of calf starter on rumen properties and blood concentrations of metabolites and hormones in dairy calves under a high plane of milk feeding

Hitomi Satoh[1] | Rika Fukumori[1] | Ren Kumano[1] | Maho Kamata[2] | Kensuke Shimada[3,4] | Kenichi Izumi[2] | Shin Oikawa[1]

[1]Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan

[2]Department of Sustainable Agriculture, College of Agriculture, Food and Environment Sciences, Rakuno Gakuen University, Ebetsu, Japan

[3]The National Federation of Dairy Co-operative Associations (ZEN-RAKU-REN), Shinjuku, Tokyo, Japan

[4]Department of Animal and Bioscience, University of Guelph, Guelph, Ontario, N1G2W1, Canada

Correspondence
Rika Fukumori and Shin Oikawa, Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu 069-8501, Japan.
Email: fukumori@rakuno.ac.jp; oishin@rakuno.ac.jp

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Abstract

The objective of this study was to investigate the effects of calf starters with different starch content on rumen and blood properties in calves fed under a high plane of nutrition program. Twenty-seven Holstein calves (14 female, 13 male) were assigned to one of three starter treatment groups in a randomized block design: high-starch (41.8%) ($n = 9$), H; medium-starch (31.9%) ($n = 9$), M; low-starch (22.0%) ($n = 9$), L. Milk replacer on powder basis was fed up to 1.2 kg/day as fed, gradually reduced from 6 weeks of age; calves were weaned at 8 weeks of age. Each starter (up to 3.5 kg/day as fed) and chopped hay were provided ad libitum from 5 days of age. Blood was collected from 4 to 13 weeks of age. Rumen fluid was collected at 6, 8, 10, and 13 weeks of age. Serum urea nitrogen concentration after weaning was the lowest in H. Plasma IGF-1 concentrations were higher in H than in L. Ruminal pH was not different, but the molar proportion of ruminal propionate was higher in H than in L throughout the study period. In summary, a high-starch starter may increase propionate production and microbial protein synthesis in the rumen, inducing higher plasma IGF-1 concentrations.

KEYWORDS
calf starter, growth performance, metabolites, starch content, weaning transition

1 | INTRODUCTION

Restricted milk feeding for early weaning causes hunger and stress in calves, leading to reduced growth performance (Khan et al., 2010). Therefore, a high plane of milk feeding has recently become popular for the purposes of boosting growth, health, animal welfare, and prospects during the suckling period (Soberon et al., 2012). A high plane of nutrition by increased milk feeding accelerates preweaning growth rates by increasing feeding volume but leads to a decrease in starter intake (Hill et al., 2010). Furthermore, the rapid increase in starter intake at weaning places a greater burden on the underdeveloped rumen.

Although calves are developing at a fast rate and have high nutritional requirements, their gastrointestinal tracts are underdeveloped. Therefore, feeding management appropriate to the development of the gastrointestinal tract is necessary to prevent stunted growth after weaning (Baldwin et al., 2004). The calf's primary energy source changes from glucose to volatile fatty acids (VFA) during weaning transition, but the undeveloped rumen has less ability to buffer or absorb VFA. Rumen development requires the physical stimulation of the feed and chemical stimulation of fermentation products such as butyrate and propionate. Physical stimulation develops the muscular layer and chemical stimulation increases number and length of rumen papillae (Sander et al., 1959; Tamate et al., 1962). Thus, for smooth

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animals

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Article

A Case–Control Study on the Usefulness of Serum Lecithin: Cholesterol Acyltransferase Activity as a Predictor of Retained Placenta in Close-Up Dairy Cows

Hiroki Satoh [1], Kyoko Chisato [1], Rika Fukumori [1], Mohamed Tharwat [2] and Shin Oikawa [1,*]

[1] Veterinary Herd Health, Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu 069-8501, Hokkaido, Japan; s21161058@g.rakuno.ac.jp (H.S.); k-chisato@rakuno.ac.jp (K.C.); fukumori@rakuno.ac.jp (R.F.)
[2] Department of Clinical Sciences, College of Veterinary Medicine, Qassim University, P. O. Box 6622, Buraidah 51452, Saudi Arabia; atieh@qu.edu.sa
* Correspondence: oishin@rakuno.ac.jp; Tel.: +81-11-388-4825

Simple Summary: Retained placenta (RP) is one of the most periparturient diseases of dairy cows, in which the placenta is not expelled from the body within 24 h of calving. This condition increases the risk of other periparturient diseases and decreased milk production and reproductive efficiency. In order to reliably predict PR, this study focused on the activity of lecithin:cholesterol acyltransferase (LCAT) and compared its usefulness in the prepartum prediction of PR with the concentration of non-esterified fatty acids (NEFA). LCAT is an enzyme synthesized in the liver that converts free cholesterol to cholesteryl esters, which is known to be acutely related to and reduced by periparturient diseases. NEFA is a fatty acid that increases in the blood when animals are in negative energy balance and has been reported as a useful prepartum predictor of some perinatal diseases. This study was carried out at a single farm with approximately 200 Holstein parous cows from February 2010 to February 2016. Twenty-seven parous cows between 2 and 21 days (close-up stage) before their expected calving dates that developed RP (RP group) were assessed. They were compared with 60 clinically healthy cows (controls) that did not develop RP and were matched with the RP group for sampling period and parity. The results of this study were as follows: LCAT showed adequate discriminative ability of PR occurrence comparable to that of NEFA. However, LCAT or NEFA plus RFS showed higher discrimination ability than both alone. These results indicate that LCAT has a useful ability to predict the occurrence of RP.

Abstract: The purpose of this study was to investigate the usefulness of the activity of lecithin:cholesterol acyltransferase (LCAT), the enzyme responsible for esterification of cholesterol in plasma, as a predictor of retained placenta (RP) in close-up cows, compared with the non-esterified fatty acids (NEFA) concentration. This study was conducted as a case–control study between February 2010 and February 2016, on a single farm with approximately 200 Holstein parous cows in Hokkaido, Japan. Of the 1187 dairy cattle that calved, 835 dairy cattle were enrolled that underwent routine regular health examinations including blood sampling, body condition score (BCS) and the rumen fill score (RFS) at the close-up stage between 2 and 21 days before their expected calving dates. Of these, 27 cows that were multiparous and had RP were designated as the RP group. The controls were 60 clinically healthy cows that did not develop RP and were matched for the sampling period and parity with the RP group. The LCAT activity and NEFA concentration were significantly ($p < 0.01$) lower and higher, respectively, in the RP group than in controls. There was no significant difference in cholesteryl esters, free cholesterol concentrations and BCS between the two groups. However, RFS was significantly ($p < 0.01$) lower in the RP group than in the controls. Cows with LCAT activity of <450 U were 3.6 times more likely to develop RP than those with higher values, whereas those with NEFA levels above 0.4 mEq/L were 5.4 times more likely to. The area under the curve of receiver operator characteristic curves showed that LCAT activity was as efficient as the NEFA concentration in the diagnostic prediction of RP, suggesting it to be a useful predictor. Logistic regression analysis with LCAT or NEFA and RFS as explanatory variables resulted in

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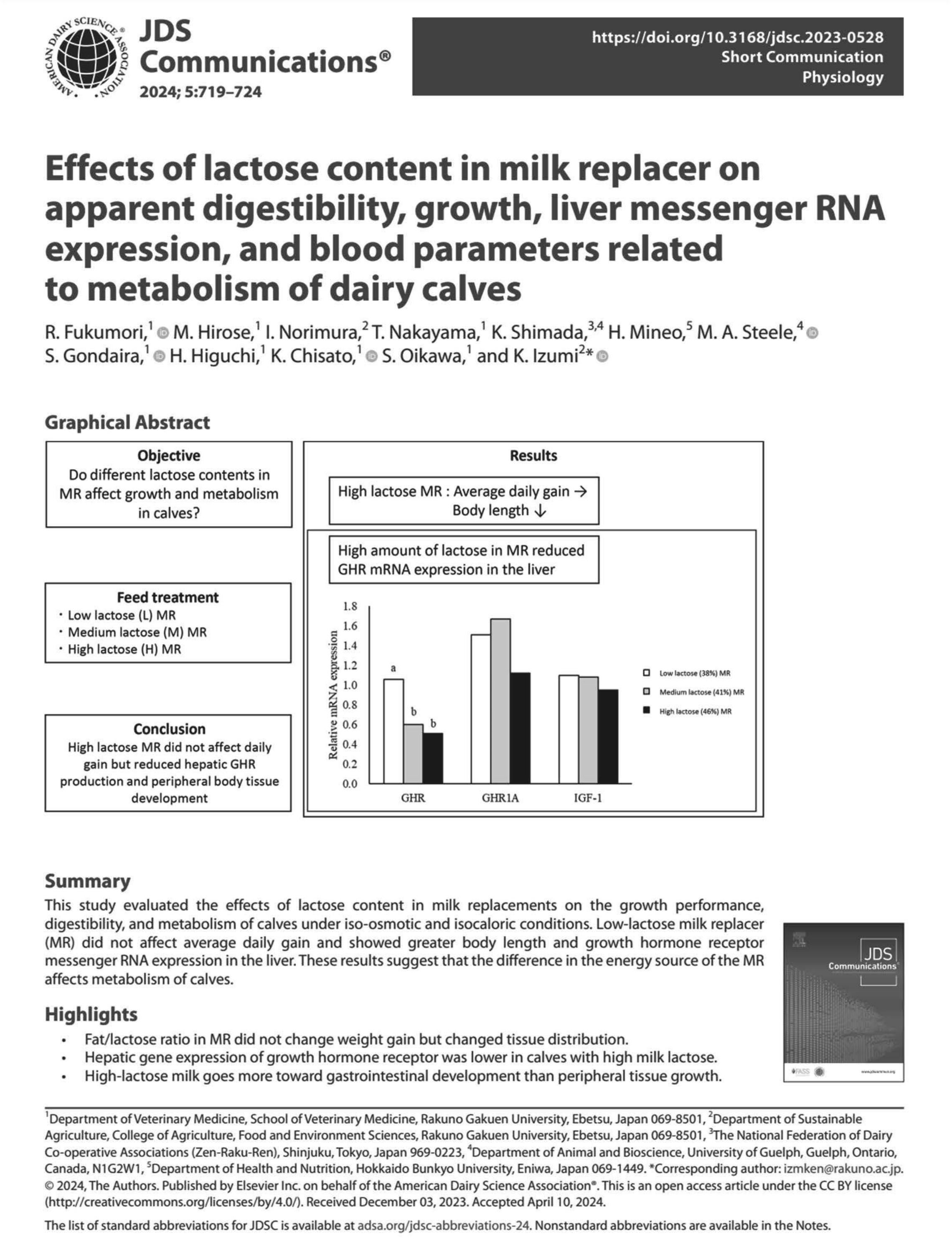

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Short Communication
Physiology

Effects of lactose content in milk replacer on apparent digestibility, growth, liver messenger RNA expression, and blood parameters related to metabolism of dairy calves

R. Fukumori,[1] M. Hirose,[1] I. Norimura,[2] T. Nakayama,[1] K. Shimada,[3,4] H. Mineo,[5] M. A. Steele,[4] S. Gondaira,[1] H. Higuchi,[1] K. Chisato,[1] S. Oikawa,[1] and K. Izumi[2]*

Graphical Abstract

Objective
Do different lactose contents in MR affect growth and metabolism in calves?

Feed treatment
- Low lactose (L) MR
- Medium lactose (M) MR
- High lactose (H) MR

Conclusion
High lactose MR did not affect daily gain but reduced hepatic GHR production and peripheral body tissue development

Results

High lactose MR : Average daily gain →
Body length ↓

High amount of lactose in MR reduced GHR mRNA expression in the liver

Summary

This study evaluated the effects of lactose content in milk replacements on the growth performance, digestibility, and metabolism of calves under iso-osmotic and isocaloric conditions. Low-lactose milk replacer (MR) did not affect average daily gain and showed greater body length and growth hormone receptor messenger RNA expression in the liver. These results suggest that the difference in the energy source of the MR affects metabolism of calves.

Highlights

- Fat/lactose ratio in MR did not change weight gain but changed tissue distribution.
- Hepatic gene expression of growth hormone receptor was lower in calves with high milk lactose.
- High-lactose milk goes more toward gastrointestinal development than peripheral tissue growth.

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[1]Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan 069-8501, [2]Department of Sustainable Agriculture, College of Agriculture, Food and Environment Sciences, Rakuno Gakuen University, Ebetsu, Japan 069-8501, [3]The National Federation of Dairy Co-operative Associations (Zen-Raku-Ren), Shinjuku, Tokyo, Japan 969-0223, [4]Department of Animal and Bioscience, University of Guelph, Guelph, Ontario, Canada, N1G2W1, [5]Department of Health and Nutrition, Hokkaido Bunkyo University, Eniwa, Japan 069-1449. *Corresponding author: izmken@rakuno.ac.jp.
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The list of standard abbreviations for JDSC is available at adsa.org/jdsc-abbreviations-24. Nonstandard abbreviations are available in the Notes.

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最終責任者　Kenichi Izumi (Corresponding Author)

獣医臨床病理学（Veterinary Clinicopathology）

Kazuyuki Suzuki

Professor

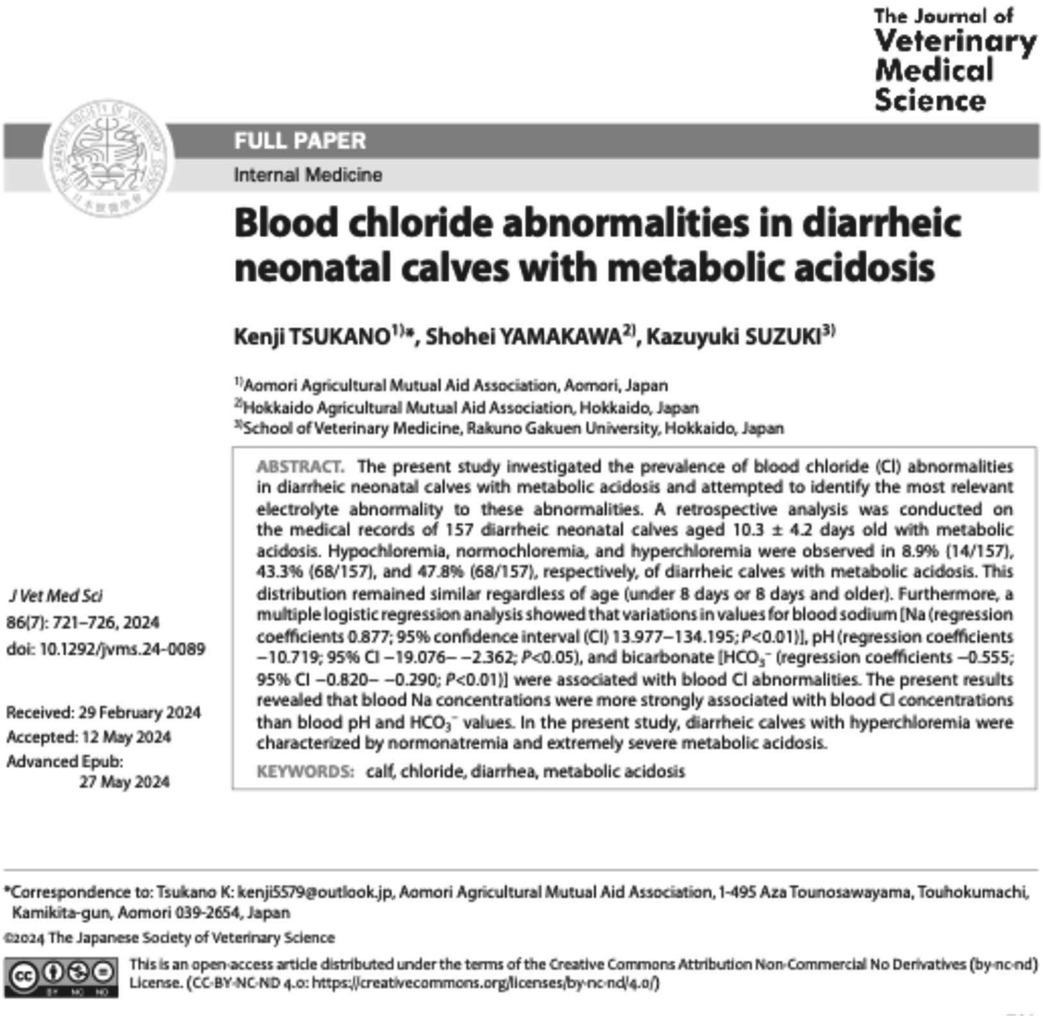
教授　鈴木　一由

I. 筆頭または責任著者　＜First or Corresponding Author＞

II. その他　＜Others＞

1）Blood chloride abnormalities in diarrheic neonatal calves with metabolic acidosis.
Tsukano K, Yamakawa S, **Suzuki K**.
J Vet Med Sci 86:721–726. 2024. doi: 10.1292/jvms.24-0089.

2）Characteristics of failure of passive transfer at the herd level using the serum immunoglobulin G concentration as an indicator on dairy farms in eastern Hokkaido, Japan.
Kayasaki S, Satoh H, Oguchi K, Chisato K, Fukumori R, Higuchi H, **Suzuki K**, Oikawa S.
J Vet Med Sci 86:809–815. 2024. doi: 10.1292/jvms.24-0054.



The Journal of
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FULL PAPER
Internal Medicine

Blood chloride abnormalities in diarrheic neonatal calves with metabolic acidosis

Kenji TSUKANO[1)]*, Shohei YAMAKAWA[2)], Kazuyuki SUZUKI[3)]

[1)]Aomori Agricultural Mutual Aid Association, Aomori, Japan
[2)]Hokkaido Agricultural Mutual Aid Association, Hokkaido, Japan
[3)]School of Veterinary Medicine, Rakuno Gakuen University, Hokkaido, Japan

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ABSTRACT. The present study investigated the prevalence of blood chloride (Cl) abnormalities in diarrheic neonatal calves with metabolic acidosis and attempted to identify the most relevant electrolyte abnormality to these abnormalities. A retrospective analysis was conducted on the medical records of 157 diarrheic neonatal calves aged 10.3 ± 4.2 days old with metabolic acidosis. Hypochloremia, normochloremia, and hyperchloremia were observed in 8.9% (14/157), 43.3% (68/157), and 47.8% (68/157), respectively, of diarrheic calves with metabolic acidosis. This distribution remained similar regardless of age (under 8 days or 8 days and older). Furthermore, a multiple logistic regression analysis showed that variations in values for blood sodium [Na (regression coefficients 0.877; 95% confidence interval (CI) 13.977–134.195; $P<0.01$)], pH (regression coefficients −10.719; 95% CI −19.076– −2.362; $P<0.05$), and bicarbonate [HCO_3^- (regression coefficients −0.555; 95% CI −0.820– −0.290; $P<0.01$)] were associated with blood Cl abnormalities. The present results revealed that blood Na concentrations were more strongly associated with blood Cl concentrations than blood pH and HCO_3^- values. In the present study, diarrheic calves with hyperchloremia were characterized by normonatremia and extremely severe metabolic acidosis.

KEYWORDS: calf, chloride, diarrhea, metabolic acidosis

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*Correspondence to: Tsukano K: kenji5579@outlook.jp, Aomori Agricultural Mutual Aid Association, 1-495 Aza Tounosawayama, Touhokumachi, Kamikita-gun, Aomori 039-2654, Japan

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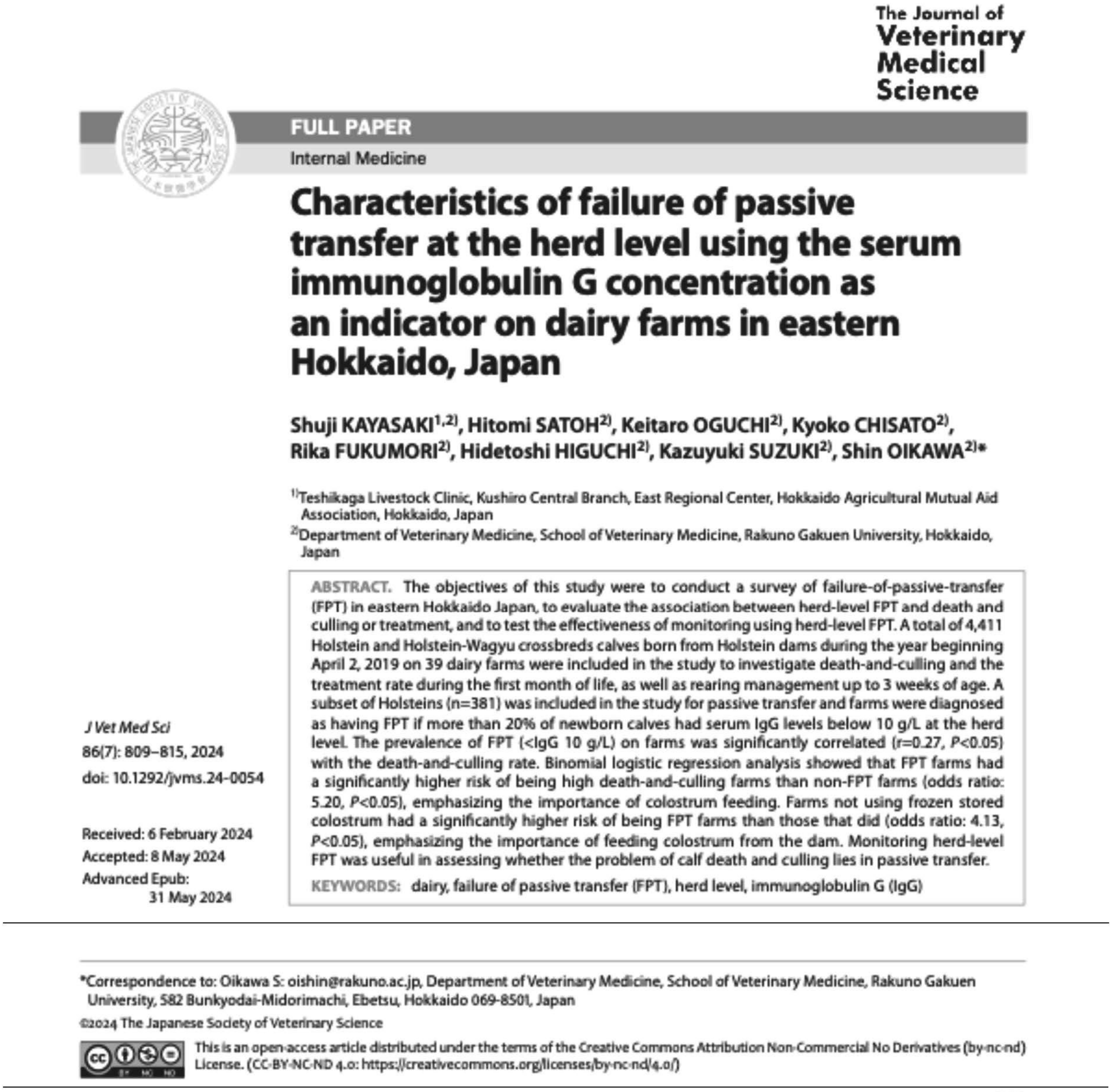

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FULL PAPER
Internal Medicine

Characteristics of failure of passive transfer at the herd level using the serum immunoglobulin G concentration as an indicator on dairy farms in eastern Hokkaido, Japan

Shuji KAYASAKI[1,2], Hitomi SATOH[2], Keitaro OGUCHI[2], Kyoko CHISATO[2], Rika FUKUMORI[2], Hidetoshi HIGUCHI[2], Kazuyuki SUZUKI[2], Shin OIKAWA[2]*

[1]Teshikaga Livestock Clinic, Kushiro Central Branch, East Regional Center, Hokkaido Agricultural Mutual Aid Association, Hokkaido, Japan
[2]Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Hokkaido, Japan

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ABSTRACT. The objectives of this study were to conduct a survey of failure-of-passive-transfer (FPT) in eastern Hokkaido Japan, to evaluate the association between herd-level FPT and death and culling or treatment, and to test the effectiveness of monitoring using herd-level FPT. A total of 4,411 Holstein and Holstein-Wagyu crossbreds calves born from Holstein dams during the year beginning April 2, 2019 on 39 dairy farms were included in the study to investigate death-and-culling and the treatment rate during the first month of life, as well as rearing management up to 3 weeks of age. A subset of Holsteins (n=381) was included in the study for passive transfer and farms were diagnosed as having FPT if more than 20% of newborn calves had serum IgG levels below 10 g/L at the herd level. The prevalence of FPT (<IgG 10 g/L) on farms was significantly correlated (r=0.27, $P<0.05$) with the death-and-culling rate. Binomial logistic regression analysis showed that FPT farms had a significantly higher risk of being high death-and-culling farms than non-FPT farms (odds ratio: 5.20, $P<0.05$), emphasizing the importance of colostrum feeding. Farms not using frozen stored colostrum had a significantly higher risk of being FPT farms than those that did (odds ratio: 4.13, $P<0.05$), emphasizing the importance of feeding colostrum from the dam. Monitoring herd-level FPT was useful in assessing whether the problem of calf death and culling lies in passive transfer.

KEYWORDS: dairy, failure of passive transfer (FPT), herd level, immunoglobulin G (IgG)

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*Correspondence to: Oikawa S: oishin@rakuno.ac.jp, Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyodai-Midorimachi, Ebetsu, Hokkaido 069-8501, Japan

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最終責任者　Shin Oikawa (Corresponding Author)

獣医薬理学（Veterinary Pharmacology）

Hiroki Teraoka

Professor

教授　寺岡　宏樹

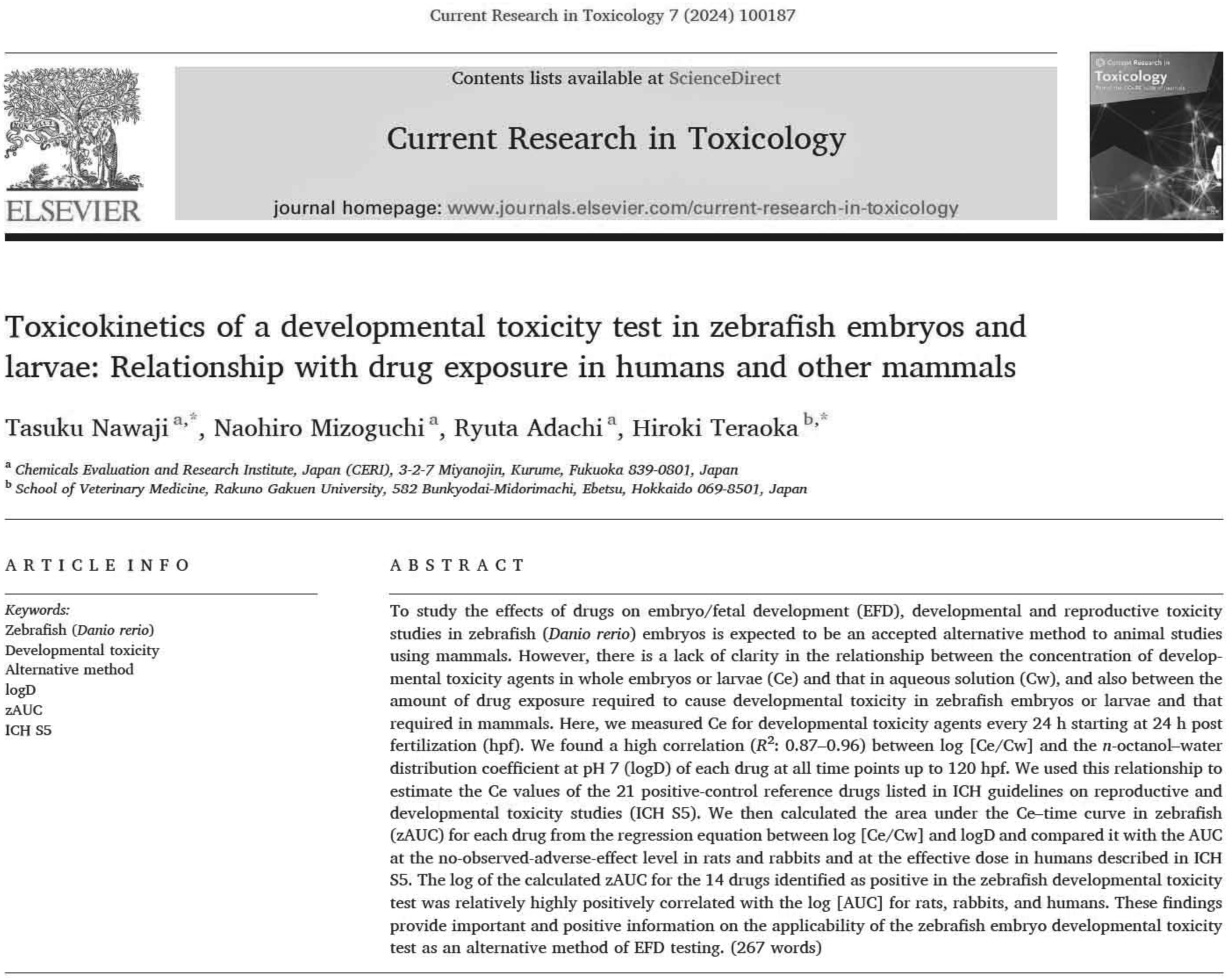
I. 筆頭または責任著者　＜First or Corresponding Author＞

1）Toxicokinetics of a developmental toxicity test in zebrafish embryos and larvae: Relationship with drug exposure in humans and other mammals.
Nawaji T, Mizoguchi N, Adachi R, **Teraoka H.**
Curr Res Toxicol 7: 100187. 2024. doi: 10.1016/j.crtox.2024.100187.

2）Tyrosinase inhibition prevents non-coplanar polychlorinated biphenyls and polybrominated diphenyl ethers-induced hyperactivity in developing zebrafish: I nteraction between pigmentation and neurobehavior.
Tanaka Y, Shindo A, Dong W, Nakamura T, Ogura K, Nomiyama K, **Teraoka H.**
Neurotoxicol Teratol 104: 107373. 2024. doi:10.1016/j.ntt.2024.107373.

3）Possible Shifts in the Genetic Diversity of Red-crowned Cranes (*Grus japonensis*) in Hokkaido, Japan: Indications of Continental Gene Flow.
Dong W, Tomita K, Sawada A, Hasebe M, Inoue M, Momose K, Nakamura T, **Teraoka H**.
Animals (Basel) 14: 1633. 2024. doi: 10.3390/ani14111633.

II. その他　＜Others＞



Current Research in Toxicology 7 (2024) 100187

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Toxicokinetics of a developmental toxicity test in zebrafish embryos and larvae: Relationship with drug exposure in humans and other mammals

Tasuku Nawaji [a,*], Naohiro Mizoguchi [a], Ryuta Adachi [a], Hiroki Teraoka [b,*]

[a] Chemicals Evaluation and Research Institute, Japan (CERI), 3-2-7 Miyanojin, Kurume, Fukuoka 839-0801, Japan
[b] School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyodai-Midorimachi, Ebetsu, Hokkaido 069-8501, Japan

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Zebrafish (*Danio rerio*)
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ABSTRACT

To study the effects of drugs on embryo/fetal development (EFD), developmental and reproductive toxicity studies in zebrafish (*Danio rerio*) embryos is expected to be an accepted alternative method to animal studies using mammals. However, there is a lack of clarity in the relationship between the concentration of developmental toxicity agents in whole embryos or larvae (Ce) and that in aqueous solution (Cw), and also between the amount of drug exposure required to cause developmental toxicity in zebrafish embryos or larvae and that required in mammals. Here, we measured Ce for developmental toxicity agents every 24 h starting at 24 h post fertilization (hpf). We found a high correlation (R^2: 0.87–0.96) between log [Ce/Cw] and the *n*-octanol–water distribution coefficient at pH 7 (logD) of each drug at all time points up to 120 hpf. We used this relationship to estimate the Ce values of the 21 positive-control reference drugs listed in ICH guidelines on reproductive and developmental toxicity studies (ICH S5). We then calculated the area under the Ce–time curve in zebrafish (zAUC) for each drug from the regression equation between log [Ce/Cw] and logD and compared it with the AUC at the no-observed-adverse-effect level in rats and rabbits and at the effective dose in humans described in ICH S5. The log of the calculated zAUC for the 14 drugs identified as positive in the zebrafish developmental toxicity test was relatively highly positively correlated with the log [AUC] for rats, rabbits, and humans. These findings provide important and positive information on the applicability of the zebrafish embryo developmental toxicity test as an alternative method of EFD testing. (267 words)

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Tyrosinase inhibition prevents non-coplanar polychlorinated biphenyls and polybrominated diphenyl ethers-induced hyperactivity in developing zebrafish: Interaction between pigmentation and neurobehavior

Yasuaki Tanaka[a], Asako Shindo[a,b], Wenjing Dong[a], Tatsuro Nakamura[a], Kyoko Ogura[c], Kei Nomiyama[c], Hiroki Teraoka[a,*]

[a] *School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu 069-8501, Japan*
[b] *Department of Biological Sciences, Osaka University, Osaka 560-0043, Japan*
[c] *Center for Marine Environmental Studies (CMES), Ehime University, 2-5 Bunkyo-cho, Matsuyama, Ehime 790-8577, Japan*

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ABSTRACT

Non-coplanar polychlorinated biphenyl (PCB) mixture Aroclor 1254 and polybrominated diphenyl ether (PBDE) BDE-47 are known to impede neurogenesis and neuronal development. We previously reported that exposure to PCB and PBDE leads to increased embryonic movement in zebrafish by decreasing dopamine levels. In this study, we studied the connection between the melanin and dopamine synthesis pathways in this context. Both genetic and chemical inhibition of tyrosinase, the rate-limiting enzyme in melanin synthesis, not only led to reduced pigmentation but also inhibit PCB/PBDE-induced embryonic hyperactivity. Furthermore, PCB and PBDE rarely affected tyrosinase expression in the potential pigment cells, suggesting that these compounds reduce dopamine through enzymatic regulation, including a competitive interaction for the substrate tyrosine. Our results provide new insights into the interactions between melanogenesis and dopaminergic neuronal activity, which may contribute to understanding the mechanisms underlying PCB/PBDE toxicity in developing organisms.

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animals

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Article

Possible Shifts in the Genetic Diversity of Red-crowned Cranes (*Grus japonensis*) in Hokkaido, Japan: Indications of Continental Gene Flow

Wenjing Dong [1], Kai Tomita [1], Akira Sawada [2], Makoto Hasebe [3], Masako Inoue [4], Kunikazu Momose [4], Tatsuro Nakamura [1] and Hiroki Teraoka [1,4,*]

[1] School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu 069-8501, Japan; dongwenjing_2015@163.com (W.D.); s21861114@g.rakuno.ac.jp (K.T.); t-naka@rakuno.ac.jp (T.N.)
[2] Faculty of Human Sciences, Waseda University, Tokorozawa 359-1192, Japan; akira.sawada.1312@gmail.com
[3] NPO Sarobetsu Eco Network, Toyotomi 098-4100, Japan; hasebe@sarobetsu.or.jp
[4] NPO Red-crowned Crane Conservancy, Kushiro 085-0036, Japan; masako@seagreen.ocn.ne.jp (M.I.); momosekunikazu@gmail.com (K.M.)
* Correspondence: hteraoka08@gmail.com or hteraoka@rakuno.ac.jp

Simple Summary: The red-crowned cranes consist of two populations: continental (Far East Eurasia) and island (Hokkaido, Japan) cranes. It was once thought that these two populations lived independently. Having recovered from near extinction more than a century ago, the island population in Hokkaido, Japan, now exhibits very low genetic diversity, raising concerns about potentially devastating effects from infectious diseases. In 2018, a possible mating between a continental male and an island female was observed in northern Hokkaido. This study investigates their offspring or their blood relatives by examining the major histocompatibility complex (MHC) in cranes from northern and southeastern Hokkaido between 2008 and 2022. We identified 58 MHC types based on nucleotide sequences. MHC types from the possible continental male were predominantly found in cranes from northern Hokkaido. Genetic analysis also suggested clear population differentiation between northern and southeastern Hokkaido. The results suggest that genetic traits from the continental population have been integrated into the Hokkaido cranes, particularly in the northern population. This genetic exchange may improve the disease resistance and environmental adaptability of the Hokkaido crane population, providing valuable insights for conservation efforts.

Abstract: Red-crowned cranes (*Grus japonensis*) consist of two distinct groups: the continental population and the island population. The island population, localized in Hokkaido, Japan, exhibits very low genetic diversity due to its rapid recovery from the brink of extinction. Our previous research in 2018 highlighted a possible mating between a male from the continental population, with the Gj5 haplotype, and a female from the island population, with the Gj2 haplotype, at Hitominuma Sawmp shore in northern Hokkaido. The present study attempted to unravel the distribution of their offspring by examining the major histocompatibility complex (MHC) of this mixed breeding pair compared with samples collected from cranes in northern and southeastern Hokkaido between 2008 and 2022. The analysis identified 55 MHC types, including 10 known types in a dataset of 89 crane samples, based on amino acid sequences. A total of 58 MHC types were recognized, based on nucleotide sequences, as there were many cases in which the same amino acid sequence had different nucleotide sequences. The five DNA types of MHC in the Hitominuma Swamp male were predominantly identified in eight cranes from northern Hokkaido and one chick from southeastern Hokkaido. In addition, population genetic analysis, based on insertion/deletion (InDel) polymorphisms, indicates distinct population differentiation between the northern and southeastern regions of Hokkaido. These results suggest that genetic contributions from the continental red-crowned crane population have already been integrated into the Hokkaido populations, with a more pronounced influence in northern Hokkaido.

Keywords: genetic diversity; *Grus japonensis*; Hokkaido; eastern Eurasia; MHC; Red-crowned crane

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最終責任者　Hiroki Teraoka (Corresponding Author)

Shidow Torisu

Professor

教授　鳥巣　至道

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1）Laparoscopic treatment of congenital portosystemic shunts with portal pressure measurement and portal angiography in 36 dogs.
Shigemoto J, Kaneko Y, Kawazu M, Naganobu K, **Torisu S.**
Front Vet Sci 11:1291006. 2024. doi: 10.3389/fvets.2024.1291006.

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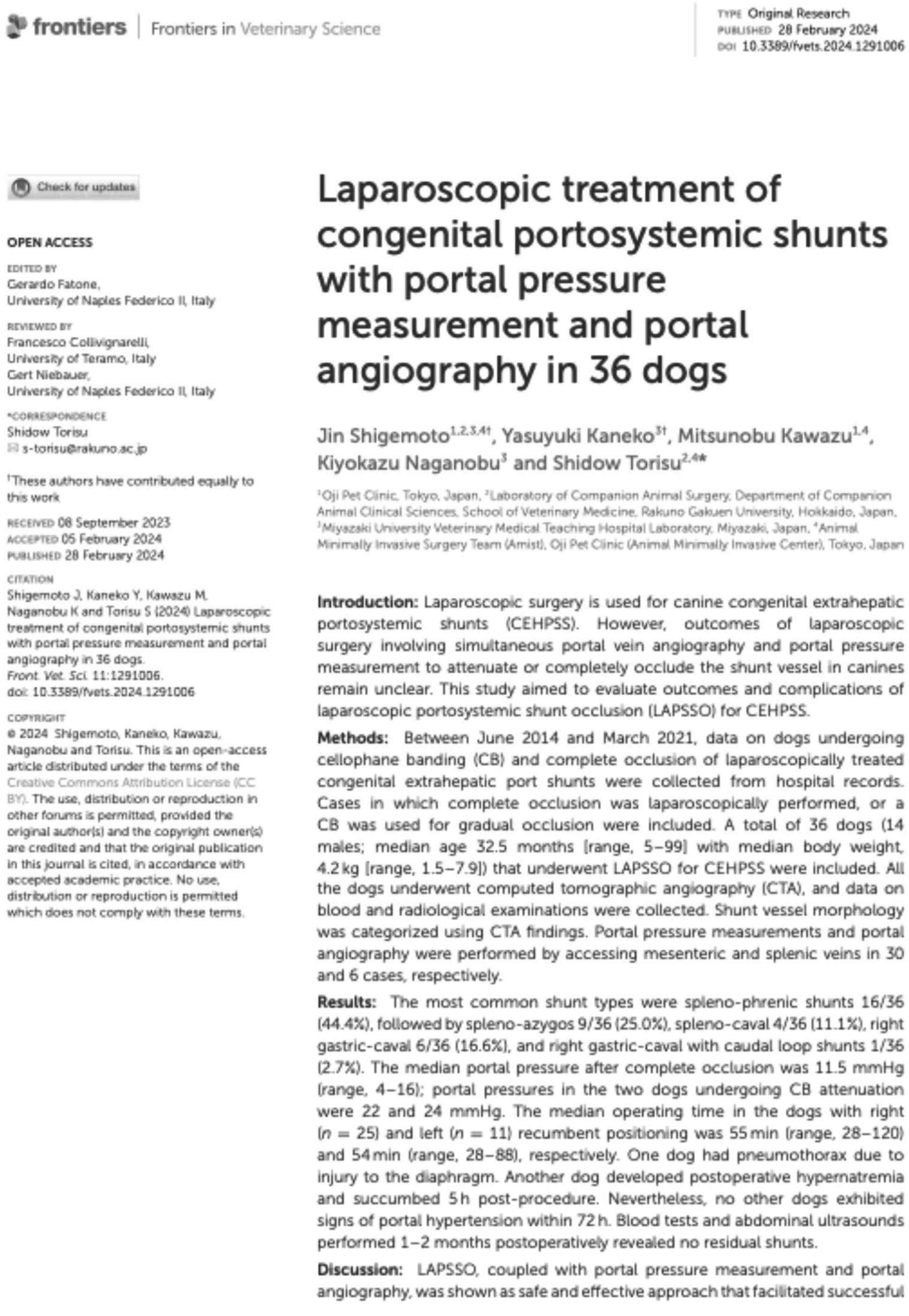
1）A chronic intermittent haemodialysis pig model for functional evaluation of dialysis membranes.
Yamamoto S, Umeno H, Sano Y, Koremoto M, Goda Y, Kaneko Y, **Torisu S,** Tsuruda T, Fujimoto S.
Int J Artif Organs 47:321–328. 2024. doi: 10.1177/03913988241253152.



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Gert Niebauer,
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*CORRESPONDENCE
Shidow Torisu
✉ s-torisu@rakuno.ac.jp

†These authors have contributed equally to this work

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Laparoscopic treatment of congenital portosystemic shunts with portal pressure measurement and portal angiography in 36 dogs

Jin Shigemoto[1,2,3,4†], Yasuyuki Kaneko[3†], Mitsunobu Kawazu[1,4], Kiyokazu Naganobu[3] and Shidow Torisu[2,4*]

[1]Oji Pet Clinic, Tokyo, Japan, [2]Laboratory of Companion Animal Surgery, Department of Companion Animal Clinical Sciences, School of Veterinary Medicine, Rakuno Gakuen University, Hokkaido, Japan, [3]Miyazaki University Veterinary Medical Teaching Hospital Laboratory, Miyazaki, Japan, [4]Animal Minimally Invasive Surgery Team (Amist), Oji Pet Clinic (Animal Minimally Invasive Center), Tokyo, Japan

Introduction: Laparoscopic surgery is used for canine congenital extrahepatic portosystemic shunts (CEHPSS). However, outcomes of laparoscopic surgery involving simultaneous portal vein angiography and portal pressure measurement to attenuate or completely occlude the shunt vessel in canines remain unclear. This study aimed to evaluate outcomes and complications of laparoscopic portosystemic shunt occlusion (LAPSSO) for CEHPSS.

Methods: Between June 2014 and March 2021, data on dogs undergoing cellophane banding (CB) and complete occlusion of laparoscopically treated congenital extrahepatic port shunts were collected from hospital records. Cases in which complete occlusion was laparoscopically performed, or a CB was used for gradual occlusion were included. A total of 36 dogs (14 males; median age 32.5 months [range, 5–99] with median body weight, 4.2 kg [range, 1.5–7.9]) that underwent LAPSSO for CEHPSS were included. All the dogs underwent computed tomographic angiography (CTA), and data on blood and radiological examinations were collected. Shunt vessel morphology was categorized using CTA findings. Portal pressure measurements and portal angiography were performed by accessing mesenteric and splenic veins in 30 and 6 cases, respectively.

Results: The most common shunt types were spleno-phrenic shunts 16/36 (44.4%), followed by spleno-azygos 9/36 (25.0%), spleno-caval 4/36 (11.1%), right gastric-caval 6/36 (16.6%), and right gastric-caval with caudal loop shunts 1/36 (2.7%). The median portal pressure after complete occlusion was 11.5 mmHg (range, 4–16); portal pressures in the two dogs undergoing CB attenuation were 22 and 24 mmHg. The median operating time in the dogs with right ($n = 25$) and left ($n = 11$) recumbent positioning was 55 min (range, 28–120) and 54 min (range, 28–88), respectively. One dog had pneumothorax due to injury to the diaphragm. Another dog developed postoperative hypernatremia and succumbed 5 h post-procedure. Nevertheless, no other dogs exhibited signs of portal hypertension within 72 h. Blood tests and abdominal ultrasounds performed 1–2 months postoperatively revealed no residual shunts.

Discussion: LAPSSO, coupled with portal pressure measurement and portal angiography, was shown as safe and effective approach that facilitated successful

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最終責任者　Shidow Torisu (Corresponding Author)

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A chronic intermittent haemodialysis pig model for functional evaluation of dialysis membranes

Shushi Yamamoto [1] [2], Hiroshi Umeno [3], Yusuke Sano [3], Masahide Koremoto [4], Yoshimichi Goda [2], Yasuyuki Kaneko [5], Shidow Torisu [1], Toshihiro Tsuruda [2], Shouichi Fujimoto [6]

Affiliations – collapse

Affiliations

1. Division of Companion Animal Surgery, Department of Small Animal Clinical Sciences, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido Prefecture, Japan.
2. Department of Hemo-Vascular Advanced Medicine, Cardiorenal Reseach Laboratory, Faculty of Medicine, University of Miyazaki, Miyazaki, Japan.
3. Medical Technology and Material Laboratory, Asahi Kasei Medical Co. Ltd., Fuji, Shizuoka, Japan.
4. Product Development Strategy Department, Asahi Kasei Medical Co. Ltd., Chiyoda-ku, Tokyo, Japan.
5. Veterinary Teaching Hospital, Faculty of Agriculture, University of Miyazaki, Miyazaki, Japan.
6. M&M Collaboration Research Laboratory, Department of Medical Environment Innovation, Faculty of Medicine, University of Miyazaki, Miyazaki, Japan.

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Abstract

Performance evaluation of new dialysis membranes is primarily performed in vitro, which can lead to differences in clinical results. Currently, data on dialysis membrane performance and safety are available only for haemodialysis patients. Herein, we aimed to establish an in vivo animal model of dialysis that could be extrapolated to humans. We created a bilateral nephrectomy pig model of renal failure, which placed a double-lumen catheter with the hub exposed dorsally. Haemodialysis was performed in the same manner as in humans, during which clinically relevant physiologic data were evaluated. Next, to evaluate the utility of this model, the biocompatibility of two kinds of membranes coated with or without vitamin E used in haemodiafiltration therapy were compared. Haemodialysis treatment was successfully performed in nephrectomized pigs under the same dialysis conditions (4 h per session, every other day, for 2 weeks). In accordance with human clinical data, regular dialysis alleviated renal failure in pigs. The vitamin E-coated membrane showed a significant reduction rate of advanced oxidation protein products during dialysis than non-coated membrane. In conclusion, this model mimics the pathophysiology and dialysis condition of patients undergoing haemodialysis. This dialysis treatment model of renal failure will be useful for evaluating the performance and safety of dialysis membranes.

Keywords: Haemodialysis; acute renal failure; animal models; dialysis membrane; pig; vitamin E-coated membrane.

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最終責任者　Syushi Yamamoto (First and Corresponding Author)

食品衛生学（Food Microbiology and Food Safety）

Masaru Usui

Professor

教授　臼井　優

I. 筆頭または責任著者　＜First or Corresponding Author＞

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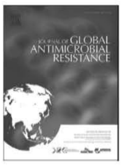

Transferable linezolid resistance genes (*optrA* and *poxtA*) in enterococci derived from livestock compost at Japanese farms

Akira Fukuda[a], Chie Nakajima[b,c,d], Yasuhiko Suzuki[b,c,d], Masaru Usui[a,*]

[a] *Department of Health and Environmental Sciences, Laboratory of Food Microbiology and Food Safety, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan*
[b] *Division of Bioresources, Hokkaido University International Institute for Zoonosis Control, Sapporo, Japan*
[c] *International Collaboration Unit, Hokkaido University International Institute for Zoonosis Control, Sapporo, Japan*
[d] *Division of Research Support, Hokkaido University Institute for Vaccine Research and Development, Sapporo, Japan*

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ABSTRACT

Objectives: Linezolid is a last-resort antimicrobial in human clinical settings to treat multidrug-resistant Gram-positive bacterial infections. Mobile linezolid resistance genes (*optrA*, *poxtA*, and *cfr*) have been detected in various sources worldwide. However, the presence of linezolid-not-susceptible bacteria and mobile linezolid resistance genes in Japan remains uncertain. Therefore, we clarified the existence of linezolid-not-susceptible bacteria and mobile linezolid resistance genes in farm environments in Japan.

Methods: Enterococci isolates from faeces compost collected from 10 pig and 11 cattle farms in Japan in 2021 were tested for antimicrobial susceptibility and possession of mobile linezolid resistance genes. Whole-genome sequencing of *optrA* and/or *poxtA* genes positive-enterococci was performed.

Results: Of 103 enterococci isolates, 12 from pig farm compost were not-susceptible (2 resistant and 10 intermediate) to linezolid. These 12 isolates carried mobile linezolid resistance genes on plasmids or chromosomes (5 *optrA*-positive *Enterococcus faecalis*, 6 *poxtA*-positive *E. hirae* or *E. thailandicus*, and 1 *optrA*- and *poxtA*-positive *E. faecium*). The genetic structures of *optrA*- and *poxA*-carrying plasmids were almost identical to those reported in other countries. These plasmids were capable of transferring among *E. faecium* and *E. faecalis* strains. The *optrA*- and *poxtA*-positive *E. faecium* belonged to ST324 (clade A2), a high-risk multidrug-resistant clone. The *E. faecalis* carrying *optrA* gene on its chromosome was identified as ST593.

Conclusions: Although linezolid is not used in livestock, linezolid-not-susceptible enterococci could be indirectly selected by frequently used antimicrobials, such as phenicols. Moreover, various enterococci species derived from livestock compost may serve as reservoirs of linezolid resistance genes carried on globally disseminated plasmids and multidrug-resistant high-risk clones.

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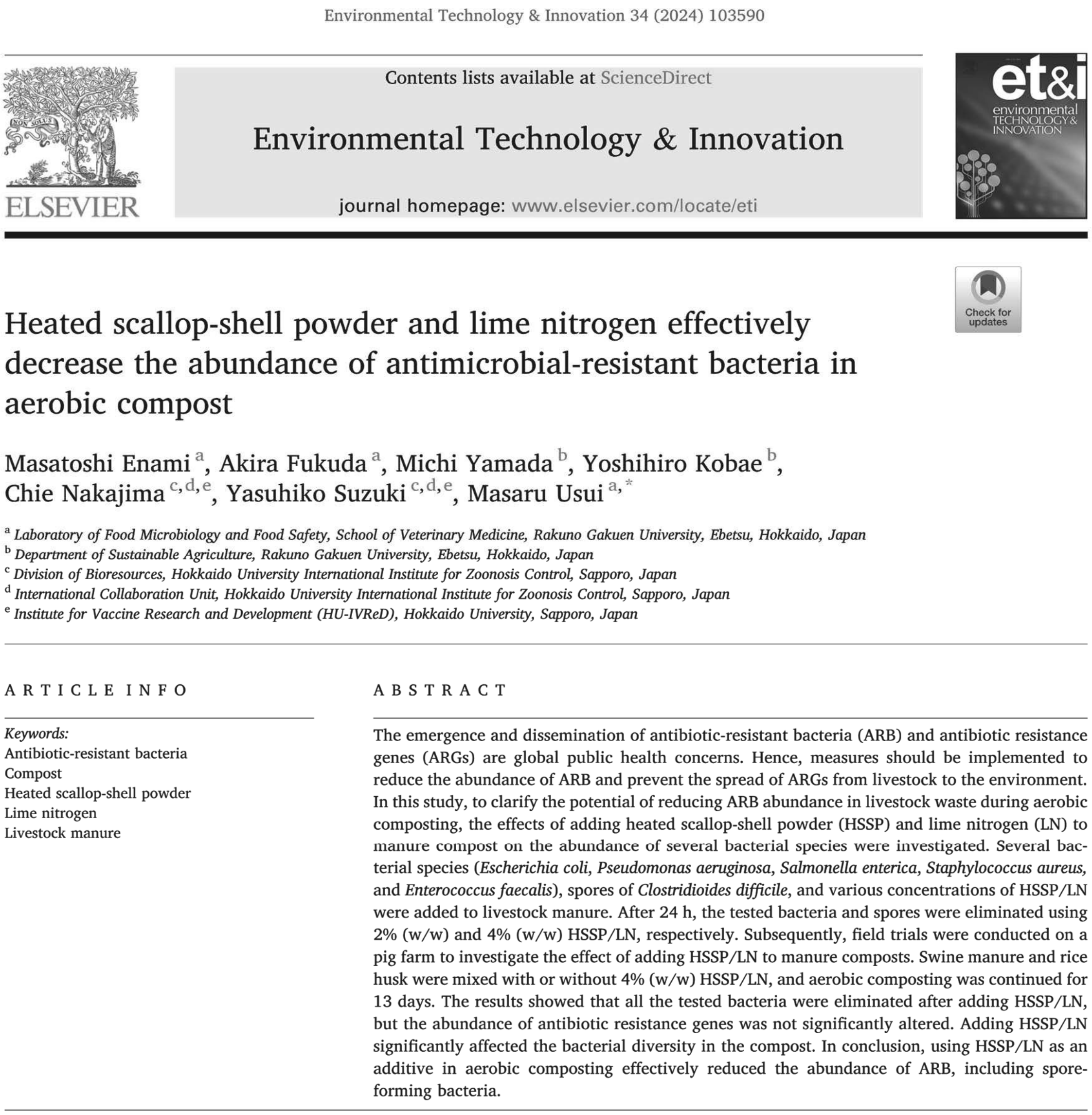
最終責任者 Masaru Usui(Corresponding Author)



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Heated scallop-shell powder and lime nitrogen effectively decrease the abundance of antimicrobial-resistant bacteria in aerobic compost

Masatoshi Enami [a], Akira Fukuda [a], Michi Yamada [b], Yoshihiro Kobae [b],
Chie Nakajima [c,d,e], Yasuhiko Suzuki [c,d,e], Masaru Usui [a,*]

[a] *Laboratory of Food Microbiology and Food Safety, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan*
[b] *Department of Sustainable Agriculture, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan*
[c] *Division of Bioresources, Hokkaido University International Institute for Zoonosis Control, Sapporo, Japan*
[d] *International Collaboration Unit, Hokkaido University International Institute for Zoonosis Control, Sapporo, Japan*
[e] *Institute for Vaccine Research and Development (HU-IVReD), Hokkaido University, Sapporo, Japan*

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ABSTRACT

The emergence and dissemination of antibiotic-resistant bacteria (ARB) and antibiotic resistance genes (ARGs) are global public health concerns. Hence, measures should be implemented to reduce the abundance of ARB and prevent the spread of ARGs from livestock to the environment. In this study, to clarify the potential of reducing ARB abundance in livestock waste during aerobic composting, the effects of adding heated scallop-shell powder (HSSP) and lime nitrogen (LN) to manure compost on the abundance of several bacterial species were investigated. Several bacterial species (*Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella enterica*, *Staphylococcus aureus*, and *Enterococcus faecalis*), spores of *Clostridioides difficile*, and various concentrations of HSSP/LN were added to livestock manure. After 24 h, the tested bacteria and spores were eliminated using 2% (w/w) and 4% (w/w) HSSP/LN, respectively. Subsequently, field trials were conducted on a pig farm to investigate the effect of adding HSSP/LN to manure composts. Swine manure and rice husk were mixed with or without 4% (w/w) HSSP/LN, and aerobic composting was continued for 13 days. The results showed that all the tested bacteria were eliminated after adding HSSP/LN, but the abundance of antibiotic resistance genes was not significantly altered. Adding HSSP/LN significantly affected the bacterial diversity in the compost. In conclusion, using HSSP/LN as an additive in aerobic composting effectively reduced the abundance of ARB, including spore-forming bacteria.

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RESEARCH ARTICLE

Low-frequency transmission and persistence of antimicrobial-resistant bacteria and genes from livestock to agricultural soil and crops through compost application

Akira Fukuda[1], Masato Suzuki[2], Kohei Makita[3], Masaru Usui[1]*

1 Food Microbiology and Food Safety Unit, Division of Preventive Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan, 2 Department of Bacteriology II, National Institute of Infectious Diseases, Tokyo, Japan, 3 Veterinary Epidemiology Unit, Division of Preventive Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan

* usuima@rakuno.ac.jp

Abstract

Livestock excrement is composted and applied to agricultural soils. If composts contain antimicrobial-resistant bacteria (ARB), they may spread to the soil and contaminate cultivated crops. Therefore, we investigated the degree of transmission of ARB and related antimicrobial resistance genes (ARGs) and, as well as clonal transmission of ARB from livestock to soil and crops through composting. This study was conducted at Rakuno Gakuen University farm in Hokkaido, Japan. Samples of cattle feces, solid and liquid composts, agricultural soil, and crops were collected. The abundance of *Escherichia coli*, coliforms, *β*-lactam-resistant *E. coli*, and *β*-lactam-resistant coliforms, as well as the copy numbers of ARG (specifically the *bla* gene related to *β*-lactam-resistant bacteria), were assessed using qPCR through colony counts on CHROMagar ECC with or without ampicillin, respectively, 160 days after compost application. After the application of the compost to the soil, there was an initial increase in *E. coli* and coliform numbers, followed by a subsequent decrease over time. This trend was also observed in the copy numbers of the *bla* gene. In the soil, 5.0 CFU g^{-1} *E. coli* was detected on day 0 (the day post-compost application), and then, *E. coli* was not quantified on 60 days post-application. Through phylogenetic analysis involving single nucleotide polymorphisms (SNPs) and using whole-genome sequencing, it was discovered that clonal $bla_{\text{CTX-M}}$-positive *E. coli* and bla_{TEM}-positive *Escherichia fergusonii* were present in cattle feces, liquid compost, and soil on day 0 as well as 7 days post-application. This showed that livestock-derived ARB were transmitted from compost to soil and persisted for at least 7 days in soil. These findings indicate a potential low-level transmission of livestock-associated bacteria to agricultural soil through composts was observed at low frequency, dissemination was detected. Therefore, decreasing ARB abundance during composting is important for public health.

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Carbapenem and colistin-resistant hypervirulent *Klebsiella pneumoniae*: An emerging threat transcending the egyptian food chain

Rana Fahmi Sabala [a,b], Akira Fukuda [b], Chie Nakajima [c,d,e], Yasuhiko Suzuki [c,d,e], Masaru Usui [b,*], Mohamed Elhadidy [f,g,h,**]

[a] *Department of Food Hygiene and Control, Faculty of Veterinary Medicine, Mansoura University, Mansoura, Egypt*
[b] *Laboratory of Food Microbiology and Food Safety, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan*
[c] *Division of Bioresources, Hokkaido University International Institute for Zoonosis Control, Sapporo, Japan*
[d] *International Collaboration Unit, Hokkaido University International Institute for Zoonosis Control, Sapporo, Japan*
[e] *Division of Research Support, Hokkaido University Institute for Vaccine Research and Development, Sapporo, Japan*
[f] *Center for Genomics, Helmy Institute for Medical Sciences, Zewail City of Science and Technology, Giza, Egypt*
[g] *Biomedical Sciences Program, University of Science and Technology, Zewail City of Science and Technology, Giza, Egypt*
[h] *Department of Bacteriology, Mycology and Immunology, Faculty of Veterinary Medicine, Mansoura University, Mansoura, Egypt*

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ABSTRACT

Background: Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) is a great public health problem and is associated with many disease outbreaks and high mortality rates. Alarmingly, *K. pneumoniae* has been isolated from food in several recent studies. This study aimed to investigate the prevalence and characteristics of CRKP in food samples from Egypt.

Methods: A total of 311 food samples (including 116 minced meat, 92 chicken meat, 75 diced meat, and 28 mutton) were collected from local markets in Egypt and were screened for CRKP with the determination of their antimicrobial resistance profiles. The whole genome sequence was done for 23 CRKP isolates to clarify the relationship between CRKP from food and human cases in Egypt using the SNP core genome. The conjugation probability of the $bla_{\text{NDM-5}}$ harboring plasmid was identified using oriTfinder

Results: CRKP was isolated from 11% (35/311) of the samples, with 45.71% (16/35) of them showing resistance to colistin, one of the last-resort options for treating CRKP-mediated infections. In addition to the carbapenem and colistin resistance, the CRKP isolates frequently exhibited resistance to multiple antimicrobials including β-lactams, fluoroquinolones, aminoglycosides, tetracyclines, and chloramphenicol. In addition, most of the CRKP were potentially hypervirulent *K. pneumoniae* (HvKP) identified as phylogroup Kp1 and of high-risk groups as detected in STs reported in many human outbreaks globally, such as ST383 and ST147. The core-genome phylogeny showed similarities between the isolates from this study and those previously isolated from clinical human samples in Egypt. In addition, analysis of the plasmid on which bla_{NDM} is encoded revealed that several antimicrobial resistance genes such as $bla_{\text{OXA-9}}$, $bla_{\text{CTX-M-15}}$, *aac(6')-Ib, qnrS1,* and several virulence genes are encoded on the same plasmid.

Conclusions: This study is significant for food safety and public health and is important to further identify the change in the epidemiology of CRKP infections, especially the consumption of contaminated food products.

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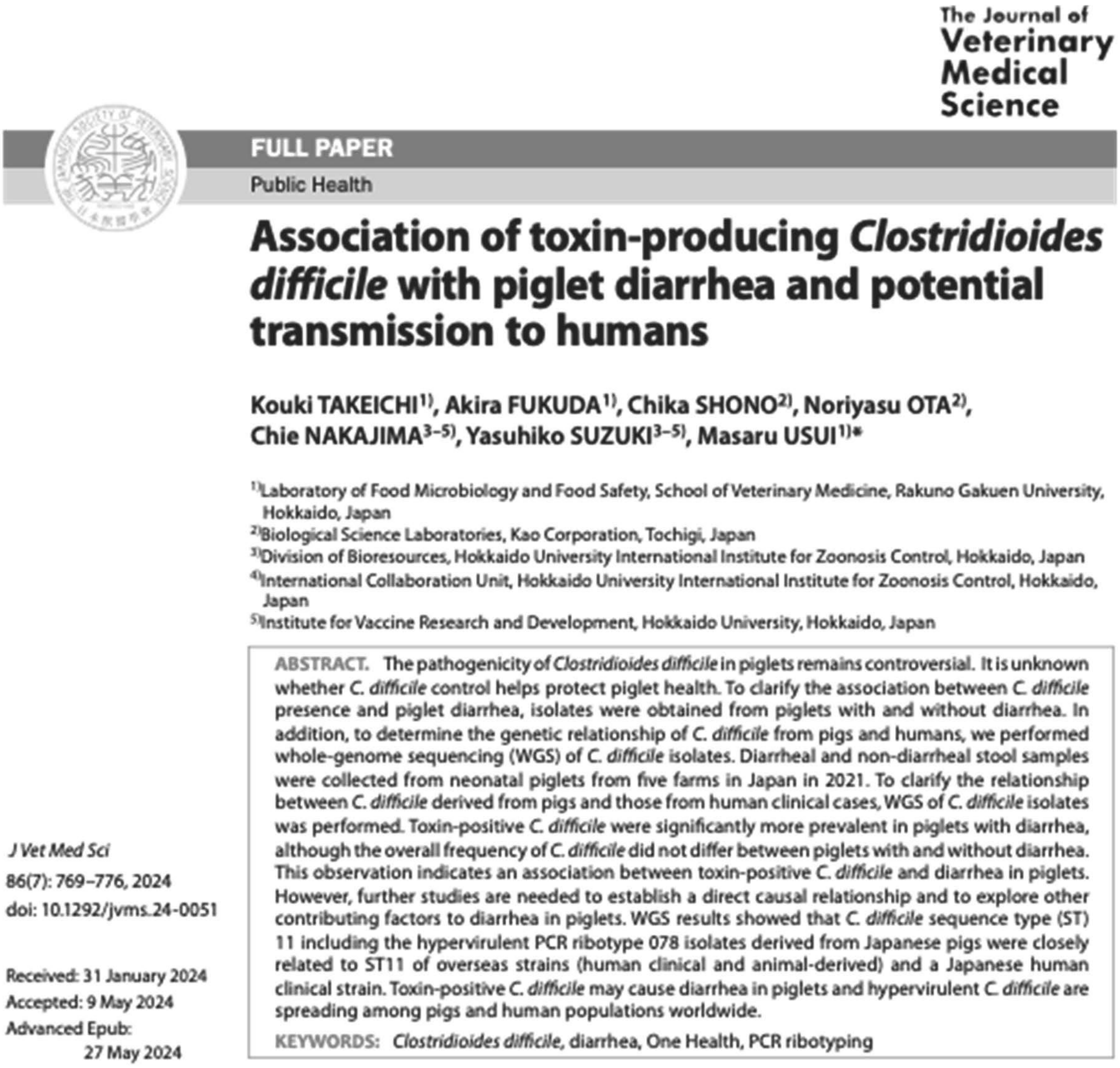

The Journal of
Veterinary
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Science

FULL PAPER

Public Health

Association of toxin-producing *Clostridioides difficile* with piglet diarrhea and potential transmission to humans

Kouki TAKEICHI[1], Akira FUKUDA[1], Chika SHONO[2], Noriyasu OTA[2], Chie NAKAJIMA[3–5], Yasuhiko SUZUKI[3–5], Masaru USUI[1]*

[1]Laboratory of Food Microbiology and Food Safety, School of Veterinary Medicine, Rakuno Gakuen University, Hokkaido, Japan
[2]Biological Science Laboratories, Kao Corporation, Tochigi, Japan
[3]Division of Bioresources, Hokkaido University International Institute for Zoonosis Control, Hokkaido, Japan
[4]International Collaboration Unit, Hokkaido University International Institute for Zoonosis Control, Hokkaido, Japan
[5]Institute for Vaccine Research and Development, Hokkaido University, Hokkaido, Japan

ABSTRACT. The pathogenicity of *Clostridioides difficile* in piglets remains controversial. It is unknown whether *C. difficile* control helps protect piglet health. To clarify the association between *C. difficile* presence and piglet diarrhea, isolates were obtained from piglets with and without diarrhea. In addition, to determine the genetic relationship of *C. difficile* from pigs and humans, we performed whole-genome sequencing (WGS) of *C. difficile* isolates. Diarrheal and non-diarrheal stool samples were collected from neonatal piglets from five farms in Japan in 2021. To clarify the relationship between *C. difficile* derived from pigs and those from human clinical cases, WGS of *C. difficile* isolates was performed. Toxin-positive *C. difficile* were significantly more prevalent in piglets with diarrhea, although the overall frequency of *C. difficile* did not differ between piglets with and without diarrhea. This observation indicates an association between toxin-positive *C. difficile* and diarrhea in piglets. However, further studies are needed to establish a direct causal relationship and to explore other contributing factors to diarrhea in piglets. WGS results showed that *C. difficile* sequence type (ST) 11 including the hypervirulent PCR ribotype 078 isolates derived from Japanese pigs were closely related to ST11 of overseas strains (human clinical and animal-derived) and a Japanese human clinical strain. Toxin-positive *C. difficile* may cause diarrhea in piglets and hypervirulent *C. difficile* are spreading among pigs and human populations worldwide.

KEYWORDS: *Clostridioides difficile*, diarrhea, One Health, PCR ribotyping

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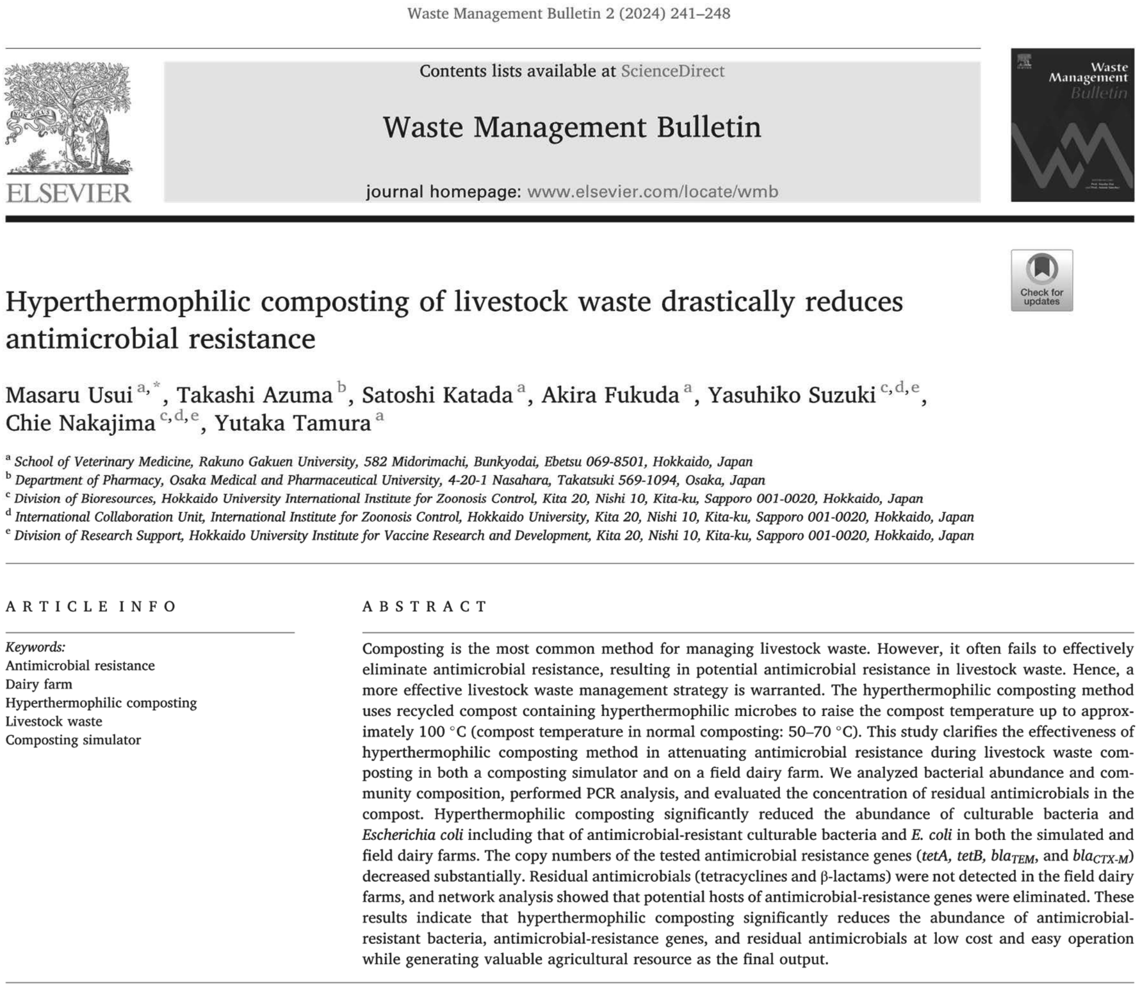

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Hyperthermophilic composting of livestock waste drastically reduces antimicrobial resistance

Masaru Usui [a,*], Takashi Azuma [b], Satoshi Katada [a], Akira Fukuda [a], Yasuhiko Suzuki [c,d,e], Chie Nakajima [c,d,e], Yutaka Tamura [a]

[a] *School of Veterinary Medicine, Rakuno Gakuen University, 582 Midorimachi, Bunkyodai, Ebetsu 069-8501, Hokkaido, Japan*
[b] *Department of Pharmacy, Osaka Medical and Pharmaceutical University, 4-20-1 Nasahara, Takatsuki 569-1094, Osaka, Japan*
[c] *Division of Bioresources, Hokkaido University International Institute for Zoonosis Control, Kita 20, Nishi 10, Kita-ku, Sapporo 001-0020, Hokkaido, Japan*
[d] *International Collaboration Unit, International Institute for Zoonosis Control, Hokkaido University, Kita 20, Nishi 10, Kita-ku, Sapporo 001-0020, Hokkaido, Japan*
[e] *Division of Research Support, Hokkaido University Institute for Vaccine Research and Development, Kita 20, Nishi 10, Kita-ku, Sapporo 001-0020, Hokkaido, Japan*

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Composting simulator

ABSTRACT

Composting is the most common method for managing livestock waste. However, it often fails to effectively eliminate antimicrobial resistance, resulting in potential antimicrobial resistance in livestock waste. Hence, a more effective livestock waste management strategy is warranted. The hyperthermophilic composting method uses recycled compost containing hyperthermophilic microbes to raise the compost temperature up to approximately 100 °C (compost temperature in normal composting: 50–70 °C). This study clarifies the effectiveness of hyperthermophilic composting method in attenuating antimicrobial resistance during livestock waste composting in both a composting simulator and on a field dairy farm. We analyzed bacterial abundance and community composition, performed PCR analysis, and evaluated the concentration of residual antimicrobials in the compost. Hyperthermophilic composting significantly reduced the abundance of culturable bacteria and *Escherichia coli* including that of antimicrobial-resistant culturable bacteria and *E. coli* in both the simulated and field dairy farms. The copy numbers of the tested antimicrobial resistance genes (*tetA, tetB*, bla_{TEM}, and $bla_{CTX\text{-}M}$) decreased substantially. Residual antimicrobials (tetracyclines and β-lactams) were not detected in the field dairy farms, and network analysis showed that potential hosts of antimicrobial-resistance genes were eliminated. These results indicate that hyperthermophilic composting significantly reduces the abundance of antimicrobial-resistant bacteria, antimicrobial-resistance genes, and residual antimicrobials at low cost and easy operation while generating valuable agricultural resource as the final output.

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最終責任者　Masaru Usui (First Author and Corresponding Author)

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RESEARCH

Rapid detection of causative bacteria including multiple infections of bovine respiratory disease using 16S rRNA amplicon-based nanopore sequencing

Shingo Okamura[1,2] · **Akira Fukuda**[1] · **Masaru Usui**[1]

Received: 24 June 2024 / Accepted: 20 September 2024

Abstract

Bovine respiratory disease (BRD) is a multifaceted condition that poses a primary challenge in calf rearing. Viruses and bacteria are etiological agents of BRD. Viral BRD is typically managed symptomatically, whereas bacterial BRD is predominantly managed through the empirical administration of antimicrobials. However, this empirical administration has raised concerns regarding the emergence of antimicrobial-resistant bacteria. Thus, rapid identification of pathogenic bacteria and judicious selection of antimicrobials are required. This study evaluated the usefulness of 16S rRNA analysis through nanopore sequencing for the rapid identification of BRD-causing bacteria. A comparative evaluation of nanopore sequencing and traditional culture method was performed on 100 calf samples detected with BRD. Nanopore sequencing facilitated the identification of bacteria at the species level in bovine nasal swabs, ear swabs, and lung tissue samples within approximately 6 h. Of the 92 samples in which BRD-causing bacteria were identified via nanopore sequencing, 82 (89%) were concordant with the results of culture isolation. In addition, the occurrence of multiple infections exceeded that of singular infections. These results suggest that 16S rRNA sequencing via nanopore technology is effective in reducing analysis time and accurately identifying BRD-causing bacteria. This method is particularly advantageous for the initial detectable screening of BRD.

Keywords Bovine respiratory disease · Nanopore sequence · 16S rRNA sequencing · BRD-causing bacteria

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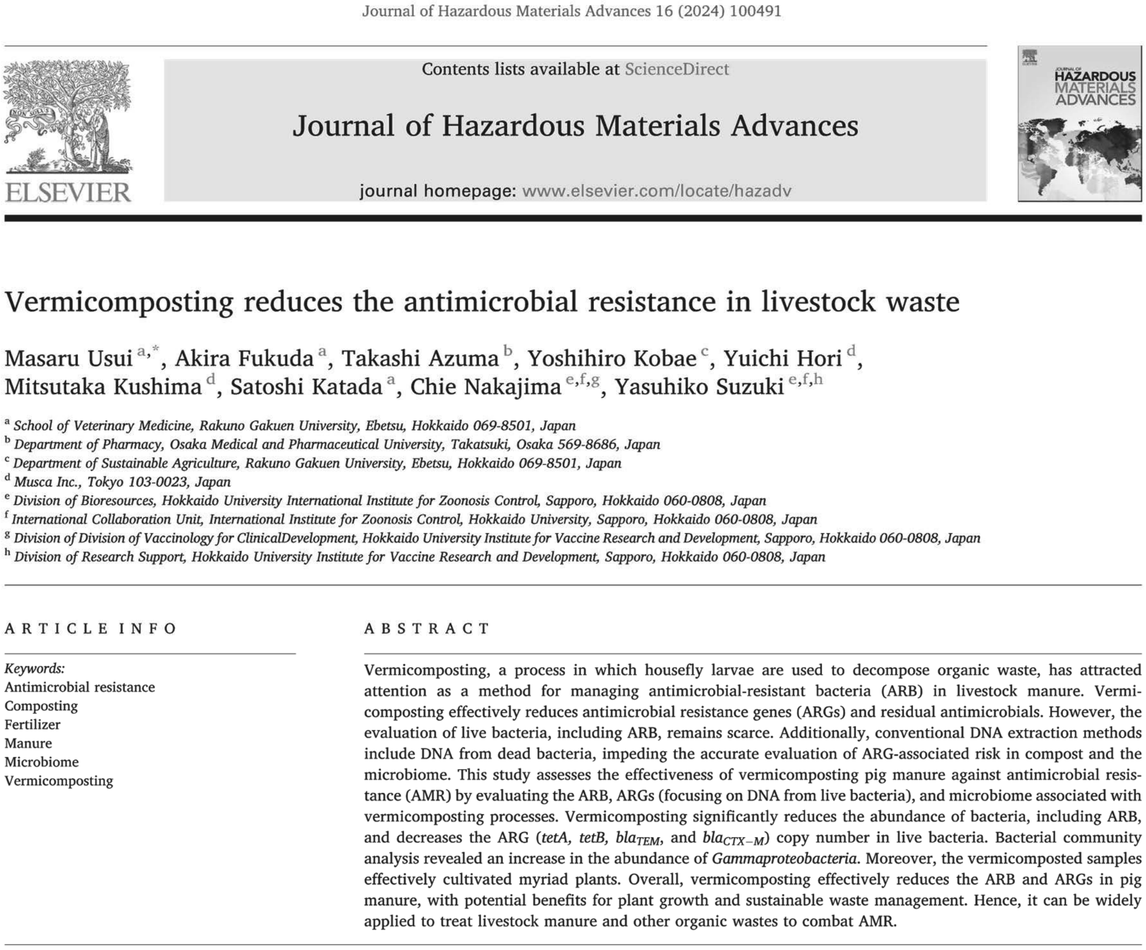

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Vermicomposting reduces the antimicrobial resistance in livestock waste

Masaru Usui [a,*], Akira Fukuda [a], Takashi Azuma [b], Yoshihiro Kobae [c], Yuichi Hori [d], Mitsutaka Kushima [d], Satoshi Katada [a], Chie Nakajima [e,f,g], Yasuhiko Suzuki [e,f,h]

[a] *School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan*
[b] *Department of Pharmacy, Osaka Medical and Pharmaceutical University, Takatsuki, Osaka 569-8686, Japan*
[c] *Department of Sustainable Agriculture, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan*
[d] *Musca Inc., Tokyo 103-0023, Japan*
[e] *Division of Bioresources, Hokkaido University International Institute for Zoonosis Control, Sapporo, Hokkaido 060-0808, Japan*
[f] *International Collaboration Unit, International Institute for Zoonosis Control, Hokkaido University, Sapporo, Hokkaido 060-0808, Japan*
[g] *Division of Division of Vaccinology for ClinicalDevelopment, Hokkaido University Institute for Vaccine Research and Development, Sapporo, Hokkaido 060-0808, Japan*
[h] *Division of Research Support, Hokkaido University Institute for Vaccine Research and Development, Sapporo, Hokkaido 060-0808, Japan*

ARTICLE INFO

Keywords:
Antimicrobial resistance
Composting
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Microbiome
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ABSTRACT

Vermicomposting, a process in which housefly larvae are used to decompose organic waste, has attracted attention as a method for managing antimicrobial-resistant bacteria (ARB) in livestock manure. Vermicomposting effectively reduces antimicrobial resistance genes (ARGs) and residual antimicrobials. However, the evaluation of live bacteria, including ARB, remains scarce. Additionally, conventional DNA extraction methods include DNA from dead bacteria, impeding the accurate evaluation of ARG-associated risk in compost and the microbiome. This study assesses the effectiveness of vermicomposting pig manure against antimicrobial resistance (AMR) by evaluating the ARB, ARGs (focusing on DNA from live bacteria), and microbiome associated with vermicomposting processes. Vermicomposting significantly reduces the abundance of bacteria, including ARB, and decreases the ARG (*tetA*, *tetB*, bla_{TEM}, and bla_{CTX-M}) copy number in live bacteria. Bacterial community analysis revealed an increase in the abundance of *Gammaproteobacteria*. Moreover, the vermicomposted samples effectively cultivated myriad plants. Overall, vermicomposting effectively reduces the ARB and ARGs in pig manure, with potential benefits for plant growth and sustainable waste management. Hence, it can be widely applied to treat livestock manure and other organic wastes to combat AMR.

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AMERICAN SOCIETY FOR MICROBIOLOGY | Microbiology Spectrum

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| Antimicrobial Chemotherapy | Research Article

WQ-3810, a fluoroquinolone with difluoropyridine derivative as the R1 group exerts high potency against quinolone-resistant *Campylobacter jejuni*

Kentaro Koide,[1,2] Hyun Kim,[2] Matthew V. X. Whelan,[3] Lawrence P. Belotindos,[1] Wimonrat Tanomsridachchai,[1] Ruchirada Changkwanyeun,[4] Masaru Usui,[5] Tadhg Ó Cróinín,[3] Jeewan Thapa,[1] Chie Nakajima,[1,6,7] Yasuhiko Suzuki[1,6,7]

AUTHOR AFFILIATIONS See affiliation list on p. 12.

ABSTRACT Quinolone-resistant *Campylobacter jejuni* have been increasing worldwide. Quinolones exert their antibacterial activity by inhibiting DNA gyrase, but most of the isolates acquire quinolone resistance via an amino acid substitution in the A subunit of DNA gyrase. WQ-3810 is a quinolone antibiotic that has been reported to have high potency even to DNA gyrase with amino acid substitutions in several bacterial species; however, there was no information on *C. jejuni*. Hence, this study aimed to evaluate the activity of WQ-3810 to inhibit wild-type/mutant DNA gyrases of *C. jejuni* and the bacterial growth for accessing the potency for the treatment of quinolone-resistant *C. jejuni* infection. The inhibitory activity of WQ-3810 was assessed and compared with ciprofloxacin and nalidixic acid by calculating the half maximal inhibitory concentration (IC_{50}) against wild-type/mutant DNA gyrases. Next, the minimum inhibitory concentration (MIC) of WQ-3810 and five other quinolones was determined for *C. jejuni* including quinolone-resistant strains with amino acid substitutions in GyrA. Furthermore, the interaction between WQ-3810 and wild-type/mutant DNA gyrase was speculated using docking simulations. The IC_{50} of WQ-3810 against wild-type DNA gyrase was 1.03 μg/mL and not different from that of ciprofloxacin. However, those of WQ-3810 against mutant DNA gyrases were much lower than ciprofloxacin. The MICs of WQ-3810 ranged <0.016–0.031 μg/mL and were the lowest against both quinolone-susceptible and quinolone-resistant strains among the examined quinolones. The results obtained by the docking simulation agreed well with this observation. WQ-3810 seems to be a promising antimicrobial agent for the infections caused by quinolone-resistant *C. jejuni*.

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Article

On-Site Inactivation for Disinfection of Antibiotic-Resistant Bacteria in Hospital Effluent by UV and UV-LED

Takashi Azuma [1,*], Masaru Usui [2], Tomohiro Hasei [1] and Tetsuya Hayashi [1]

[1] Department of Pharmacy, Osaka Medical and Pharmaceutical University, Takatsuki 569-1094, Japan; tomohiro.hasei@ompu.ac.jp (T.H.); tetsuhaya456@gmail.com (T.H.)
[2] Food Microbiology and Food Safety, Department of Health and Environmental Sciences, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu 069-8501, Japan; usuima@rakuno.ac.jp
[*] Correspondence: takashi.azuma@ompu.ac.jp; Tel./Fax: +81-72-690-1055

Abstract: The problem of antimicrobial resistance (AMR) is not limited to the medical field but is also becoming prevalent on a global scale in the environmental field. Environmental water pollution caused by the discharge of wastewater into aquatic environments has caused concern in the context of the sustainable development of modern society. However, there have been few studies focused on the treatment of hospital wastewater, and the potential consequences of this remain unknown. This study evaluated the efficacy of the inactivation of antimicrobial-resistant bacteria (AMRB) and antimicrobial resistance genes (AMRGs) in model wastewater treatment plant (WWTP) wastewater and hospital effluent based on direct ultraviolet (UV) light irradiation provided by a conventional mercury lamp with a peak wavelength of 254 nm and an ultraviolet light-emitting diode (UV-LED) with a peak emission of 280 nm under test conditions in which the irradiance of both was adjusted to the same intensity. The overall results indicated that both UV- and UV-LED-mediated disinfection effectively inactivated the AMRB in both wastewater types (>99.9% after 1–3 min of UV and 3 min of UV-LED treatment). Additionally, AMRGs were also removed (0.2–1.4 $\log_{10}$ for UV 254 nm and 0.1–1.3 $\log_{10}$ for UV 280 nm), and notably, there was no statistically significant decrease ($p < 0.05$) in the AMRGs between the UV and UV-LED treatments. The results of this study highlight the importance of utilizing a local inactivation treatment directly for wastewater generated by a hospital prior to its flow into a WWTP as sewage. Although additional disinfection treatment at the WWTP is likely necessary to remove the entire quantity of AMRB and AMRGs, the present study contributes to a significant reduction in the loads of WWTP and urgent prevention of the spread of infectious diseases, thus alleviating the potential threat to the environment and human health risks associated with AMR problems.

Keywords: hospital wastewater; ultraviolet-light emitting diode (UV-LED); UV lamp; disinfection; antimicrobial-resistant bacteria (AMRB); antimicrobial resistance genes (AMRGs); wastewater treatment plant (WWTP); river environment

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Makita et al.
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CABI One Health

RESEARCH

Quantitative release assessment for beta-lactamase-producing *Escherichia coli* of dairy origin into vegetables

Kohei Makita[1]*, Dongsheng Zhang[1], Ayaka Okamura[1], Akira Fukuda[1], Natsumi Tokunaga[1], Tetsuo Asai[2], Yoko Shimazaki[3] and Masaru Usui[1]

Abstract

Outbreaks of food poisoning associated with vegetables contaminated with *Escherichia coli* have been reported globally. This study was conducted to assess the probability of releasing beta-lactamase-producing *E. coli* of dairy farm origin into vegetables in Japan. A release assessment model connecting dairy farms to vegetable farms was developed. Data on the indicated diseases and antimicrobial use in dairy cattle were obtained from the agricultural insurance program in Hokkaido Prefecture between 2016 and 2019. Data on *bla*-harboring *E. coli* in cattle were obtained from the Japan Veterinary Antimicrobial Resistance Monitoring System. Microbiological field sampling was conducted at dairy and vegetable farms. Inoculation experiments in vegetables were conducted. All processes in the model simulation were iterated for 1000 times. The estimated proportion of dairy farms holding cattle with *bla*-harboring *E. coli* was 6.00% (95% CI: 4.81–7.35%). Beta-lactams were used in 71.76% (333,098/464,204 average annual cases) of indicated diseases. The estimated concentration of *bla*-harboring *E. coli* in mixed fresh manure at affected farms was 3.33 $\log_{10}$ CFU/g (95% CI: 3.33–3.34). The concentrations were reduced to 0.83 (95% CI: 0.34–1.25) and −0.54 $\log_{10}$ CFU/g (95% CI: −1.04 to −0.05) in soil after immature manure, and slurry spraying, respectively. The estimated concentrations in the soil of fields of radish, leafy vegetables, tomato, and spring-seeded and autumn-seeded onions at harvest were −1.99 (95% CI: −2.48 to −1.57), −2.87 (95% CI: −3.36 to −2.42), −3.82 (95% CI: −4.32 to −3.40), −5.36 (95% CI: −5.85 to −4.93), and −5.94 (95% CI: −6.43 to −5.52) $\log_{10}$ CFU/g, respectively. The concentrations in the bodies of leafy green spinach and lettuce were −9.88 (95% CI: −10.38 to −9.43) and −10.91 (95% CI, −11.52 to −8.05) $\log_{10}$ CFU/g, respectively. The probability of ingesting *bla*-harboring *E. coli* of dairy origin with raw vegetables in Japan was thus assessed to be very low.

One Health impact statement

This study applied a release assessment in the World Organisation for Animal Health framework for antimicrobial resistance risk assessment to connect the antimicrobial use for dairy cattle, manure production and vegetable farming. As vegetable is often consumed raw, the assessment is directly associated with human health. Although the environmental continuum was not explored, the reduction of the hazard on the soil of vegetable farms was considered. The study involved the engagement with dairy and vegetable farmers and the agriculture industry in understanding farming behavior and value chain. The approach in this study can be applied to the complex problems across the animal-human-environment interface.

Keywords: risk assessment, vegetable, *Escherichia coli*, dairy, beta-lactams, manure

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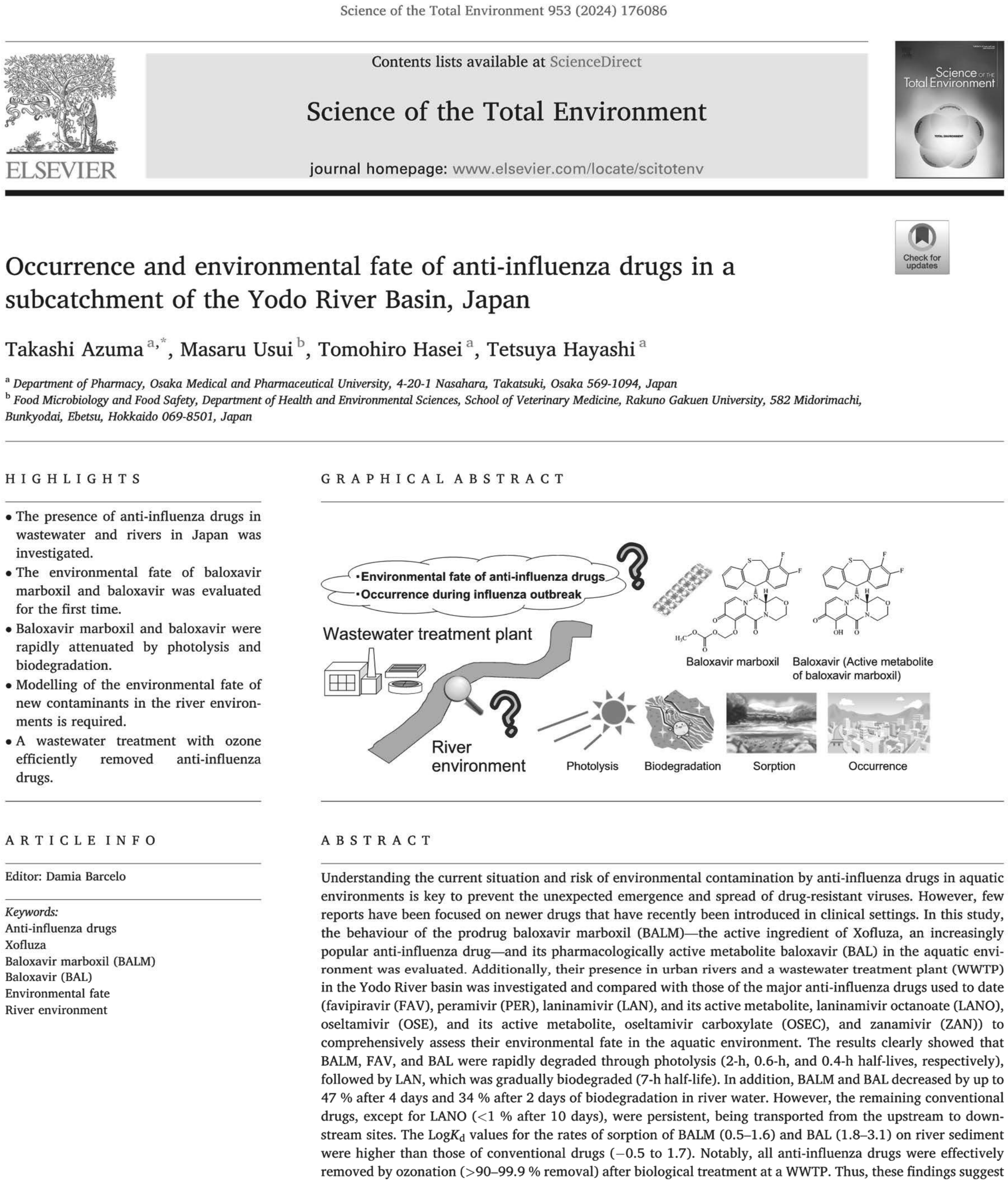

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Occurrence and environmental fate of anti-influenza drugs in a subcatchment of the Yodo River Basin, Japan

Takashi Azuma [a,*], Masaru Usui [b], Tomohiro Hasei [a], Tetsuya Hayashi [a]

[a] Department of Pharmacy, Osaka Medical and Pharmaceutical University, 4-20-1 Nasahara, Takatsuki, Osaka 569-1094, Japan
[b] Food Microbiology and Food Safety, Department of Health and Environmental Sciences, School of Veterinary Medicine, Rakuno Gakuen University, 582 Midorimachi, Bunkyodai, Ebetsu, Hokkaido 069-8501, Japan

HIGHLIGHTS

- The presence of anti-influenza drugs in wastewater and rivers in Japan was investigated.
- The environmental fate of baloxavir marboxil and baloxavir was evaluated for the first time.
- Baloxavir marboxil and baloxavir were rapidly attenuated by photolysis and biodegradation.
- Modelling of the environmental fate of new contaminants in the river environments is required.
- A wastewater treatment with ozone efficiently removed anti-influenza drugs.

GRAPHICAL ABSTRACT

ARTICLE INFO

Editor: Damia Barcelo

Keywords:
Anti-influenza drugs
Xofluza
Baloxavir marboxil (BALM)
Baloxavir (BAL)
Environmental fate
River environment

ABSTRACT

Understanding the current situation and risk of environmental contamination by anti-influenza drugs in aquatic environments is key to prevent the unexpected emergence and spread of drug-resistant viruses. However, few reports have been focused on newer drugs that have recently been introduced in clinical settings. In this study, the behaviour of the prodrug baloxavir marboxil (BALM)—the active ingredient of Xofluza, an increasingly popular anti-influenza drug—and its pharmacologically active metabolite baloxavir (BAL) in the aquatic environment was evaluated. Additionally, their presence in urban rivers and a wastewater treatment plant (WWTP) in the Yodo River basin was investigated and compared with those of the major anti-influenza drugs used to date (favipiravir (FAV), peramivir (PER), laninamivir (LAN), and its active metabolite, laninamivir octanoate (LANO), oseltamivir (OSE), and its active metabolite, oseltamivir carboxylate (OSEC), and zanamivir (ZAN)) to comprehensively assess their environmental fate in the aquatic environment. The results clearly showed that BALM, FAV, and BAL were rapidly degraded through photolysis (2-h, 0.6-h, and 0.4-h half-lives, respectively), followed by LAN, which was gradually biodegraded (7-h half-life). In addition, BALM and BAL decreased by up to 47 % after 4 days and 34 % after 2 days of biodegradation in river water. However, the remaining conventional drugs, except for LANO (<1 % after 10 days), were persistent, being transported from the upstream to downstream sites. The LogK_d values for the rates of sorption of BALM (0.5–1.6) and BAL (1.8–3.1) on river sediment were higher than those of conventional drugs (−0.5 to 1.7). Notably, all anti-influenza drugs were effectively removed by ozonation (>90–99.9 % removal) after biological treatment at a WWTP. Thus, these findings suggest

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Crop contamination evaluation by antimicrobial-resistant bacteria via livestock waste compost-fertilized field soil

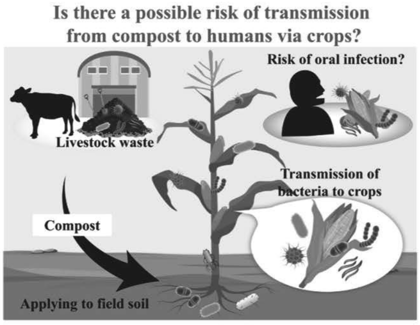
Yoshihiro Suzuki[a,*], Tomoyuki Horita[a], Emi Nishimura[b], Hui Xie[b], Soichiro Tamai[b], Ikuo Kobayashi[c], Akira Fukuda[d], Masaru Usui[d]

[a] *Department of Civil and Environmental Engineering, Faculty of Engineering, University of Miyazaki, Miyazaki 889–2192, Japan*
[b] *Department of Environment and Resource Sciences, Interdisciplinary Graduate School of Agriculture and Engineering, University of Miyazaki, Miyazaki 889–2192, Japan*
[c] *Sumiyoshi Livestock Science Station, Faculty of Agriculture, University of Miyazaki, Miyazaki 880–0192, Japan*
[d] *Laboratory of Food Microbiology and Food Safety, Department of Health and Environmental Sciences, School of Veterinary Medicine, Rakuno Gakuen University, Hokkaido 069–8501, Japan*

HIGHLIGHTS

- Ampicillin (AMP)-resistant *E. coli* was absent in all samples during the full survey.
- Numerous AMP-resistant coliforms were present in field solids and corn stems/roots.
- *Enterobacter bugandensis* and *E. asburiae* were the major AMP-resistant coliforms.
- AMP-resistant coliform spreading from fully matured compost to crops is unlikely.
- Use of fully matured compost is the most important for safe farm management.

GRAPHICAL ABSTRACT



ARTICLE INFO

Keywords:
Escherichia coli
Coliform bacteria
Antimicrobial resistance
Corn farm
Compost

ABSTRACT

Antimicrobial-resistant bacteria, selected by antimicrobial agent use in livestock, are emerging and their spread to crops from feces via composting represents a public health concern as they are ultimately transmitted to humans. In this study, we investigated *Escherichia coli* and other ampicillin (AMP)-resistant coliform spread conditions in field soil and dent corn, an agricultural crop, on a livestock-derived compost-applying farm. No AMP-resistant *E. coli* was detected in any samples of field soil and dent corn. In contrast, AMP-resistant and extended-spectrum β-lactam (ESBL) producing coliforms were consistently present in field soil and dent corn during the entire study period. In particular, extremely high AMP-resistant coliform levels were detected in dent corn stems and roots. AMP-resistant coliform detection in crops is pivotal and raises significant concerns regarding antimicrobial-resistant bacterial spread. Furthermore, AMP-resistant coliform isolate identification defined *Enterobacter bugandensis* and *Enterobacter asburiae* as the dominant species among AMP-resistant

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最終責任者　Yoshihiro Suzuki (First Author and Corresponding Author)

獣医解剖学（Veterinary Anatomy）

Takafumi Watanabe

Professor

教授　渡邉　敬文

I. 筆頭または責任著者　＜First or Corresponding Author＞

1）Morphological and biochemical characterization of Holstein cow skin at the tail root region susceptible to Chorioptes bovis and texanus parasitism.
Fujii M, Hashimoto H, Fukumoto S, Maeda N, Hasegawa Y, Iwasaki T, Hosotani M, Ueda H, **Watanabe T.**
J Vet Med Sci 86:877–884. 2024. doi: 10.1292/jvms.24-0057.

II.　その他　＜Others＞

1）Laminin 511 E8 fragment promotes to form basement membrane-like structure in human skin equivalents.
Fujisaki H, **Watanabe T**, Yoshihara S, Fukuda H, Tomono Y, Tometsuka C, Mizuno K, Nishiyama T, Hattori S.
Regen Ther 26:717–728. 2024. doi: 10.1016/j.reth.2024.08.014.

The Journal of
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FULL PAPER
Anatomy

Morphological and biochemical characterization of Holstein cow skin at the tail root region susceptible to *Chorioptes bovis* and *texanus* parasitism

Emi FUJII[1,2], Hotaka HASHIMOTO[1], Shin-ichiro FUKUMOTO[1], Naoyuki MAEDA[3], Yasuhiro HASEGAWA[3], Tomohito IWASAKI[3] Marina HOSOTANI[1], Hiromi UEDA[1], Takafumi WATANABE[1]*

[1] Department of Veterinary Anatomy, School of Veterinary Medicine, Rakuno Gakuen University, Hokkaido, Japan
[2] Shikaoi Veterinary Clinic, Hokkaido NOSAI, Hokkaido, Japan
[3] Department of Food Science and Human Wellness, College of Agriculture, Food and Environment Science, Rakuno Gakuen University, Hokkaido, Japan

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ABSTRACT. Cattle mange causes extreme itchiness, and the associated stress is an animal welfare concern that leads to economic losses due to decreased cattle productivity and deworming costs. This study investigated the reason why Chorioptic mites, *C. bovis* and *C. texanus*, preferentially infest the tail root region (rTR) and performed histological and biochemical analysis focusing on the volatile components of host odors that serve as the starting point for infestation of parasitic arthropods. Skin samples were taken from the rTR, lateral abdominal, and central masseteric, with the latter two designated as comparison sites. The two and three-dimensional histological analysis measured each sebaceous and sweat gland percentage per unit volume. The q-PCR analyzed the expression levels of *ALDH1A1* and *LOC785756*, which are genes associated with volatile odoriferous compounds that serve as repellency and attractive messengers for ticks. Immunohistochemistry stained three sites with anti-androgen binding protein beta-like (ABPβ-like), encoded by *LOC785756*, antibody. The three-dimensional analysis showed that sebaceous glands in the rTR tend to be more continuous and existed in larger masses than in other regions. The expression level of *LOC785756* was significantly higher in the rTR, and immunohistochemistry revealed the presence of ABPβ-like in the sebaceous gland with strong positive signals in the rTR. These results suggest that *C. bovis/texanus* selectively infests the rTR because that skin has well-developed sebaceous glands, including a large amount of ABPβ-like, which acts as a mite attractant.

KEYWORDS: *Chorioptes*, Holstein, parasitism, sebaceous gland, skin

Ectoparasites cause several diseases in livestock animals, including cattle mange, which is the widespread skin disease worldwide [5, 11, 15, 22, 23]. Cattle mange causes extreme itchiness, and the associated stress is an animal welfare concern that leads to economic losses due to decreased cattle productivity and deworming costs [5, 6, 23]. Ivermectin, eprinomectin, moxidectin, and doramectin are commonly used for deworming [4, 13, 15, 16, 23]. However, the parasitic infestation may recur and periodic deworming is therefore recommended [23].

Mange symptoms include itching, hair loss, injury, bleeding, and thickening of the skin at the parasite site. It has been suggested that mite feces and saliva are allergens that cause allergic dermatitis in their hosts [6, 10], but the symptoms vary depending on the species of causative mite [5, 15, 16, 22, 23]. Cattle mange is caused by mite parasitism from three genera of the suborder Astigmata, including *Sarcoptes*, *Psoroptes*, and *Chorioptes* [16, 23]. Behavior and morphology of these three genera of mite vary widely depending on feeding habitat [1–3, 5, 6, 15, 23]. *Sarcoptes* are latent mites that tunnel into the epidermis and feed on intercellular (lymph) fluid. The legs are short, and all leg ends have claws to facilitate burrowing into the epidermis [3]. *Psoroptes* are non-burrowing mites that feed superficially on lipid emulsion of the lymph, skin cells, and skin exudates by abrading the epidermis [1, 6, 10]. *Psoroptes* have a terminal sucker on a relatively long jointed pre-tarsus [1]. *Chorioptes* is non-burrowing mites that live on the skin surface

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*Correspondence to: Watanabe T: t-watanabe@rakuno.ac.jp, Department of Veterinary Anatomy, School of Veterinary Medicine, Rakuno Gakuen University, Midorimachi 582, Bunkyodai, Ebetsu, Hokkaido 069-8501, Japan

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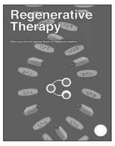

Original Article

Laminin 511 E8 fragment promotes to form basement membrane-like structure in human skin equivalents

Hitomi Fujisaki [a], [*], Takafumi Watanabe [b], Shusuke Yoshihara [b], Hideki Fukuda [b], Yasuko Tomono [c], Chisa Tometsuka [a], Kazunori Mizuno [a], Toshio Nishiyama [d], Shunji Hattori [a]

[a] *Nippi Research Institute of Biomatrix, 520-11 Kuwabara, Toride, Ibaraki 302-0017, Japan*
[b] *Laboratory of Veterinary Anatomy, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan*
[c] *Sigei Medical Research Institute, Okayama, Japan*
[d] *Tokyo University of Agriculture and Technology, Fuchu, Tokyo, Japan*

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ABSTRACT

Introduction: Laminin 511 (LM511), a component of the skin basement membrane (BM), is known to enhance the adhesion of some cell types and it has been reported to affect cell behavior. A recombinant fragment consisting of the integrin recognition site; E8 region of LM511 (511E8) has also been studied. 511E8 has been reported by many as a superior culture substrate. However, the effects of 511E8 on human skin cells remain unclear. In this study, we added 511E8 during the culture period of a reconstituted skin equivalent (SE) and investigated its effect on the formation of BM-like structures.
Methods: SEs were formed by air-liquid culture of human foreskin keratinocytes (HFKs) on contracted type I collagen (Col-I) gels containing human fibroblasts. We compared the BM-like structures formed with and without 511E8 during HFKs culture periods. Morphological analysis, gene expression analysis of extracellular matrix components, and localization analysis of 511E8 in order to identify where 511E8 works were performed.
Results: Immunohistochemical observation by light microscopy showed an accumulation of BM components between the gels and cell layers regardless of the addition of 511E8. There was a stronger and more continuous positive staining for LM $\alpha3$, type IV collagen, and type VII collagen in the 511E8-added group compared to the no-added group. Transmission electron microscopic observation showed that the continuity of BM-like structures was increased with the addition of 511E8. Furthermore, gene expression analysis showed that the 511E8 addition increased some BM component genes expression, with collagen type IV and type VII $\alpha1$ chains showing significant increases. His-tagged 511E8 was stained around the basal cells of HFK layers, not in basal regions. Co-staining with anti-His-tag and anti-integrin $\beta1$ antibodies revealed the co-localization of theses in some intercellular regions among basal cells.
Conclusion: These results suggest that 511E8 effected on HFKs, enhancing the production of BM components and strengthening the anchoring between the Col-I gels and the HFK layers.

1. Introduction

Laminin (LM) is a heterotrimeric protein consisting of α-, β-, and γ-chains that forms a superfamily and influences cell behavior such as epithelial cell adhesion and proliferation. In human, five types of α-chains ($\alpha1$-$\alpha5$), three β-chains ($\beta1$-$\beta3$), and three γ-chains ($\gamma1$-$\gamma3$) have been reported. More than 12 LM isoforms have been identified by combining them, and their tissue localization has been reported [1]. Laminin 332 (LM332), is composed of $\alpha3$, $\beta3$, and $\gamma2$

Abbreviations: BM, basement membrane; Col-I, type I collagen; Col-III, type III collagen; Col-IV, type IV collagen; Col-VII, type VII collagen; Col-XII, type XII collagen; Col-XVII, type XVII collagen; DAPI 4′, 6-diamidino-2-phenylindole; DMEM, Dulbecco's Modified Eagle's Medium; FACIT, fibril associated collagen with interrupted triple helices; FBS, fetal bovine serum; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; HE, hematoxylin and eosin; HFFs, human foreskin fibroblasts; HFKs, human foreskin keratinocytes; iPS, induced Pluripotent Stem; LM, laminin; PBS (−), phosphate buffered saline without calcium and magnesium; qPCR, quantitative polymerase chain reaction; SE, skin equivalent; TEM, transmission electron microscopy; 511E8, E8 region fragment of LM511.

[*] Corresponding author.
E-mail address: fujisaki@nippi-inc.co.jp (H. Fujisaki).

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最終責任者　Shunji Hattori (Corresponding Author)

獣医麻酔学（Veterinary Anesthesiology）

Kazuto Yamashita

Professor

教授　山下　和人

I. 筆頭または責任著者　＜First or Corresponding Author＞

II.　その他　＜Others＞

1） The anti-inflammatory effects of Fuzapladib in an endotoxemic porcine model.
Sugita C, Itami T, Miyasho T, Chen IY, Hirokawa T, Tsukui H, Kato M, Shibuya M, Sano Y, Kato K, **Yamashita K.**
J Vet Med Sci 86:1145–1155. 2024. doi: 10.1292/jvms.24-0190.

2） Cardiorespiratory effects of intramuscular alfaxalone combined with low-dose medetomidine and butorphanol in dogs anesthetized with sevoflurane.
Kato K, Itami T, Oyama N, **Yamashita K.**
Open Vet J 14: 1251–1258. 2024. doi: 10.5455/OVJ.2024.v14.i5.20.

3） Estimating the change in pleural pressure using the change in central venous pressure in various clinical scenarios: a pig model study.
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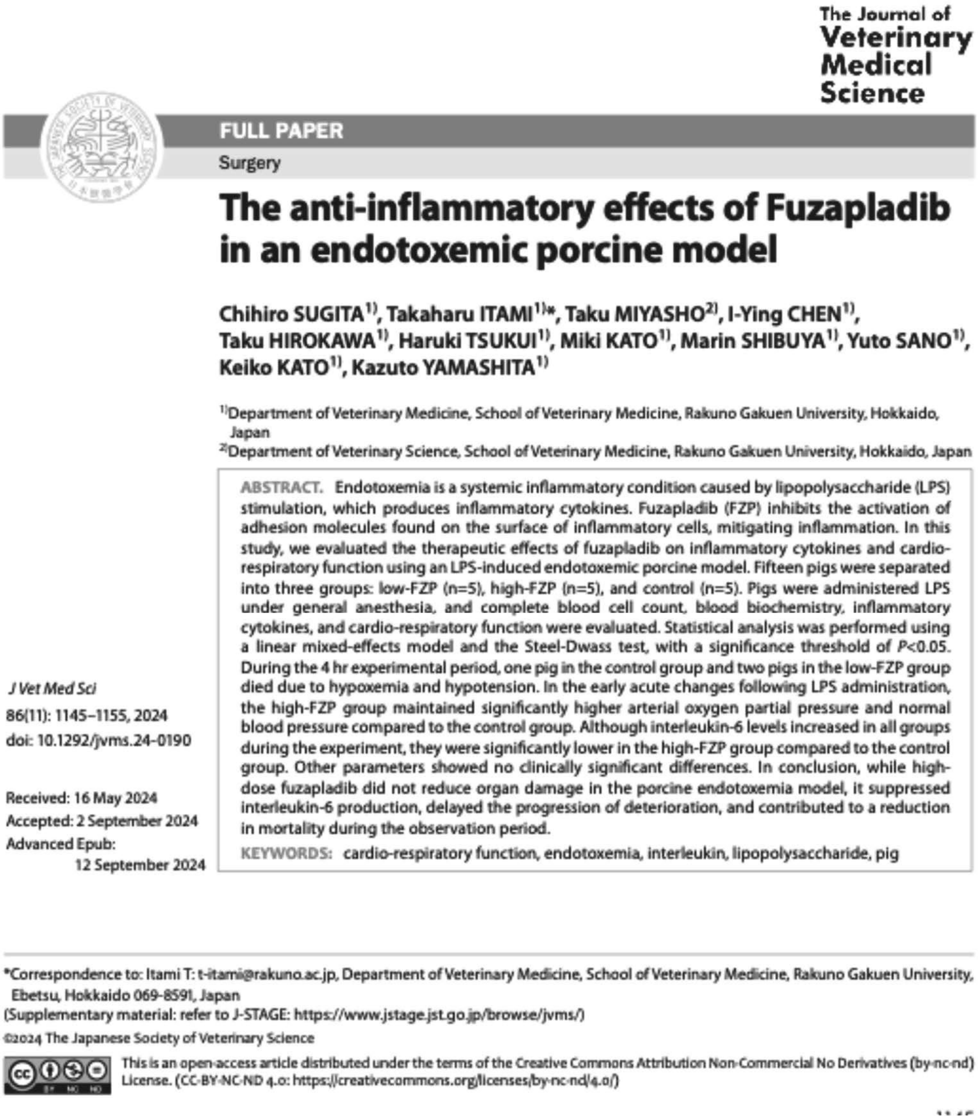

The Journal of
Veterinary
Medical
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FULL PAPER

Surgery

The anti-inflammatory effects of Fuzapladib in an endotoxemic porcine model

Chihiro SUGITA[1], Takaharu ITAMI[1]*, Taku MIYASHO[2], I-Ying CHEN[1], Taku HIROKAWA[1], Haruki TSUKUI[1], Miki KATO[1], Marin SHIBUYA[1], Yuto SANO[1], Keiko KATO[1], Kazuto YAMASHITA[1]

[1]Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Hokkaido, Japan
[2]Department of Veterinary Science, School of Veterinary Medicine, Rakuno Gakuen University, Hokkaido, Japan

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ABSTRACT. Endotoxemia is a systemic inflammatory condition caused by lipopolysaccharide (LPS) stimulation, which produces inflammatory cytokines. Fuzapladib (FZP) inhibits the activation of adhesion molecules found on the surface of inflammatory cells, mitigating inflammation. In this study, we evaluated the therapeutic effects of fuzapladib on inflammatory cytokines and cardio-respiratory function using an LPS-induced endotoxemic porcine model. Fifteen pigs were separated into three groups: low-FZP (n=5), high-FZP (n=5), and control (n=5). Pigs were administered LPS under general anesthesia, and complete blood cell count, blood biochemistry, inflammatory cytokines, and cardio-respiratory function were evaluated. Statistical analysis was performed using a linear mixed-effects model and the Steel-Dwass test, with a significance threshold of $P<0.05$. During the 4 hr experimental period, one pig in the control group and two pigs in the low-FZP group died due to hypoxemia and hypotension. In the early acute changes following LPS administration, the high-FZP group maintained significantly higher arterial oxygen partial pressure and normal blood pressure compared to the control group. Although interleukin-6 levels increased in all groups during the experiment, they were significantly lower in the high-FZP group compared to the control group. Other parameters showed no clinically significant differences. In conclusion, while high-dose fuzapladib did not reduce organ damage in the porcine endotoxemia model, it suppressed interleukin-6 production, delayed the progression of deterioration, and contributed to a reduction in mortality during the observation period.

KEYWORDS: cardio-respiratory function, endotoxemia, interleukin, lipopolysaccharide, pig

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*Correspondence to: Itami T: t-itami@rakuno.ac.jp, Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8591, Japan

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最終責任者　Takaharu Itami (Corresponding Author)

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Cardiorespiratory effects of intramuscular alfaxalone combined with low-dose medetomidine and butorphanol in dogs anesthetized with sevoflurane

Keiko Kato, Takaharu Itami*, Norihiko Oyama and Kazuto Yamashita

Department of Companion Animal Clinical Sciences, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan

Abstract
Background: The intramuscular (IM) administration of 7.5–10 mg/kg of alfaxalone produces anesthetic effects that enable endotracheal intubation with mild cardiorespiratory depression in dogs. However, the effects of IM co-administration of medetomidine, butorphanol, and alfaxalone on cardiorespiratory function under inhalation anesthesia have not been studied.
Aim: To assess the cardiorespiratory function following the IM co-administration of 5 μg/kg of medetomidine, 0.3 mg/kg of butorphanol, and 2.5 mg/kg of alfaxalone (MBA) in dogs anesthetized with sevoflurane.
Methods: Seven intact healthy Beagles (three males and four females, aged 3–6 years old and weighing 10.0–18.1 kg) anesthetized with a predetermined minimum alveolar concentration (MAC) of sevoflurane were included in this study. The baseline cardiorespiratory variable values were recorded using the thermodilution method with a pulmonary artery catheter after stabilization for 15 minutes at 1.3 times their individual sevoflurane MAC. The cardiorespiratory variables were measured again following the IM administration of MBA. Data are expressed as median [interquartile range] and compared with the corresponding baseline values using the Friedman test and Sheff's method. A $p < 0.05$ was considered statistically significant.
Results: The intramuscular administration of MBA transiently decreased the cardiac index [baseline: 3.46 (3.18–3.69), 5 minutes: 1.67 (1.57–1.75) l/minute/m^2 : $p < 0.001$], respiratory frequency, and arterial pH. In contrast, it increased the systemic vascular resistance index [baseline: 5,367 (3,589–6,617), 5 minutes:10,197 (9,955–15,005) dynes second/cm^5/m^2 : $p = 0.0092$], mean pulmonary arterial pressure, and arterial partial pressure of carbon dioxide.
Conclusion: The intramuscular administration of MBA in dogs anesthetized with sevoflurane transiently decreased cardiac output due to vasoconstriction. Although spontaneous breathing was maintained, MBA administration resulted in respiratory acidosis due to hypoventilation. Thus, it is important to administer MBA with caution to dogs with insufficient cardiovascular function. In addition, ventilatory support is recommended.
Keywords: Alfaxalone, Medetomidine, Butorphanol, Dog, Cardiorespiratory effects.

***Corresponding Author:** Takaharu Itami. Department of Companion Animal Clinical Sciences, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan. Email: *t-itami@rakuno.ac.jp*

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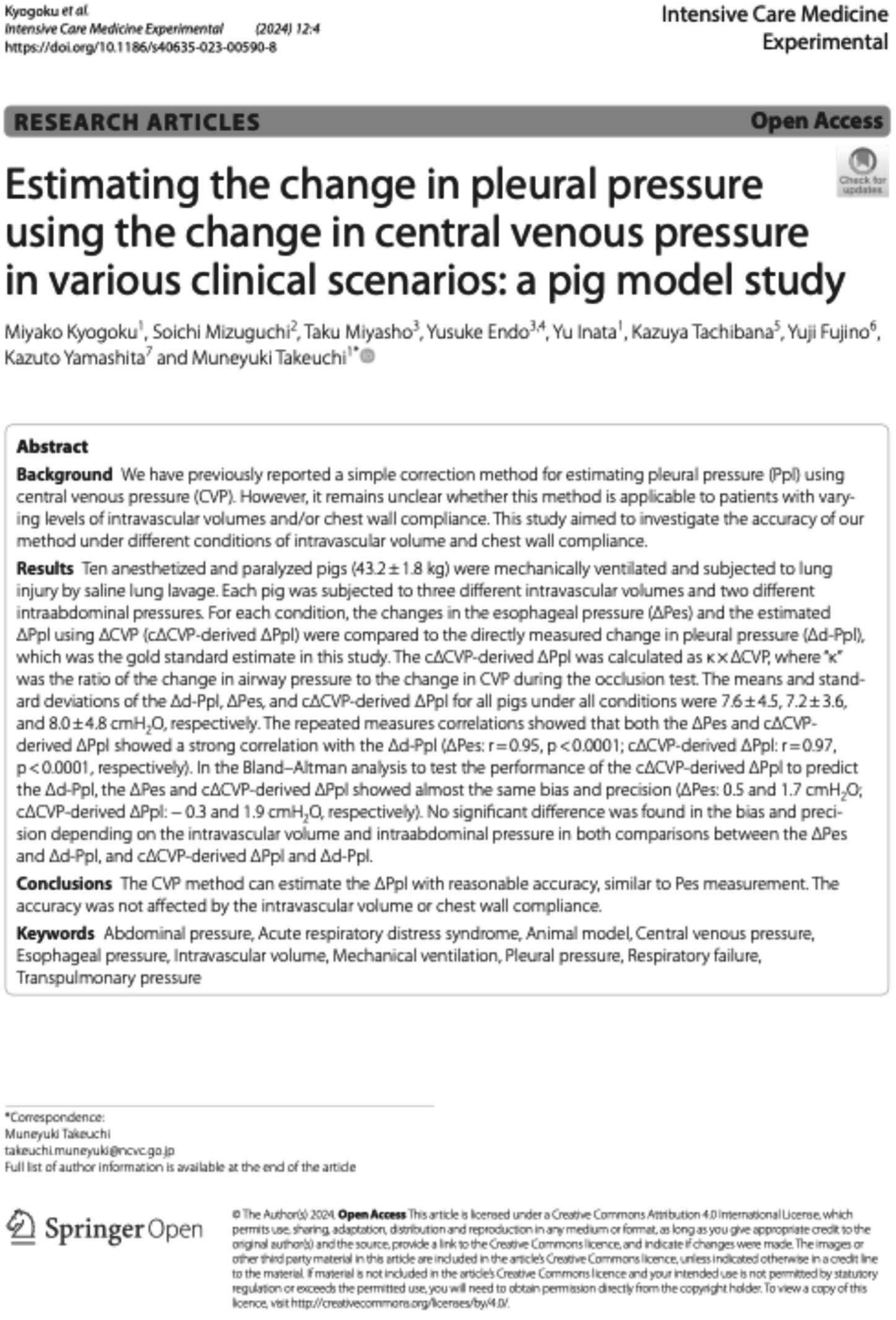
最終責任者 Takaharu Itami (Corresponding Author)



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Intensive Care Medicine
Experimental

RESEARCH ARTICLES **Open Access**

Estimating the change in pleural pressure using the change in central venous pressure in various clinical scenarios: a pig model study

Miyako Kyogoku[1], Soichi Mizuguchi[2], Taku Miyasho[3], Yusuke Endo[3,4], Yu Inata[1], Kazuya Tachibana[5], Yuji Fujino[6], Kazuto Yamashita[7] and Muneyuki Takeuchi[1*]

Abstract

Background We have previously reported a simple correction method for estimating pleural pressure (Ppl) using central venous pressure (CVP). However, it remains unclear whether this method is applicable to patients with varying levels of intravascular volumes and/or chest wall compliance. This study aimed to investigate the accuracy of our method under different conditions of intravascular volume and chest wall compliance.

Results Ten anesthetized and paralyzed pigs (43.2 ± 1.8 kg) were mechanically ventilated and subjected to lung injury by saline lung lavage. Each pig was subjected to three different intravascular volumes and two different intraabdominal pressures. For each condition, the changes in the esophageal pressure (ΔPes) and the estimated ΔPpl using ΔCVP (cΔCVP-derived ΔPpl) were compared to the directly measured change in pleural pressure (Δd-Ppl), which was the gold standard estimate in this study. The cΔCVP-derived ΔPpl was calculated as κ × ΔCVP, where "κ" was the ratio of the change in airway pressure to the change in CVP during the occlusion test. The means and standard deviations of the Δd-Ppl, ΔPes, and cΔCVP-derived ΔPpl for all pigs under all conditions were 7.6 ± 4.5, 7.2 ± 3.6, and 8.0 ± 4.8 cmH_2O, respectively. The repeated measures correlations showed that both the ΔPes and cΔCVP-derived ΔPpl showed a strong correlation with the Δd-Ppl (ΔPes: $r = 0.95$, $p < 0.0001$; cΔCVP-derived ΔPpl: $r = 0.97$, $p < 0.0001$, respectively). In the Bland–Altman analysis to test the performance of the cΔCVP-derived ΔPpl to predict the Δd-Ppl, the ΔPes and cΔCVP-derived ΔPpl showed almost the same bias and precision (ΔPes: 0.5 and 1.7 cmH_2O; cΔCVP-derived ΔPpl: − 0.3 and 1.9 cmH_2O, respectively). No significant difference was found in the bias and precision depending on the intravascular volume and intraabdominal pressure in both comparisons between the ΔPes and Δd-Ppl, and cΔCVP-derived ΔPpl and Δd-Ppl.

Conclusions The CVP method can estimate the ΔPpl with reasonable accuracy, similar to Pes measurement. The accuracy was not affected by the intravascular volume or chest wall compliance.

Keywords Abdominal pressure, Acute respiratory distress syndrome, Animal model, Central venous pressure, Esophageal pressure, Intravascular volume, Mechanical ventilation, Pleural pressure, Respiratory failure, Transpulmonary pressure

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*Correspondence:
Muneyuki Takeuchi
takeuchi.muneyuki@ncvc.go.jp
Full list of author information is available at the end of the article

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最終責任者　Muneyuki Takeuchi (Corresponding Author)

Tatsuya Ando

Associate Professor

准教授　安藤　達哉

I. 筆頭または責任著者　＜First or Corresponding Author＞

II. その他　＜Others＞

1）Changes in mammary infection status in dairy cows during the dry period using dry cow therapy approaches on three farms.
Nagahata H, Komori N, Fukutome M, Sugiura T, Hisaeda K, Gondaira S, Higuchi H, Ando T, **Nakada K.**.
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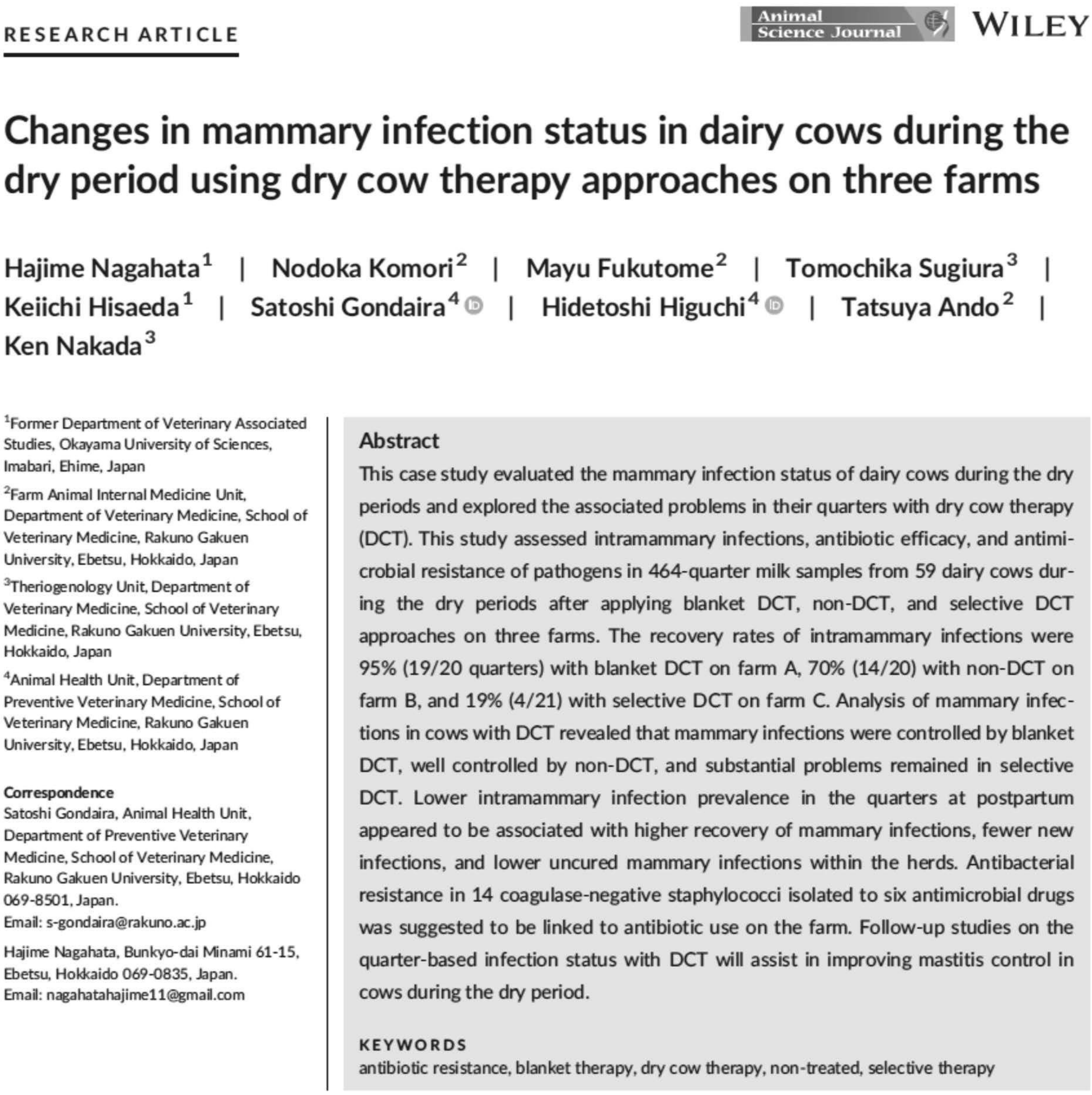

RESEARCH ARTICLE

Animal Science Journal | WILEY

Changes in mammary infection status in dairy cows during the dry period using dry cow therapy approaches on three farms

Hajime Nagahata[1] | Nodoka Komori[2] | Mayu Fukutome[2] | Tomochika Sugiura[3] | Keiichi Hisaeda[1] | Satoshi Gondaira[4] | Hidetoshi Higuchi[4] | Tatsuya Ando[2] | Ken Nakada[3]

[1]Former Department of Veterinary Associated Studies, Okayama University of Sciences, Imabari, Ehime, Japan

[2]Farm Animal Internal Medicine Unit, Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

[3]Theriogenology Unit, Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

[4]Animal Health Unit, Department of Preventive Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

Correspondence
Satoshi Gondaira, Animal Health Unit, Department of Preventive Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan.
Email: s-gondaira@rakuno.ac.jp

Hajime Nagahata, Bunkyo-dai Minami 61-15, Ebetsu, Hokkaido 069-0835, Japan.
Email: nagahatahajime11@gmail.com

Abstract

This case study evaluated the mammary infection status of dairy cows during the dry periods and explored the associated problems in their quarters with dry cow therapy (DCT). This study assessed intramammary infections, antibiotic efficacy, and antimicrobial resistance of pathogens in 464-quarter milk samples from 59 dairy cows during the dry periods after applying blanket DCT, non-DCT, and selective DCT approaches on three farms. The recovery rates of intramammary infections were 95% (19/20 quarters) with blanket DCT on farm A, 70% (14/20) with non-DCT on farm B, and 19% (4/21) with selective DCT on farm C. Analysis of mammary infections in cows with DCT revealed that mammary infections were controlled by blanket DCT, well controlled by non-DCT, and substantial problems remained in selective DCT. Lower intramammary infection prevalence in the quarters at postpartum appeared to be associated with higher recovery of mammary infections, fewer new infections, and lower uncured mammary infections within the herds. Antibacterial resistance in 14 coagulase-negative staphylococci isolated to six antimicrobial drugs was suggested to be linked to antibiotic use on the farm. Follow-up studies on the quarter-based infection status with DCT will assist in improving mastitis control in cows during the dry period.

KEYWORDS
antibiotic resistance, blanket therapy, dry cow therapy, non-treated, selective therapy

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最終責任者　Satoshi Gondaira and Hajime Nagahata (Corresponding Authors)

獣医ウイルス学ユニット（Veterinary Virology）

Tomo Daidoji

Associate Professor

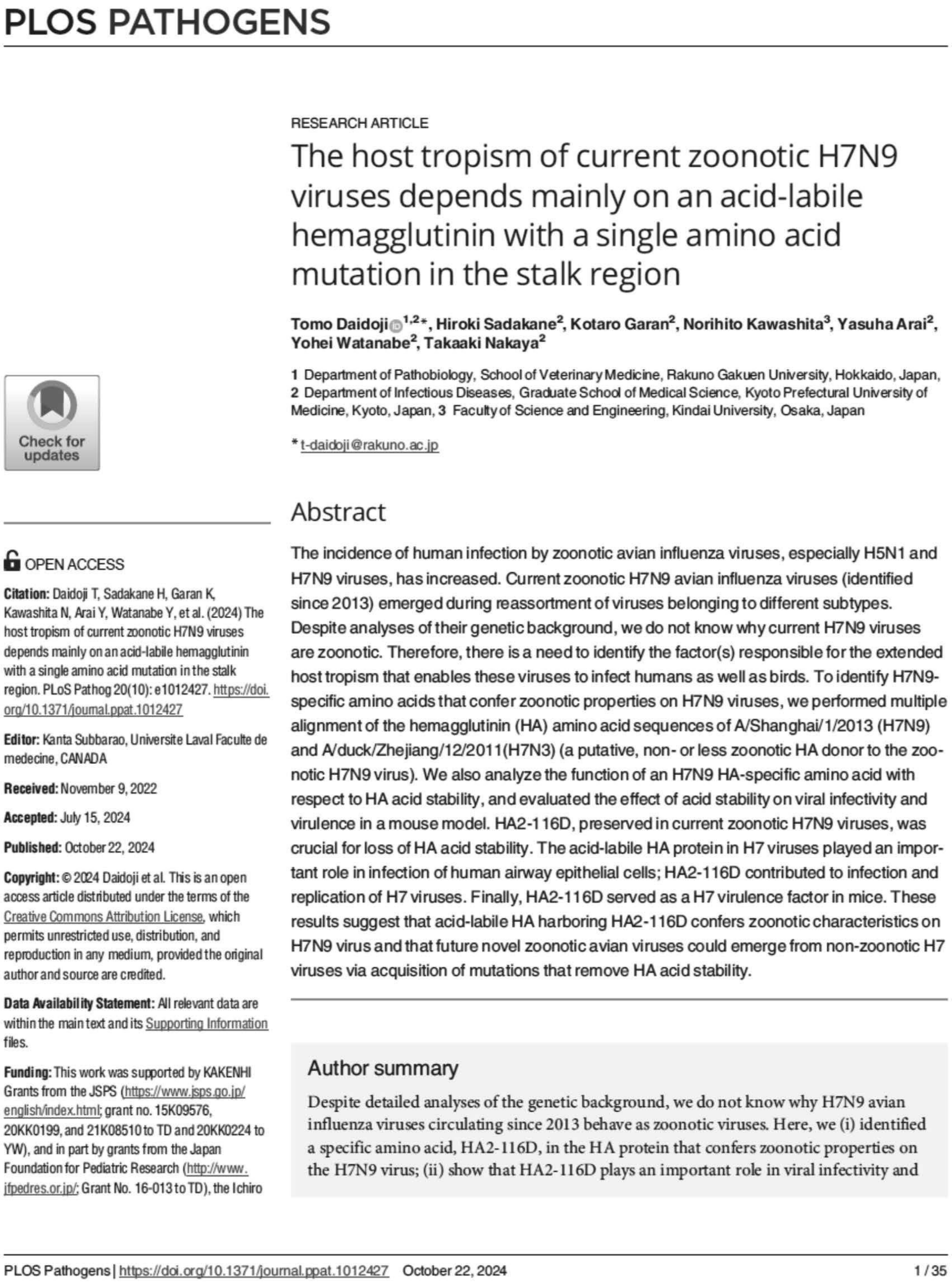
准教授　大道寺　智

I. 筆頭または責任著者　＜First or Corresponding Author＞

1）The host tropism of current zoonotic H7N9 viruses depends mainly on an acid-labile hemagglutinin with a single amino acid mutation in the stalk region.
Daidoji T, Sadakane H, Garan K, Kawashita N, Arai Y, Watanabe Y, Nakaya T.
PLoS Pathog 20:e1012427. 2024. doi: 10.1371/journal.ppat.1012427.

II. その他　＜Others＞

1）Emergence of SARS-CoV-2 with Dual-Drug Resistant Mutations During a Long-Term Infection in a Kidney Transplant Recipient.
Tanino Y, Nishioka K, Yamamoto C, Watanabe Y, **Daidoji T,** Kawamoto M, Uda S, Kirito S, Nakagawa Y, Kasamatsu Y, Kawahara Y, Sakai Y, Nobori S, Inaba T, Ota B, Fujita N, Hoshino A, Nukui Y, Nakaya T.
Infect Drug Resist 17:531–541. 2024. doi: 10.2147/IDR.S438915



PLOS PATHOGENS

RESEARCH ARTICLE

The host tropism of current zoonotic H7N9 viruses depends mainly on an acid-labile hemagglutinin with a single amino acid mutation in the stalk region

Tomo Daidoji[1,2]*, **Hiroki Sadakane**[2], **Kotaro Garan**[2], **Norihito Kawashita**[3], **Yasuha Arai**[2], **Yohei Watanabe**[2], **Takaaki Nakaya**[2]

1 Department of Pathobiology, School of Veterinary Medicine, Rakuno Gakuen University, Hokkaido, Japan, 2 Department of Infectious Diseases, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan, 3 Faculty of Science and Engineering, Kindai University, Osaka, Japan

* t-daidoji@rakuno.ac.jp

Abstract

The incidence of human infection by zoonotic avian influenza viruses, especially H5N1 and H7N9 viruses, has increased. Current zoonotic H7N9 avian influenza viruses (identified since 2013) emerged during reassortment of viruses belonging to different subtypes. Despite analyses of their genetic background, we do not know why current H7N9 viruses are zoonotic. Therefore, there is a need to identify the factor(s) responsible for the extended host tropism that enables these viruses to infect humans as well as birds. To identify H7N9-specific amino acids that confer zoonotic properties on H7N9 viruses, we performed multiple alignment of the hemagglutinin (HA) amino acid sequences of A/Shanghai/1/2013 (H7N9) and A/duck/Zhejiang/12/2011(H7N3) (a putative, non- or less zoonotic HA donor to the zoonotic H7N9 virus). We also analyze the function of an H7N9 HA-specific amino acid with respect to HA acid stability, and evaluated the effect of acid stability on viral infectivity and virulence in a mouse model. HA2-116D, preserved in current zoonotic H7N9 viruses, was crucial for loss of HA acid stability. The acid-labile HA protein in H7 viruses played an important role in infection of human airway epithelial cells; HA2-116D contributed to infection and replication of H7 viruses. Finally, HA2-116D served as a H7 virulence factor in mice. These results suggest that acid-labile HA harboring HA2-116D confers zoonotic characteristics on H7N9 virus and that future novel zoonotic avian viruses could emerge from non-zoonotic H7 viruses via acquisition of mutations that remove HA acid stability.

Author summary

Despite detailed analyses of the genetic background, we do not know why H7N9 avian influenza viruses circulating since 2013 behave as zoonotic viruses. Here, we (i) identified a specific amino acid, HA2-116D, in the HA protein that confers zoonotic properties on the H7N9 virus; (ii) show that HA2-116D plays an important role in viral infectivity and

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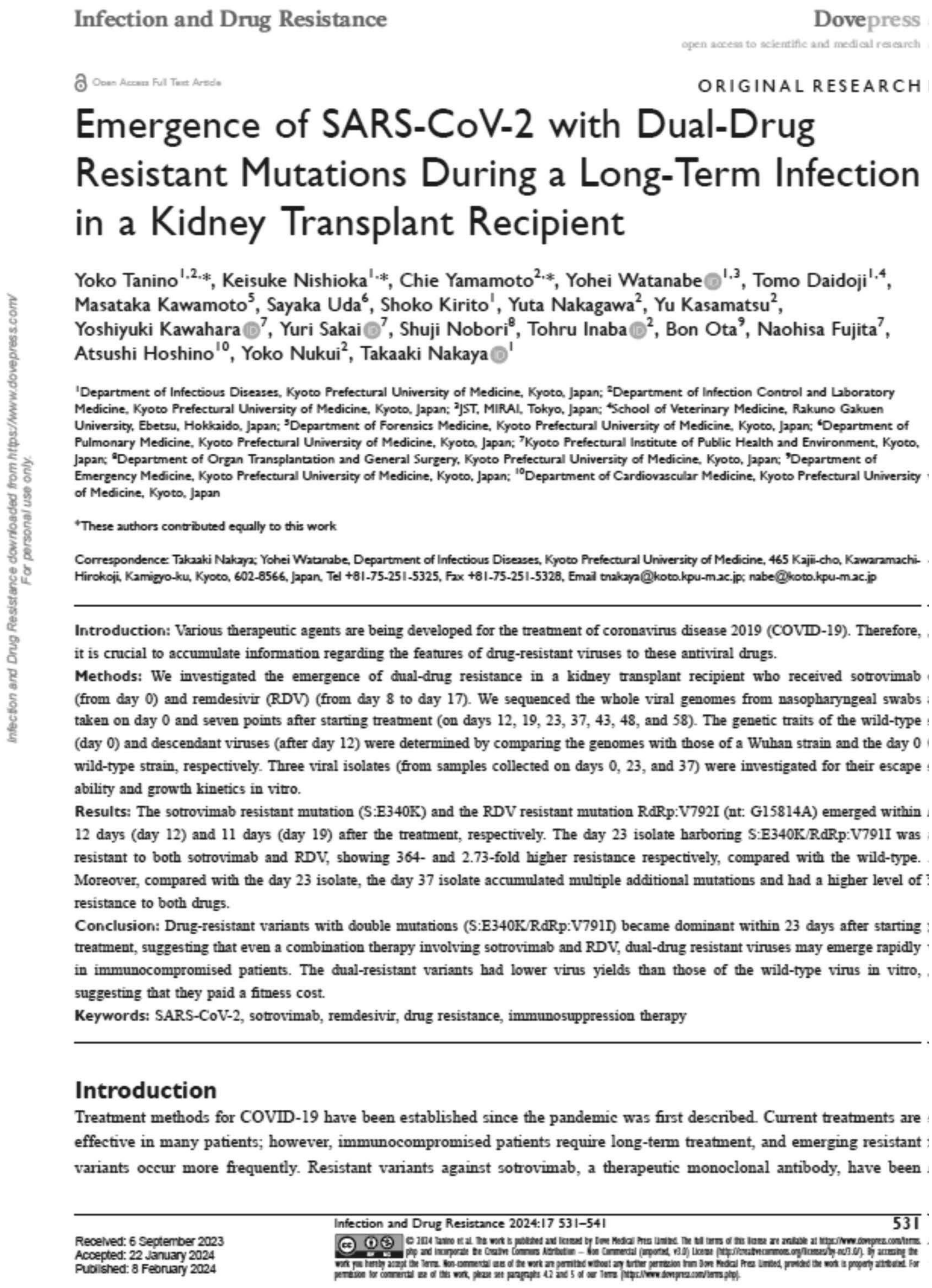
最終責任者　Tomo Daidoji (Corresponding Author)



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ORIGINAL RESEARCH

Emergence of SARS-CoV-2 with Dual-Drug Resistant Mutations During a Long-Term Infection in a Kidney Transplant Recipient

Yoko Tanino[1,2,*], Keisuke Nishioka[1,*], Chie Yamamoto[2,*], Yohei Watanabe[1,3], Tomo Daidoji[1,4], Masataka Kawamoto[5], Sayaka Uda[6], Shoko Kirito[1], Yuta Nakagawa[2], Yu Kasamatsu[2], Yoshiyuki Kawahara[7], Yuri Sakai[7], Shuji Nobori[8], Tohru Inaba[2], Bon Ota[9], Naohisa Fujita[7], Atsushi Hoshino[10], Yoko Nukui[2], Takaaki Nakaya[1]

[1]Department of Infectious Diseases, Kyoto Prefectural University of Medicine, Kyoto, Japan; [2]Department of Infection Control and Laboratory Medicine, Kyoto Prefectural University of Medicine, Kyoto, Japan; [3]JST, MIRAI, Tokyo, Japan; [4]School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan; [5]Department of Forensics Medicine, Kyoto Prefectural University of Medicine, Kyoto, Japan; [6]Department of Pulmonary Medicine, Kyoto Prefectural University of Medicine, Kyoto, Japan; [7]Kyoto Prefectural Institute of Public Health and Environment, Kyoto, Japan; [8]Department of Organ Transplantation and General Surgery, Kyoto Prefectural University of Medicine, Kyoto, Japan; [9]Department of Emergency Medicine, Kyoto Prefectural University of Medicine, Kyoto, Japan; [10]Department of Cardiovascular Medicine, Kyoto Prefectural University of Medicine, Kyoto, Japan

*These authors contributed equally to this work

Correspondence: Takaaki Nakaya; Yohei Watanabe, Department of Infectious Diseases, Kyoto Prefectural University of Medicine, 465 Kajii-cho, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto, 602-8566, Japan, Tel +81-75-251-5325, Fax +81-75-251-5328, Email tnakaya@koto.kpu-m.ac.jp; nabe@koto.kpu-m.ac.jp

Introduction: Various therapeutic agents are being developed for the treatment of coronavirus disease 2019 (COVID-19). Therefore, it is crucial to accumulate information regarding the features of drug-resistant viruses to these antiviral drugs.

Methods: We investigated the emergence of dual-drug resistance in a kidney transplant recipient who received sotrovimab (from day 0) and remdesivir (RDV) (from day 8 to day 17). We sequenced the whole viral genomes from nasopharyngeal swabs taken on day 0 and seven points after starting treatment (on days 12, 19, 23, 37, 43, 48, and 58). The genetic traits of the wild-type (day 0) and descendant viruses (after day 12) were determined by comparing the genomes with those of a Wuhan strain and the day 0 wild-type strain, respectively. Three viral isolates (from samples collected on days 0, 23, and 37) were investigated for their escape ability and growth kinetics in vitro.

Results: The sotrovimab resistant mutation (S:E340K) and the RDV resistant mutation RdRp:V792I (nt: G15814A) emerged within 12 days (day 12) and 11 days (day 19) after the treatment, respectively. The day 23 isolate harboring S:E340K/RdRp:V791I was resistant to both sotrovimab and RDV, showing 364- and 2.73-fold higher resistance respectively, compared with the wild-type. Moreover, compared with the day 23 isolate, the day 37 isolate accumulated multiple additional mutations and had a higher level of resistance to both drugs.

Conclusion: Drug-resistant variants with double mutations (S:E340K/RdRp:V791I) became dominant within 23 days after starting treatment, suggesting that even a combination therapy involving sotrovimab and RDV, dual-drug resistant viruses may emerge rapidly in immunocompromised patients. The dual-resistant variants had lower virus yields than those of the wild-type virus in vitro, suggesting that they paid a fitness cost.

Keywords: SARS-CoV-2, sotrovimab, remdesivir, drug resistance, immunosuppression therapy

Introduction

Treatment methods for COVID-19 have been established since the pandemic was first described. Current treatments are effective in many patients; however, immunocompromised patients require long-term treatment, and emerging resistant variants occur more frequently. Resistant variants against sotrovimab, a therapeutic monoclonal antibody, have been

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最終責任者　Takaaki Nakaya; Yohei Watanabe (Corresponding Author)

ハードヘルス学（Veterinary Herd Health）

Rika Fukumori

Associate professor

准教授　福森　理加

Ⅰ．筆頭または責任著者　＜First or Corresponding Author

1）Effects of starch content of calf starter on rumen properties and blood concentrations of metabolites and hormones in dairy calves under a high plane of milk replacer feeding.
Satoh H, **Fukumori R**, Kumano R, Kamata M, Shimada K, Izumi K, Oikawa S.
Anim Sci J 95:e13927. 2024. doi: 10.1111/asj.13927.

2）Effects of lactose content in milk replacer on apparent digestibility, growth, liver mRNA expression, and blood parameters related to metabolism of dairy calves.
Fukumori R, Hirose M, Norimura I, Nakayama T, Shimada K, Mineo H, Steele MA, Gondaira S, Higuchi H, Chisato K, Oikawa S, Izumi K.
JDS Communications 5:719–724. 2024. doi: 10.3168/jdsc.2023-0528.

3）Effect of feeding calf starter with calcium salts of medium-chain fatty acids on the growth and metabolic hormones in calves.
Masuda Y, **Fukumori R**, Tomoshige M, Sarentonglaga B, Sugino T, Nagao Y.
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4）Effects of amount of lactose in milk replacer on gastrointestinal function of dairy calves.
Fukumori R, Nakayama T, Hirose M, Norimura I, Izumi K, Shimada K, Mineo H, Steele M.A, Gondaira S, Higuchi H, Watanabe T, Ueda H, Sano T, Chisato K, Oikawa S.
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5）Lipoprotein composition of calves before and after weaning and comparison with adult cows.
Sato H, Kumano R, **Fukumori R**, Oikawa S.
J Vet Med Sci 87: *in press*. 2024. Dec 16. doi: 10.1292/jvms.24-0172. Online ahead of print.

Ⅱ．その他＜Others＞

1）A Case–Control Study on the Usefulness of Serum Lecithin: Cholesterol Acyltransferase Activity as a Predictor of Retained Placenta in Close-Up Dairy Cows.
Satoh H, Chisato K, **Fukumori R**, Tharwa M, Oikawa S.
Animals 14:3640. 2024. doi: 10.3390/ani14243640.

2）Metabolites and physical scores as possible predictors for postpartum culling in dairy cows.
Chisato K, Yamazaki T, Kayasaki S, **Fukumori R**, Higuchi H, Makita K, Oikawa S.
Res Vet Sci 179:105387–105387. 2024. doi: 10.1016/j.rvsc.2024.105387.

3）Characteristics of failure of passive transfer at the herd level using the serum immunoglobulin G concentration as an indicator on dairy farms in eastern Hokkaido, Japan.
Kayasaki S, Satoh H, Oguchi K, Chisato K, **Fukumori R**, Higuchi H, Suzuki K, Oikawa S.
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RESEARCH ARTICLE

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Effects of starch content of calf starter on rumen properties and blood concentrations of metabolites and hormones in dairy calves under a high plane of milk feeding

Hitomi Satoh[1] | Rika Fukumori[1] | Ren Kumano[1] | Maho Kamata[2] | Kensuke Shimada[3,4] | Kenichi Izumi[2] | Shin Oikawa[1]

[1]Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan

[2]Department of Sustainable Agriculture, College of Agriculture, Food and Environment Sciences, Rakuno Gakuen University, Ebetsu, Japan

[3]The National Federation of Dairy Co-operative Associations (ZEN-RAKU-REN), Shinjuku, Tokyo, Japan

[4]Department of Animal and Bioscience, University of Guelph, Guelph, Ontario, N1G2W1, Canada

Correspondence
Rika Fukumori and Shin Oikawa, Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu 069-8501, Japan.
Email: fukumori@rakuno.ac.jp; oishin@rakuno.ac.jp

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Abstract

The objective of this study was to investigate the effects of calf starters with different starch content on rumen and blood properties in calves fed under a high plane of nutrition program. Twenty-seven Holstein calves (14 female, 13 male) were assigned to one of three starter treatment groups in a randomized block design: high-starch (41.8%) ($n = 9$), H; medium-starch (31.9%) ($n = 9$), M; low-starch (22.0%) ($n = 9$), L. Milk replacer on powder basis was fed up to 1.2 kg/day as fed, gradually reduced from 6 weeks of age; calves were weaned at 8 weeks of age. Each starter (up to 3.5 kg/day as fed) and chopped hay were provided ad libitum from 5 days of age. Blood was collected from 4 to 13 weeks of age. Rumen fluid was collected at 6, 8, 10, and 13 weeks of age. Serum urea nitrogen concentration after weaning was the lowest in H. Plasma IGF-1 concentrations were higher in H than in L. Ruminal pH was not different, but the molar proportion of ruminal propionate was higher in H than in L throughout the study period. In summary, a high-starch starter may increase propionate production and microbial protein synthesis in the rumen, inducing higher plasma IGF-1 concentrations.

KEYWORDS
calf starter, growth performance, metabolites, starch content, weaning transition

1 | INTRODUCTION

Restricted milk feeding for early weaning causes hunger and stress in calves, leading to reduced growth performance (Khan et al., 2010). Therefore, a high plane of milk feeding has recently become popular for the purposes of boosting growth, health, animal welfare, and prospects during the suckling period (Soberon et al., 2012). A high plane of nutrition by increased milk feeding accelerates preweaning growth rates by increasing feeding volume but leads to a decrease in starter intake (Hill et al., 2010). Furthermore, the rapid increase in starter intake at weaning places a greater burden on the underdeveloped rumen.

Although calves are developing at a fast rate and have high nutritional requirements, their gastrointestinal tracts are underdeveloped. Therefore, feeding management appropriate to the development of the gastrointestinal tract is necessary to prevent stunted growth after weaning (Baldwin et al., 2004). The calf's primary energy source changes from glucose to volatile fatty acids (VFA) during weaning transition, but the undeveloped rumen has less ability to buffer or absorb VFA. Rumen development requires the physical stimulation of the feed and chemical stimulation of fermentation products such as butyrate and propionate. Physical stimulation develops the muscular layer and chemical stimulation increases number and length of rumen papillae (Sander et al., 1959; Tamate et al., 1962). Thus, for smooth

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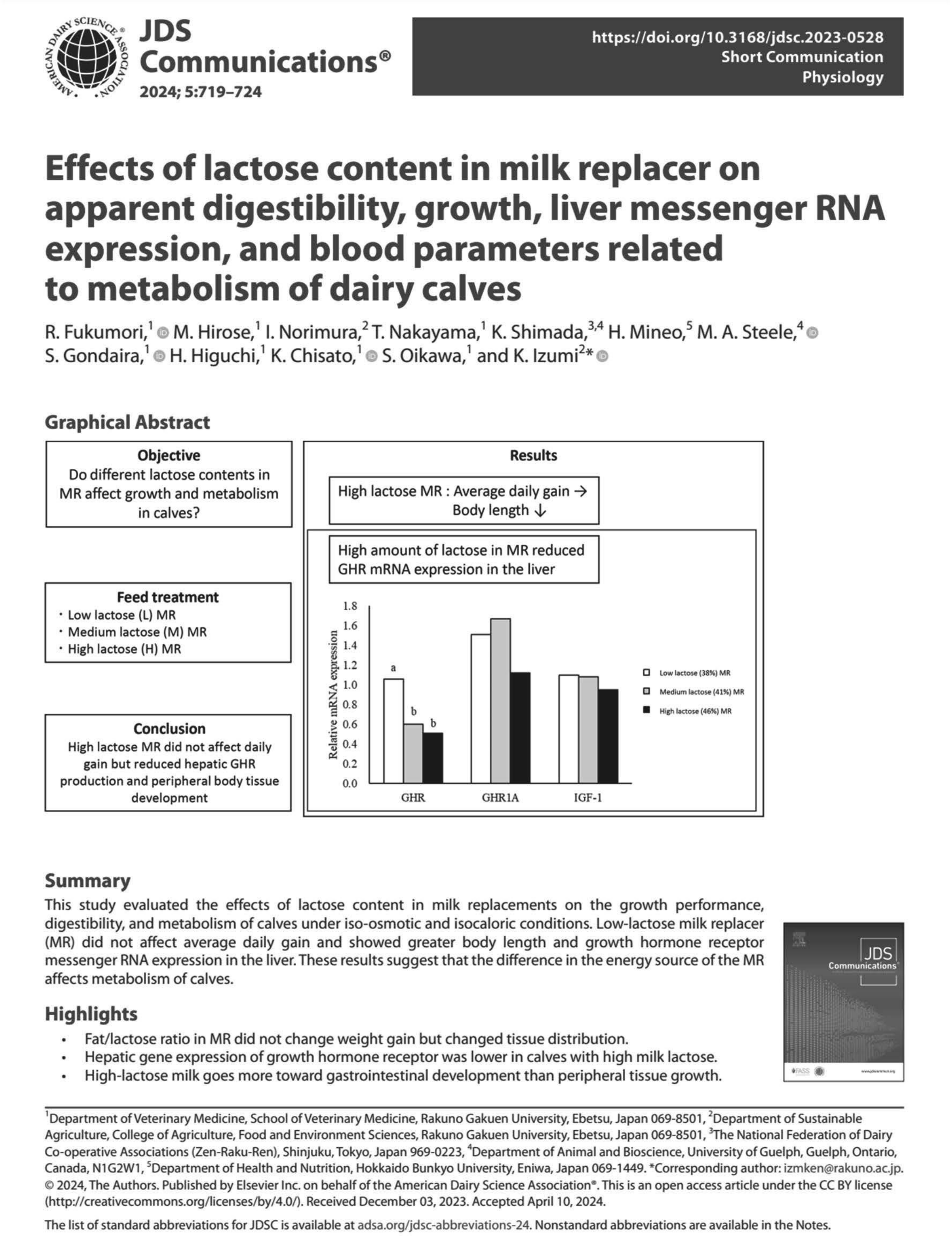
最終責任者　Rika Fukumori and Shin Oikawa (Corresponding Author)



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Short Communication
Physiology

Effects of lactose content in milk replacer on apparent digestibility, growth, liver messenger RNA expression, and blood parameters related to metabolism of dairy calves

R. Fukumori,[1] M. Hirose,[1] I. Norimura,[2] T. Nakayama,[1] K. Shimada,[3,4] H. Mineo,[5] M. A. Steele,[4] S. Gondaira,[1] H. Higuchi,[1] K. Chisato,[1] S. Oikawa,[1] and K. Izumi[2]*

Graphical Abstract

Objective
Do different lactose contents in MR affect growth and metabolism in calves?

Feed treatment
- Low lactose (L) MR
- Medium lactose (M) MR
- High lactose (H) MR

Conclusion
High lactose MR did not affect daily gain but reduced hepatic GHR production and peripheral body tissue development

Results

High lactose MR : Average daily gain →
Body length ↓

High amount of lactose in MR reduced GHR mRNA expression in the liver

Summary

This study evaluated the effects of lactose content in milk replacements on the growth performance, digestibility, and metabolism of calves under iso-osmotic and isocaloric conditions. Low-lactose milk replacer (MR) did not affect average daily gain and showed greater body length and growth hormone receptor messenger RNA expression in the liver. These results suggest that the difference in the energy source of the MR affects metabolism of calves.

Highlights

- Fat/lactose ratio in MR did not change weight gain but changed tissue distribution.
- Hepatic gene expression of growth hormone receptor was lower in calves with high milk lactose.
- High-lactose milk goes more toward gastrointestinal development than peripheral tissue growth.

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[1]Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan 069-8501, [2]Department of Sustainable Agriculture, College of Agriculture, Food and Environment Sciences, Rakuno Gakuen University, Ebetsu, Japan 069-8501, [3]The National Federation of Dairy Co-operative Associations (Zen-Raku-Ren), Shinjuku, Tokyo, Japan 969-0223, [4]Department of Animal and Bioscience, University of Guelph, Guelph, Ontario, Canada, N1G2W1, [5]Department of Health and Nutrition, Hokkaido Bunkyo University, Eniwa, Japan 069-1449. *Corresponding author: izmken@rakuno.ac.jp.
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The list of standard abbreviations for JDSC is available at adsa.org/jdsc-abbreviations-24. Nonstandard abbreviations are available in the Notes.

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Endocrinology and Physiology

Effect of feeding calf starter with calcium salts of medium-chain fatty acids on the growth and metabolic hormones in calves

Y. Masuda,[†,‡] R. Fukumori,[‖,1] M. Tomoshige,[†] B. Sarentonglaga,[†] T. Sugino,[$] and Y. Nagao[†,‡]

[†]Department of Agriculture, University Farm, Utsunomiya University, Mohka, 321-4415, Japan
[‡]United Graduate School of Agricultural Science, Tokyo University of Agriculture and Technology, Fuchu, 183-8538, Japan
[‖]School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, 069-8501, Japan
[$]Graduate School of Integrated Sciences for Life, Hiroshima University, Higashi-Hiroshima, 739-8528, Japan
[1]Corresponding author: fukumori@rakuno.ac.jp

Abstract

We investigated the effects of a calf starter supplemented with calcium salts of medium-chain fatty acids (MCFA-Ca) on growth and plasma hormone concentration in calves. Twelve Holstein calves were randomly assigned to two dietary groups (without supplementation [CON] and supplemented with MCFA-Ca [MCFA]) from 4 d of age. Calves were fed 1.0 kg/d of milk replacer until 5 wk of age and were completely weaned at 7 wk of age. Calves in the MCFA group received a calf starter containing 1% MCFA-Ca. dry matter intake (DMI) was measured daily, and body weight was measured weekly. Rumen fluid was collected at 13 wk of age to measure pH and volatile fatty acid concentration. Preprandial blood samples were collected weekly to measure the basal plasma hormone and metabolite concentrations. At 4, 8, and 13 wk of age, peri-prandial blood samples were collected every 30 min, from 60 min before feeding to 120 min after feeding, to observe metabolic responses to feeding. In addition, insulin sensitivity was assessed using euglycemic-hyperinsulinemic clamps at 4, 8, and 13 wk of age in three calves from each treatment. There were no differences in starter and hay DMI between the treatments. However, the average daily gain (ADG) after weaning was higher in the MCFA group than in the CON group. Weekly changes in plasma parameters did not differ between the treatments. Plasma concentrations of preprandial ghrelin and postprandial total ketone bodies at 13 wk of age were higher in the MCFA group than in the CON group. At 8 wk of age, peri-prandial plasma insulin concentrations were lower in the MCFA group than in the CON group. There were no differences between the treatments in terms of insulin sensitivity. The present study suggested that feeding weaning calves MCFA-Ca increases the ADG during the postweaning period, which may be mediated by endocrine signals, such as enhanced ghrelin secretion and decreased insulin secretion, without altering insulin sensitivity.

Lay Summary

Calves are prone to growth retardation because of insufficient energy intake during the weaning transition period. Starch is the main energy source used in the formulation of calf starters. However, there is a concern that preweaned calves do not have sufficient functional rumen and small intestine to digest large amounts of starch, causing diarrhea, and decreased feed intake. Medium-chain fatty acids are easily accessible to calves and are expected to have functional properties, such as increasing the plasma concentration of ghrelin, which may enhance growth by stimulating growth hormone. The effect of calf starter supplementation with medium-chain fatty acids on growth performance and metabolism has not been evaluated previously and was evaluated in this study. Medium-chain fatty acids were fed in the form of calcium salts as pelleted solid feed. The results showed that feeding medium-chain fatty acids increased plasma ghrelin concentration, decreased insulin concentration, suggesting that these metabolic changes might be beneficial for calf growth performance.

Key words: cattle, heifer growth

Abbreviations ADG, average daily gain; A/P, acetate to propionate ratio; BW, body weight; DM, dry matter; DMI, dry matter intake; EGC, euglycemic-hyperinsulinemic clamp technique; FCR, feed conversion rate; GH, growth hormone; GIR, glucose infusion rate; GLP-1, glucagon-like peptide-1; IGF-1, insulin-like growth factor-1; MCFA-Ca, calcium salts of medium-chain fatty acids; ME, metabolizable energy; MEI, metabiolizable energy intake; NEFA, non-esterified fatty acids; NDF, neutral detergent fiber; T-cho, total cholesterol; TKB, total ketone bodies; UN, urea nitrogen; VFA, volatile fatty acids

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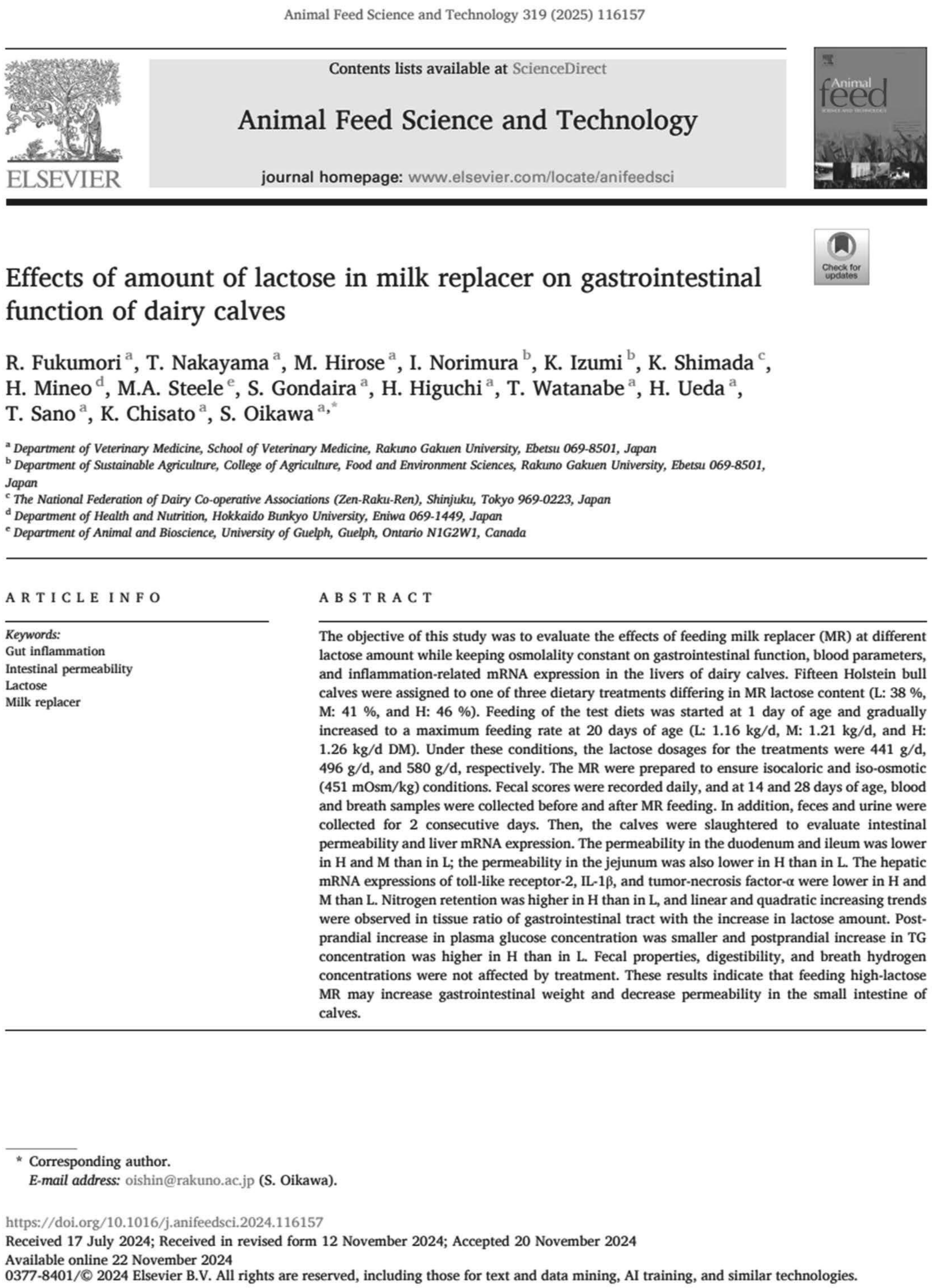

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Effects of amount of lactose in milk replacer on gastrointestinal function of dairy calves

R. Fukumori [a], T. Nakayama [a], M. Hirose [a], I. Norimura [b], K. Izumi [b], K. Shimada [c], H. Mineo [d], M.A. Steele [e], S. Gondaira [a], H. Higuchi [a], T. Watanabe [a], H. Ueda [a], T. Sano [a], K. Chisato [a], S. Oikawa [a,*]

[a] *Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu 069-8501, Japan*
[b] *Department of Sustainable Agriculture, College of Agriculture, Food and Environment Sciences, Rakuno Gakuen University, Ebetsu 069-8501, Japan*
[c] *The National Federation of Dairy Co-operative Associations (Zen-Raku-Ren), Shinjuku, Tokyo 969-0223, Japan*
[d] *Department of Health and Nutrition, Hokkaido Bunkyo University, Eniwa 069-1449, Japan*
[e] *Department of Animal and Bioscience, University of Guelph, Guelph, Ontario N1G2W1, Canada*

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Keywords:
Gut inflammation
Intestinal permeability
Lactose
Milk replacer

ABSTRACT

The objective of this study was to evaluate the effects of feeding milk replacer (MR) at different lactose amount while keeping osmolality constant on gastrointestinal function, blood parameters, and inflammation-related mRNA expression in the livers of dairy calves. Fifteen Holstein bull calves were assigned to one of three dietary treatments differing in MR lactose content (L: 38 %, M: 41 %, and H: 46 %). Feeding of the test diets was started at 1 day of age and gradually increased to a maximum feeding rate at 20 days of age (L: 1.16 kg/d, M: 1.21 kg/d, and H: 1.26 kg/d DM). Under these conditions, the lactose dosages for the treatments were 441 g/d, 496 g/d, and 580 g/d, respectively. The MR were prepared to ensure isocaloric and iso-osmotic (451 mOsm/kg) conditions. Fecal scores were recorded daily, and at 14 and 28 days of age, blood and breath samples were collected before and after MR feeding. In addition, feces and urine were collected for 2 consecutive days. Then, the calves were slaughtered to evaluate intestinal permeability and liver mRNA expression. The permeability in the duodenum and ileum was lower in H and M than in L; the permeability in the jejunum was also lower in H than in L. The hepatic mRNA expressions of toll-like receptor-2, IL-1β, and tumor-necrosis factor-α were lower in H and M than L. Nitrogen retention was higher in H than in L, and linear and quadratic increasing trends were observed in tissue ratio of gastrointestinal tract with the increase in lactose amount. Postprandial increase in plasma glucose concentration was smaller and postprandial increase in TG concentration was higher in H than in L. Fecal properties, digestibility, and breath hydrogen concentrations were not affected by treatment. These results indicate that feeding high-lactose MR may increase gastrointestinal weight and decrease permeability in the small intestine of calves.

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* Corresponding author.
E-mail address: oishin@rakuno.ac.jp (S. Oikawa).

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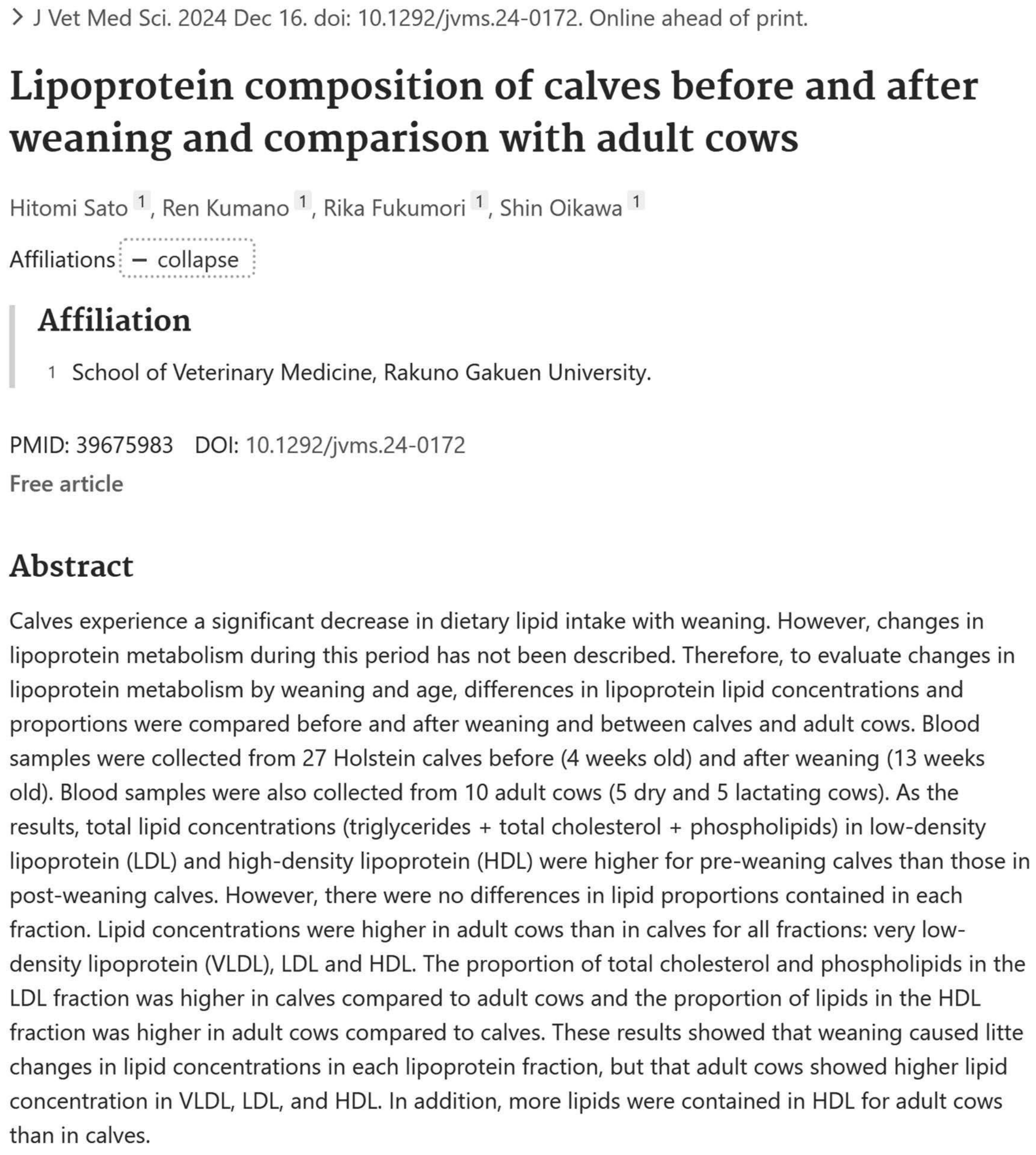

> J Vet Med Sci. 2024 Dec 16. doi: 10.1292/jvms.24-0172. Online ahead of print.

Lipoprotein composition of calves before and after weaning and comparison with adult cows

Hitomi Sato [1], Ren Kumano [1], Rika Fukumori [1], Shin Oikawa [1]

Affiliations − collapse

Affiliation

[1] School of Veterinary Medicine, Rakuno Gakuen University.

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Free article

Abstract

Calves experience a significant decrease in dietary lipid intake with weaning. However, changes in lipoprotein metabolism during this period has not been described. Therefore, to evaluate changes in lipoprotein metabolism by weaning and age, differences in lipoprotein lipid concentrations and proportions were compared before and after weaning and between calves and adult cows. Blood samples were collected from 27 Holstein calves before (4 weeks old) and after weaning (13 weeks old). Blood samples were also collected from 10 adult cows (5 dry and 5 lactating cows). As the results, total lipid concentrations (triglycerides + total cholesterol + phospholipids) in low-density lipoprotein (LDL) and high-density lipoprotein (HDL) were higher for pre-weaning calves than those in post-weaning calves. However, there were no differences in lipid proportions contained in each fraction. Lipid concentrations were higher in adult cows than in calves for all fractions: very low-density lipoprotein (VLDL), LDL and HDL. The proportion of total cholesterol and phospholipids in the LDL fraction was higher in calves compared to adult cows and the proportion of lipids in the HDL fraction was higher in adult cows compared to calves. These results showed that weaning caused litte changes in lipid concentrations in each lipoprotein fraction, but that adult cows showed higher lipid concentration in VLDL, LDL, and HDL. In addition, more lipids were contained in HDL for adult cows than in calves.

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animals

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Article

A Case–Control Study on the Usefulness of Serum Lecithin: Cholesterol Acyltransferase Activity as a Predictor of Retained Placenta in Close-Up Dairy Cows

Hiroki Satoh [1], Kyoko Chisato [1], Rika Fukumori [1], Mohamed Tharwat [2] and Shin Oikawa [1,*]

[1] Veterinary Herd Health, Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu 069-8501, Hokkaido, Japan; s21161058@g.rakuno.ac.jp (H.S.); k-chisato@rakuno.ac.jp (K.C.); fukumori@rakuno.ac.jp (R.F.)
[2] Department of Clinical Sciences, College of Veterinary Medicine, Qassim University, P. O. Box 6622, Buraidah 51452, Saudi Arabia; atieh@qu.edu.sa
* Correspondence: oishin@rakuno.ac.jp; Tel.: +81-11-388-4825

Simple Summary: Retained placenta (RP) is one of the most periparturient diseases of dairy cows, in which the placenta is not expelled from the body within 24 h of calving. This condition increases the risk of other periparturient diseases and decreased milk production and reproductive efficiency. In order to reliably predict PR, this study focused on the activity of lecithin:cholesterol acyltransferase (LCAT) and compared its usefulness in the prepartum prediction of PR with the concentration of non-esterified fatty acids (NEFA). LCAT is an enzyme synthesized in the liver that converts free cholesterol to cholesteryl esters, which is known to be acutely related to and reduced by periparturient diseases. NEFA is a fatty acid that increases in the blood when animals are in negative energy balance and has been reported as a useful prepartum predictor of some perinatal diseases. This study was carried out at a single farm with approximately 200 Holstein parous cows from February 2010 to February 2016. Twenty-seven parous cows between 2 and 21 days (close-up stage) before their expected calving dates that developed RP (RP group) were assessed. They were compared with 60 clinically healthy cows (controls) that did not develop RP and were matched with the RP group for sampling period and parity. The results of this study were as follows: LCAT showed adequate discriminative ability of PR occurrence comparable to that of NEFA. However, LCAT or NEFA plus RFS showed higher discrimination ability than both alone. These results indicate that LCAT has a useful ability to predict the occurrence of RP.

Citation: Satoh, H.; Chisato, K.; Fukumori, R.; Tharwat, M.; Oikawa, S. A Case–Control Study on the Usefulness of Serum Lecithin: Cholesterol Acyltransferase Activity as a Predictor of Retained Placenta in Close-Up Dairy Cows. *Animals* **2024**, *14*, 3640. https://doi.org/10.3390/ani14243640

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Abstract: The purpose of this study was to investigate the usefulness of the activity of lecithin:cholesterol acyltransferase (LCAT), the enzyme responsible for esterification of cholesterol in plasma, as a predictor of retained placenta (RP) in close-up cows, compared with the non-esterified fatty acids (NEFA) concentration. This study was conducted as a case–control study between February 2010 and February 2016, on a single farm with approximately 200 Holstein parous cows in Hokkaido, Japan. Of the 1187 dairy cattle that calved, 835 dairy cattle were enrolled that underwent routine regular health examinations including blood sampling, body condition score (BCS) and the rumen fill score (RFS) at the close-up stage between 2 and 21 days before their expected calving dates. Of these, 27 cows that were multiparous and had RP were designated as the RP group. The controls were 60 clinically healthy cows that did not develop RP and were matched for the sampling period and parity with the RP group. The LCAT activity and NEFA concentration were significantly ($p < 0.01$) lower and higher, respectively, in the RP group than in controls. There was no significant difference in cholesteryl esters, free cholesterol concentrations and BCS between the two groups. However, RFS was significantly ($p < 0.01$) lower in the RP group than in the controls. Cows with LCAT activity of <450 U were 3.6 times more likely to develop RP than those with higher values, whereas those with NEFA levels above 0.4 mEq/L were 5.4 times more likely to. The area under the curve of receiver operator characteristic curves showed that LCAT activity was as efficient as the NEFA concentration in the diagnostic prediction of RP, suggesting it to be a useful predictor. Logistic regression analysis with LCAT or NEFA and RFS as explanatory variables resulted in

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Metabolites and physical scores as possible predictors for postpartum culling in dairy cows

Kyoko Chisato [a], Takerou Yamazaki [b], Shuji Kayasaki [a,c], Rika Fukumori [a], Hidetoshi Higuchi [a], Kohei Makita [a], Shin Oikawa [a,*]

[a] *Division of Preventive Veterinary Medicine, Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyodai-Midorimachi, Ebetsu, Hokkaido 069-8501, Japan.*

[b] *Memanbetsu Livestock Clinic, Ozora Central Branch, Okhotsk Regional Center Hokkaido Agricultural Mutual Aid Association, Memanbetsu, Showa, Ozora-cho, Abashiri, -gun, Hokkaido 099-2356, Japan.*

[c] *Teshikaga Livestock Clinic, Kushiro Central Branch, East Regional Center, Hokkaido Agricultural Mutual Aid Association, 3-10-13 Sakuraoka, Teshikaga-cho, Kawakami-gun, Hokkaido 088-3213, Japan.*

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Dry period
Negative energy balance
Prediction
Culling

ABSTRACT

The purpose of the study was to explore the associations of serum non-esterified fatty acids (NEFA) and β-hydroxybutyrate (BHBA) concentrations with the body condition score (BCS) and rumen fill score (RFS) in order to predict the risk of postpartum culling, and to further investigate effective monitoring stages during the dry period. From October 2012 to March 2014, clinically healthy Holstein heifers and cows were sampled once before calving, and the occurrence of culling within 60 days in milk (DIM) was investigated. The discriminatory ability of each parameter was evaluated using receiver operating characteristic (ROC) analysis. Of the 720 cows sampled between 14 and 2 days before the actual day of calving in the study, 42 cull cows (mean DIM ± SE: 22.0 ± 2.6) were confirmed. The areas under the curve (AUC) of the ROC for predicting culling using serum NEFA concentrations were 0.6 and 0.7 at 14 to 2 and 7 to 2 days before calving, respectively. The AUC for the RFS was 0.7 for both periods, indicating the same diagnostic level as the serum NEFA concentration. Both the serum NEFA concentration and RFS were possible predictors in cows with ≥ 2 parities, but not in cows with 0–1 parity sampled even at 7 to 2 days before calving. The serum BHBA concentration and BCS were not suitable predictors of culling for any period or parity. These results indicate that RFS has a discriminatory ability comparable to the serum NEFA concentration for predicting culling within 60 DIM.

1. Introduction

The three weeks before and after calving are called the "transition period" (Drackley, 1999; Grummer, 1995), during which dairy cows face significant challenges in maintaining their health. Briefly, dry matter intake (DMI) decreases by approximately 30% before calving (Hayirli et al., 2002), while energy requirements surge after calving due to the onset of milk production. Thus, cows can easily fall into a negative energy balance (NEB) (Bauman and Bruce, 1980; David, 1982). The cow's body attempts to adapt to the NEB by utilizing its stored carbohydrates, lipids, and proteins. However, if the reaction is not sufficiently successful, peripartum diseases such as milk fever, retained placenta and displaced abomasum may occur. It is known that the onset of peripartum diseases increases the risk of early postpartum sale, slaughter or death (culling). Early postpartum culling generally results in significant financial losses for dairy farms (Fetrow et al., 2006; Gröhn et al., 1998). Therefore, it is beneficial for dairy farm management to predict which cows are at risk of culling.

Serum non-esterified fatty acids (NEFA) and β-hydroxybutyrate (BHBA) are known as markers of whether cows are adapted to NEB (Herdt, 2000; Leblanc, 2010). Previous studies have determined prepartum NEFA and BHBA thresholds to predict postpartum culling. Briefly, the serum NEFA concentrations for predicting postpartum culling within 50 to 60 days in milk (DIM) in Canada were ≥ 0.26 mEq/L and ≥ 0.40 mEq/L during 2 weeks and 1 week before calving, respectively, and the serum BHBA concentration for prediction was calculated to be ≥ 0.7 mM during 1 week before calving (Nicola et al., 2022; Roberts et al., 2012). These results indicate that both parameters are

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* Corresponding author at: 582 Bunkyodai-Midorimachi, Ebetsu, Hokkaido 069-8501, Japan.
E-mail address: oishin@rakuno.ac.jp (S. Oikawa).

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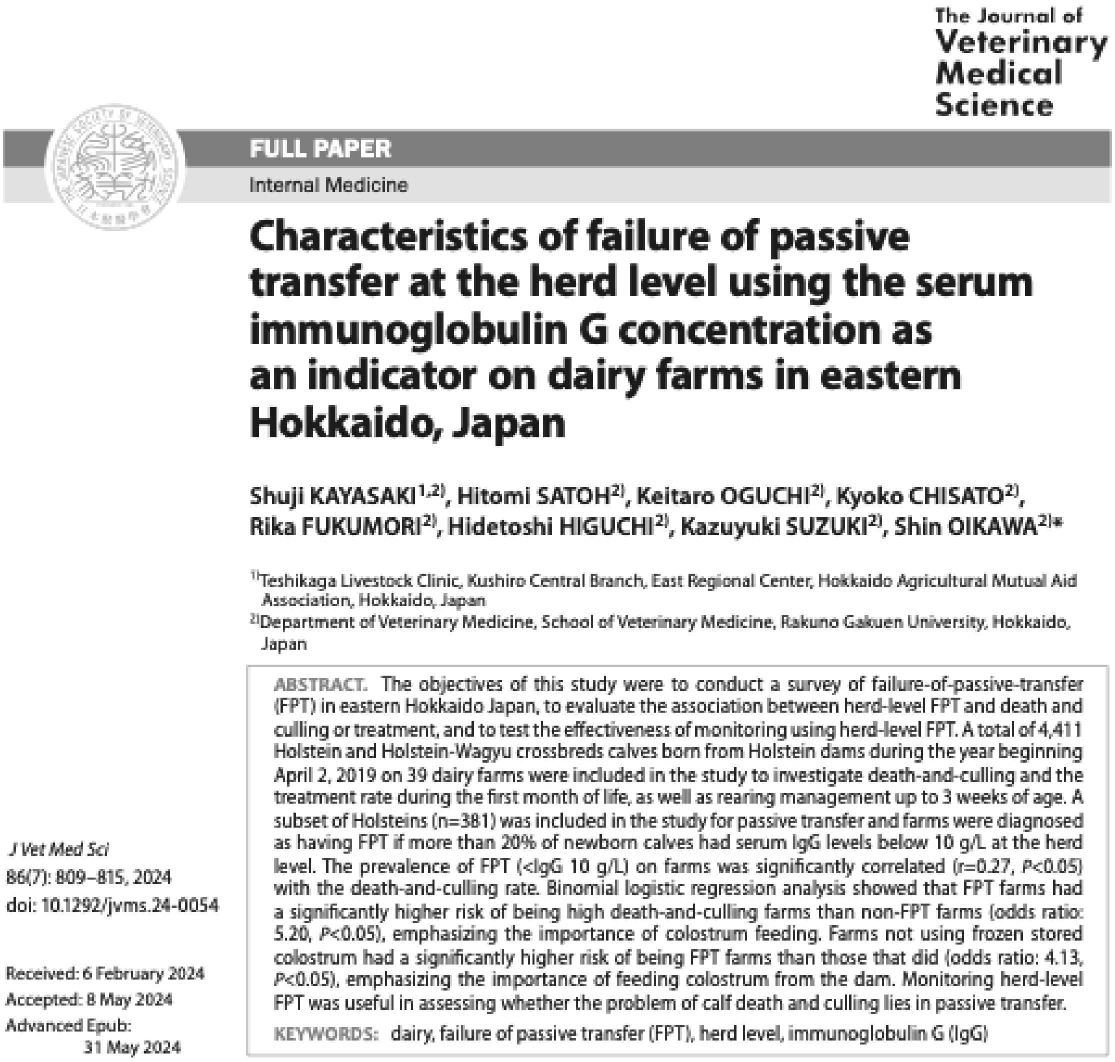

The Journal of
Veterinary
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FULL PAPER

Internal Medicine

Characteristics of failure of passive transfer at the herd level using the serum immunoglobulin G concentration as an indicator on dairy farms in eastern Hokkaido, Japan

Shuji KAYASAKI[1,2], Hitomi SATOH[2], Keitaro OGUCHI[2], Kyoko CHISATO[2], Rika FUKUMORI[2], Hidetoshi HIGUCHI[2], Kazuyuki SUZUKI[2], Shin OIKAWA[2]*

[1]Teshikaga Livestock Clinic, Kushiro Central Branch, East Regional Center, Hokkaido Agricultural Mutual Aid Association, Hokkaido, Japan

[2]Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Hokkaido, Japan

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ABSTRACT. The objectives of this study were to conduct a survey of failure-of-passive-transfer (FPT) in eastern Hokkaido Japan, to evaluate the association between herd-level FPT and death and culling or treatment, and to test the effectiveness of monitoring using herd-level FPT. A total of 4,411 Holstein and Holstein-Wagyu crossbreds calves born from Holstein dams during the year beginning April 2, 2019 on 39 dairy farms were included in the study to investigate death-and-culling and the treatment rate during the first month of life, as well as rearing management up to 3 weeks of age. A subset of Holsteins (n=381) was included in the study for passive transfer and farms were diagnosed as having FPT if more than 20% of newborn calves had serum IgG levels below 10 g/L at the herd level. The prevalence of FPT (<IgG 10 g/L) on farms was significantly correlated ($r=0.27$, $P<0.05$) with the death-and-culling rate. Binomial logistic regression analysis showed that FPT farms had a significantly higher risk of being high death-and-culling farms than non-FPT farms (odds ratio: 5.20, $P<0.05$), emphasizing the importance of colostrum feeding. Farms not using frozen stored colostrum had a significantly higher risk of being FPT farms than those that did (odds ratio: 4.13, $P<0.05$), emphasizing the importance of feeding colostrum from the dam. Monitoring herd-level FPT was useful in assessing whether the problem of calf death and culling lies in passive transfer.

KEYWORDS: dairy, failure of passive transfer (FPT), herd level, immunoglobulin G (IgG)

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Comparison of serum very low-density lipoprotein concentrations during transition in primiparous and multiparous cows

Shinya OSADA[1], Kyoko CHISATO[1], Rika FUKUMORI[1], Shin OIKAWA[1]*

[1]Department of Veterinary Herd Health, School of Veterinary Medicine, Rakuno Gakuen University, Hokkaido, Japan

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ABSTRACT. This study was carried out as an observational study in order to examine the difference of change in serum very low-density lipoprotein (VLDL) between primiparous and multiparous cows. Twenty-one clinically healthy cows (10 primiparous and 11 multiparous) were selected at 21 days prior to expected calving. Blood samples were collected in the morning (before feeding) on days −21, −7, 7, 21 and 56 days in milk (DIM). At 7 and 21 DIM, the serum non-esterified fatty acid concentration of multiparous cows was significantly higher than that of primiparous cows. The serum β-hydroxybutyrate concentration was also markedly higher in multiparous cows than in primiparous cows at 21 DIM. These results suggested that the degree of negative energy balance was greater in multiparous cows than in primiparous cows during this period. In both, serum VLDL concentrations decreased at over 7 DIM, increased at 21 DIM, and then decreased at 56 DIM. On the other hand, triglyceride and total protein concentrations of VLDL in multiparous cows were significantly lower than in primiparous cows at 21 DIM. This suggests that multiparous cows have poor triglyceride secretion from the liver and that they become more susceptible to hepatic lipidosis.

KEYWORDS: cattle, parity, transition, very low-density lipoprotein (VLDL)

In dairy cows, the transition period before and after calving is a time when the outbreak of periparturient diseases is concentrated due to significant physiological changes associated with the drastic growth of the fetus, the preparation for calving and the start of lactation. Hepatic lipidosis is often induced prepartum and is known as the underlying pathogenesis or facilitator of typical perinatal diseases such as abomasum displacement, ketosis, milk fever, and retained placenta [14–16], key factors of death and culling from a dairy herd.

The main cause of hepatic lipidosis before parturition is a negative energy balance (NEB) due to various stresses or/and failures from the feeding environment and a resultant increase in non-esterified fatty acids (NEFA) in the blood [2, 11]. In reaction to NEB, body fat is mobilized to supplement energy production [16]. Briefly, triglyceride (TG) stored in adipose tissue is decomposed by hormone-sensitive lipase, and NEFA in blood increases. Upon entering the liver, NEFA is metabolized by two pathways. The first is the pathway that produces ATP through β-oxidation to acetyl CoA, which then enters the TCA cycle. However, when the degree of NEB is high in this pathway glucose is greatly depleted, making it difficult for the acetyl CoA produced to be incorporated into the TCA cycle, resulting in increased production of ketone bodies [9]. The second is the pathway where NEFA mobilized into the liver is re-esterified to become TG, which combines with apoproteins and lipid components to form very low-density lipoproteins (VLDL) that are supplied to extrahepatic tissues as an energy source [1, 3]. However, it is known that in dairy cattle, when a large amount of NEFA flows into the liver, VLDL assembly is not in time and, as a result, TG accumulation progresses to hepatic lipidosis [6, 8, 20]. Briefly, fatty liver is induced by an increase in blood NEFA concentrations associated with mobilization of body fat before and after parturition, an increase in lipid mobilization to the liver, and insufficient secretion of VLDLs, including TGs from the liver.

Perinatal disease is known to occur more often in multiparous cows than in primiparous cows [21], which may reflect differences in lipid metabolism. A previous study reported lower TG content in the postpartum liver in primiparous cows than in multiparous cows [22]. Oikawa *et al.* also reported that there was a positive correlation between blood VLDL and NEFA with TG in nulli/primiparous cows, but not in multiparous cows [17]. From these studies, it is speculated that primiparous cows are less likely to accumulate NEFA mobilized into the liver as TG than multiparous cows. In other words, it is possible that cows with perinatal disease have abnormal lipid metabolism and develop hepatic lipidosis before calving. An increased NEFA concentration during the dry period has been shown to be a risk factor for inducing diseases [19]. It is thought that comparing serum NEFA and VLDL in primiparous and multiparous

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*Correspondence to: Oikawa S: oishin@rakuno.ac.jp, Department of Veterinary Herd Health, School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyodai-Midorimachi, Ebetsu, Hokkaido 069-8501, Japan

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animals MDPI

Article

Epidemiological Features of Postpartum Subclinical Ketosis in Dairy Herds in Hokkaido, Japan

Kyoko Chisato [1], Takerou Yamazaki [2], Shuji Kayasaki [3], Rika Fukumori [1] and Shin Oikawa [1,*]

[1] Veterinary Herd Health, Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyodai-Midorimachi, Ebetsu, Hokkaido 069-8501, Japan; k-chisato@rakuno.ac.jp (K.C.); fukumori@rakuno.ac.jp (R.F.)
[2] Memanbetsu Livestock Clinic, Ozora Central Branch, Okhotsk Regional Center, Hokkaido Agricultural Mutual Aid Association, 149-10 Memanbetsu Syouwa, Ozora-cho, Abashiri-gun, Hokkaido 099-2356, Japan; takerou_yamazaki_gb@nosai-do.or.jp
[3] Teshikaga Livestock Clinic, Kushiro Central Branch, East Regional Center, Hokkaido Agricultural Mutual Aid Association, 3-10-13 Sakuraoka, Teshikaga-cho, Kawakami-gun, Hokkaido 088-3213, Japan; s22041006@stu.rakuno.ac.jp
* Correspondence: oishin@rakuno.ac.jp; Tel.: +81-11-388-4825

Simple Summary: The aim of this study was to investigate the prevalence of subclinical ketosis (SCK) in Hokkaido, Japan, and to assess its characteristics epidemiologically at the individual and herd levels. Blood samples were taken from clinically healthy cows once within 3–88 days in milk (DIM) for blood tests. Cows with SCK were classified as SCK II within 2 weeks postpartum and SCK I from 15 DIM. The prevalence of SCK II (20.2%) tended to be higher than that of SCK I (16.5%, $p = 0.094$). The prevalence peaked around 2 weeks postpartum. The frequency of SCK I was higher at the fourth parity. The number of milking cows in herds with higher SCK (≥25%) was significantly smaller than in herds with lower SCK ($p = 0.004$). The frequency of herds with higher SCK in tie stalls with component feeding was higher than for those in free stalls and free barns fed a total mixed ration ($p = 0.054$ and $p = 0.002$). This study reveals the prevalence of SCK in Hokkaido, Japan, and shows that SCK is associated with parity and the management system.

Abstract: This study was carried out as an observational study in order to determine the prevalence of postpartum subclinical ketosis (SCK) in dairy herds in Hokkaido, Japan. From April 2012 to March 2014, blood β-hydroxybutyrate (BHBA) concentration was measured once within 3–88 days in milk (DIM) in 1394 apparently healthy cows from 108 farms to diagnose SCK (≥1.2 mM). In cows within 14 DIM, this was classified as SCK II, and from 15 DIM, this was classified as SCK I. Herds with a combined percentage of SCK I and SCK II of less than 10% were classified as SCK-negative herds, those with percentages of 10–25%, were classified as alert herds, and those with one of 25% or more, we classified as positive herds. The prevalence of SCK in the entire DIM was 17.6%. The prevalence of SCK II (20.2%) tended to occur more frequently than SCK I (16.5%, $p = 0.094$). The frequency of SCK I was higher at the fourth parity. The number of milking cows in SCK-positive herds was significantly smaller than those of the other two types of herds ($p = 0.004$). The frequency of SCK-positive herds in tie stalls and with component feeding was higher than for free stall or free barn and with total mixed ration ($p = 0.054$ and $p = 0.002$). This study reveals the prevalence of SCK in Hokkaido, Japan, and shows that SCK is associated with parity and the management system.

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Keywords: dairy cow; subclinical ketosis; prevalence; risk factor; postpartum

1. Introduction

The three weeks before and after calving are called the "transition period" [1,2], during which dramatic changes occur in the cows. This means that the fetus grows significantly in the three weeks before calving, and after calving, more energy is required for milk synthesis.

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最終責任者　Shin Oikawa (Corresponding Author)

獣医衛生学（Animal Health）

Satoshi Gondaira

Associate Professor

准教授　権平　智

I. 筆頭または責任著者　＜First or Corresponding Author＞

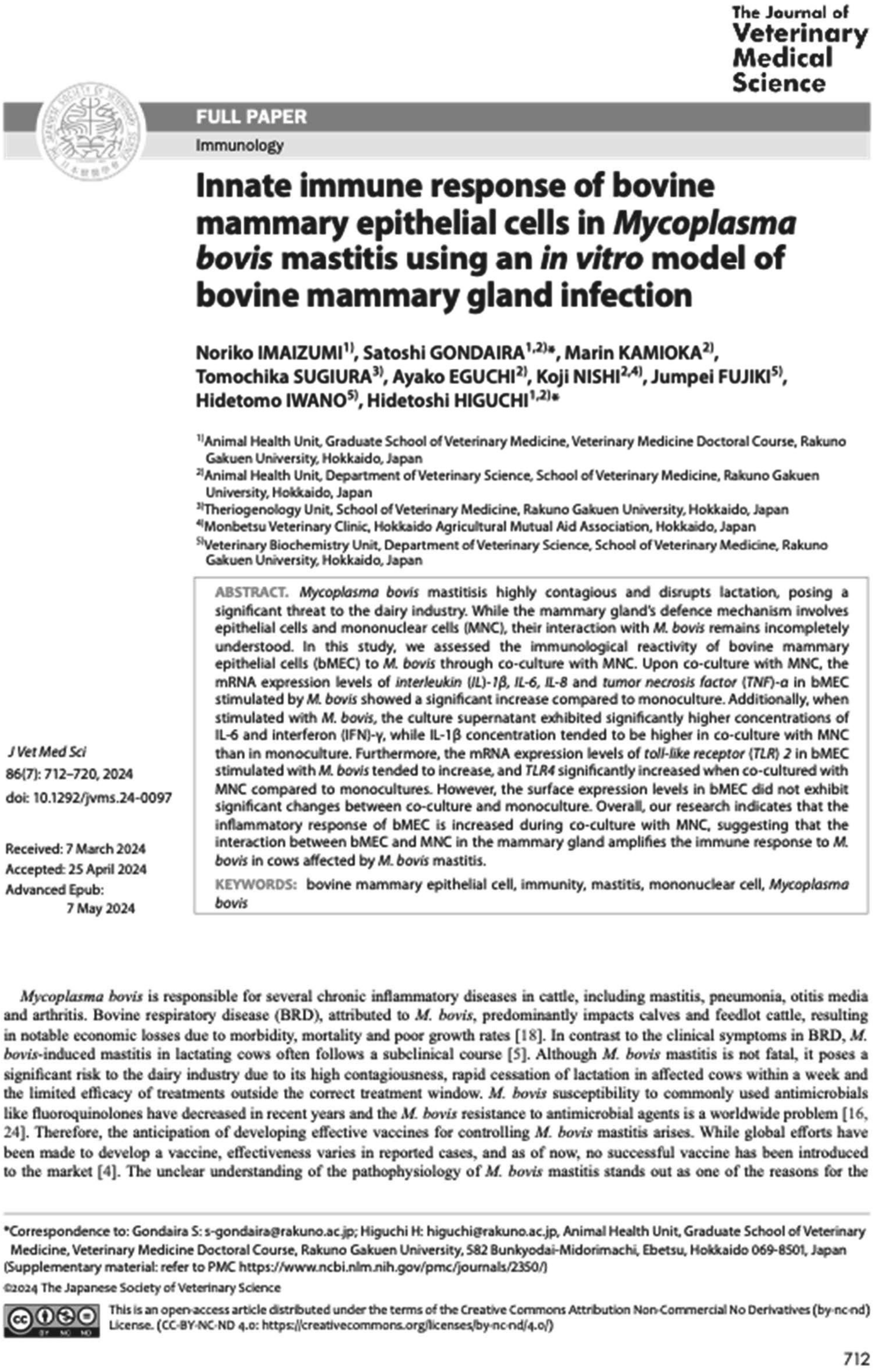
1）Innate immune response of bovine mammary epithelial cells in *Mycoplasma bovis* mastitis using an in vitro model of bovine mammary gland infection.
Imaizumi N, **Gondaira S**, Kamioka M, Sugiura T, Eguchi A, Nishi K, Fujiki J, Iwano H, Higuchi H.
J Vet Med Sci 86:712–720. 2024. doi: 10.1292/jvms.24-0097.

2）Changes in mammary infection status in dairy cows during the dry period using dry cow therapy approaches on three farms.
Nagahata H, Komori N, Fukutome M, Sugiura T, Hisaeda K, **Gondaira S**, Higuchi H, Ando T, Nakada K.
Anim Sci J 95:e13993. 2024. doi: 10.1111/asj.13993.

II. その他＜Others＞

1）Effects of amount of lactose in milk replacer on gastrointestinal function of dairy calves.
Fukumori R, Nakayama T, Hirose M, Norimura I, Izumi K, Shimada K, Mineo H, Steele MA, **Gondaira S**, Higuchi H, Watanabe T, Ueda H, Sano T, Chisato K, Oikawa S.
Anim Feed Sci Technol 116157. 2024 DOI: 10.1016/j.anifeedsci.

2）Comparative Evaluation of Microorganism Disinfection Methods for N95 Respirators.
Mitarai S, Noda J, **Gondaira S**, Uchida I, Kirisawa R.
J Biomed Res Environ Sci 5: 083–088. 2024. doi: 10.37871/jbres1874



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FULL PAPER
Immunology

Innate immune response of bovine mammary epithelial cells in *Mycoplasma bovis* mastitis using an *in vitro* model of bovine mammary gland infection

Noriko IMAIZUMI[1)], **Satoshi GONDAIRA**[1,2)]*, **Marin KAMIOKA**[2)], **Tomochika SUGIURA**[3)], **Ayako EGUCHI**[2)], **Koji NISHI**[2,4)], **Jumpei FUJIKI**[5)], **Hidetomo IWANO**[5)], **Hidetoshi HIGUCHI**[1,2)]*

[1)]Animal Health Unit, Graduate School of Veterinary Medicine, Veterinary Medicine Doctoral Course, Rakuno Gakuen University, Hokkaido, Japan
[2)]Animal Health Unit, Department of Veterinary Science, School of Veterinary Medicine, Rakuno Gakuen University, Hokkaido, Japan
[3)]Theriogenology Unit, School of Veterinary Medicine, Rakuno Gakuen University, Hokkaido, Japan
[4)]Monbetsu Veterinary Clinic, Hokkaido Agricultural Mutual Aid Association, Hokkaido, Japan
[5)]Veterinary Biochemistry Unit, Department of Veterinary Science, School of Veterinary Medicine, Rakuno Gakuen University, Hokkaido, Japan

ABSTRACT. *Mycoplasma bovis* mastitisis highly contagious and disrupts lactation, posing a significant threat to the dairy industry. While the mammary gland's defence mechanism involves epithelial cells and mononuclear cells (MNC), their interaction with *M. bovis* remains incompletely understood. In this study, we assessed the immunological reactivity of bovine mammary epithelial cells (bMEC) to *M. bovis* through co-culture with MNC. Upon co-culture with MNC, the mRNA expression levels of *interleukin (IL)-1β, IL-6, IL-8* and *tumor necrosis factor (TNF)-α* in bMEC stimulated by *M. bovis* showed a significant increase compared to monoculture. Additionally, when stimulated with *M. bovis*, the culture supernatant exhibited significantly higher concentrations of IL-6 and interferon (IFN)-γ, while IL-1β concentration tended to be higher in co-culture with MNC than in monoculture. Furthermore, the mRNA expression levels of *toll-like receptor (TLR) 2* in bMEC stimulated with *M. bovis* tended to increase, and *TLR4* significantly increased when co-cultured with MNC compared to monocultures. However, the surface expression levels in bMEC did not exhibit significant changes between co-culture and monoculture. Overall, our research indicates that the inflammatory response of bMEC is increased during co-culture with MNC, suggesting that the interaction between bMEC and MNC in the mammary gland amplifies the immune response to *M. bovis* in cows affected by *M. bovis* mastitis.

KEYWORDS: bovine mammary epithelial cell, immunity, mastitis, mononuclear cell, *Mycoplasma bovis*

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Mycoplasma bovis is responsible for several chronic inflammatory diseases in cattle, including mastitis, pneumonia, otitis media and arthritis. Bovine respiratory disease (BRD), attributed to *M. bovis*, predominantly impacts calves and feedlot cattle, resulting in notable economic losses due to morbidity, mortality and poor growth rates [18]. In contrast to the clinical symptoms in BRD, *M. bovis*-induced mastitis in lactating cows often follows a subclinical course [5]. Although *M. bovis* mastitis is not fatal, it poses a significant risk to the dairy industry due to its high contagiousness, rapid cessation of lactation in affected cows within a week and the limited efficacy of treatments outside the correct treatment window. *M. bovis* susceptibility to commonly used antimicrobials like fluoroquinolones have decreased in recent years and the *M. bovis* resistance to antimicrobial agents is a worldwide problem [16, 24]. Therefore, the anticipation of developing effective vaccines for controlling *M. bovis* mastitis arises. While global efforts have been made to develop a vaccine, effectiveness varies in reported cases, and as of now, no successful vaccine has been introduced to the market [4]. The unclear understanding of the pathophysiology of *M. bovis* mastitis stands out as one of the reasons for the

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*Correspondence to: Gondaira S: s-gondaira@rakuno.ac.jp; Higuchi H: higuchi@rakuno.ac.jp, Animal Health Unit, Graduate School of Veterinary Medicine, Veterinary Medicine Doctoral Course, Rakuno Gakuen University, 582 Bunkyodai-Midorimachi, Ebetsu, Hokkaido 069-8501, Japan
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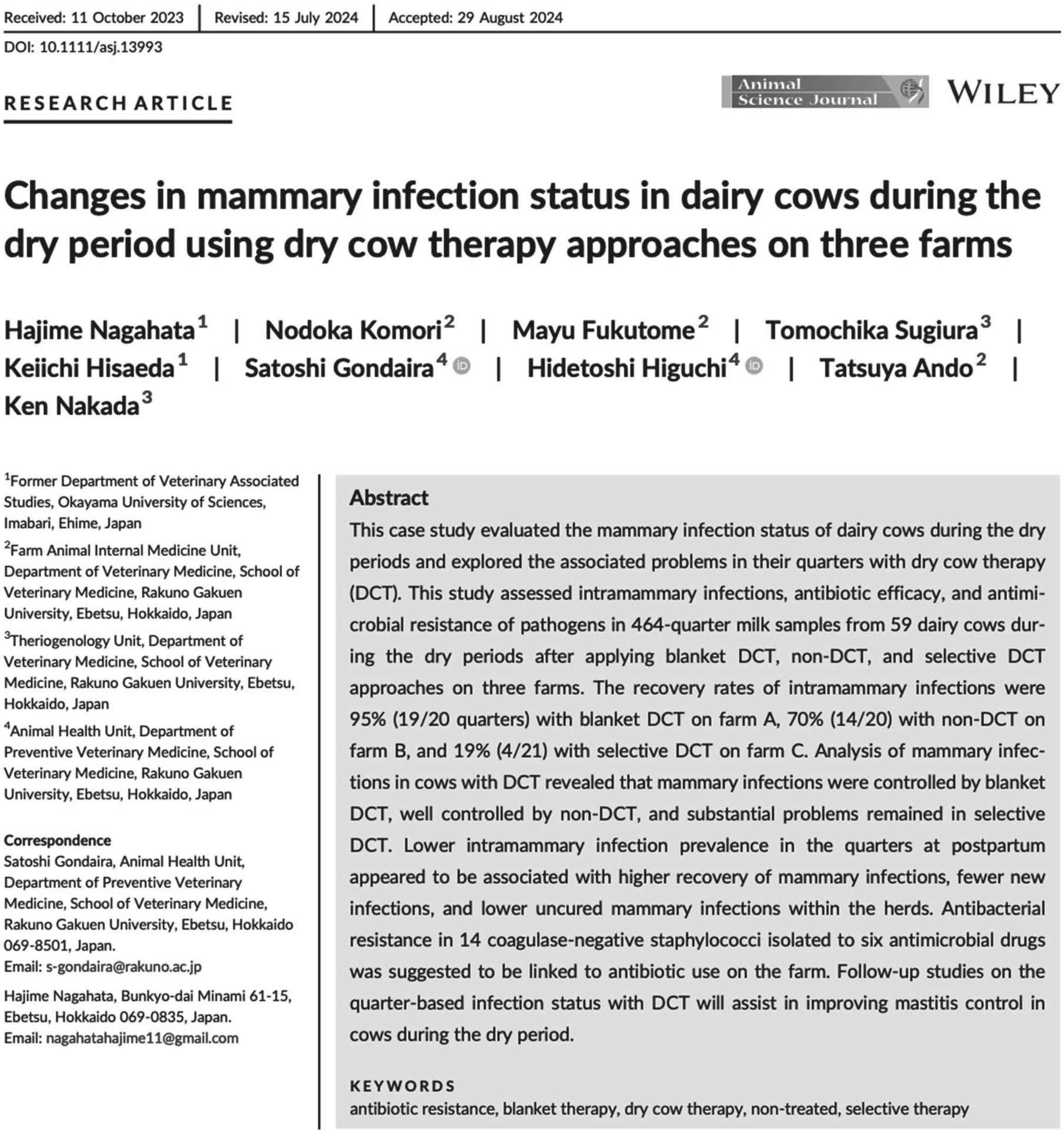

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RESEARCH ARTICLE

Animal Science Journal WILEY

Changes in mammary infection status in dairy cows during the dry period using dry cow therapy approaches on three farms

Hajime Nagahata[1] | Nodoka Komori[2] | Mayu Fukutome[2] | Tomochika Sugiura[3] | Keiichi Hisaeda[1] | Satoshi Gondaira[4] | Hidetoshi Higuchi[4] | Tatsuya Ando[2] | Ken Nakada[3]

[1]Former Department of Veterinary Associated Studies, Okayama University of Sciences, Imabari, Ehime, Japan

[2]Farm Animal Internal Medicine Unit, Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

[3]Theriogenology Unit, Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

[4]Animal Health Unit, Department of Preventive Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

Correspondence
Satoshi Gondaira, Animal Health Unit, Department of Preventive Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan.
Email: s-gondaira@rakuno.ac.jp

Hajime Nagahata, Bunkyo-dai Minami 61-15, Ebetsu, Hokkaido 069-0835, Japan.
Email: nagahatahajime11@gmail.com

Abstract

This case study evaluated the mammary infection status of dairy cows during the dry periods and explored the associated problems in their quarters with dry cow therapy (DCT). This study assessed intramammary infections, antibiotic efficacy, and antimicrobial resistance of pathogens in 464-quarter milk samples from 59 dairy cows during the dry periods after applying blanket DCT, non-DCT, and selective DCT approaches on three farms. The recovery rates of intramammary infections were 95% (19/20 quarters) with blanket DCT on farm A, 70% (14/20) with non-DCT on farm B, and 19% (4/21) with selective DCT on farm C. Analysis of mammary infections in cows with DCT revealed that mammary infections were controlled by blanket DCT, well controlled by non-DCT, and substantial problems remained in selective DCT. Lower intramammary infection prevalence in the quarters at postpartum appeared to be associated with higher recovery of mammary infections, fewer new infections, and lower uncured mammary infections within the herds. Antibacterial resistance in 14 coagulase-negative staphylococci isolated to six antimicrobial drugs was suggested to be linked to antibiotic use on the farm. Follow-up studies on the quarter-based infection status with DCT will assist in improving mastitis control in cows during the dry period.

KEYWORDS
antibiotic resistance, blanket therapy, dry cow therapy, non-treated, selective therapy

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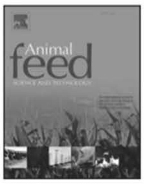

Effects of amount of lactose in milk replacer on gastrointestinal function of dairy calves

R. Fukumori [a], T. Nakayama [a], M. Hirose [a], I. Norimura [b], K. Izumi [b], K. Shimada [c], H. Mineo [d], M.A. Steele [e], S. Gondaira [a], H. Higuchi [a], T. Watanabe [a], H. Ueda [a], T. Sano [a], K. Chisato [a], S. Oikawa [a,*]

[a] *Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu 069-8501, Japan*
[b] *Department of Sustainable Agriculture, College of Agriculture, Food and Environment Sciences, Rakuno Gakuen University, Ebetsu 069-8501, Japan*
[c] *The National Federation of Dairy Co-operative Associations (Zen-Raku-Ren), Shinjuku, Tokyo 969-0223, Japan*
[d] *Department of Health and Nutrition, Hokkaido Bunkyo University, Eniwa 069-1449, Japan*
[e] *Department of Animal and Bioscience, University of Guelph, Guelph, Ontario N1G2W1, Canada*

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Lactose
Milk replacer

ABSTRACT

The objective of this study was to evaluate the effects of feeding milk replacer (MR) at different lactose amount while keeping osmolality constant on gastrointestinal function, blood parameters, and inflammation-related mRNA expression in the livers of dairy calves. Fifteen Holstein bull calves were assigned to one of three dietary treatments differing in MR lactose content (L: 38 %, M: 41 %, and H: 46 %). Feeding of the test diets was started at 1 day of age and gradually increased to a maximum feeding rate at 20 days of age (L: 1.16 kg/d, M: 1.21 kg/d, and H: 1.26 kg/d DM). Under these conditions, the lactose dosages for the treatments were 441 g/d, 496 g/d, and 580 g/d, respectively. The MR were prepared to ensure isocaloric and iso-osmotic (451 mOsm/kg) conditions. Fecal scores were recorded daily, and at 14 and 28 days of age, blood and breath samples were collected before and after MR feeding. In addition, feces and urine were collected for 2 consecutive days. Then, the calves were slaughtered to evaluate intestinal permeability and liver mRNA expression. The permeability in the duodenum and ileum was lower in H and M than in L; the permeability in the jejunum was also lower in H than in L. The hepatic mRNA expressions of toll-like receptor-2, IL-1β, and tumor-necrosis factor-α were lower in H and M than L. Nitrogen retention was higher in H than in L, and linear and quadratic increasing trends were observed in tissue ratio of gastrointestinal tract with the increase in lactose amount. Postprandial increase in plasma glucose concentration was smaller and postprandial increase in TG concentration was higher in H than in L. Fecal properties, digestibility, and breath hydrogen concentrations were not affected by treatment. These results indicate that feeding high-lactose MR may increase gastrointestinal weight and decrease permeability in the small intestine of calves.

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ORIGINAL ARTICLE

Comparative Evaluation of Microorganism Disinfection Methods for N95 Respirators

Satoshi Mitarai[1]*, Jun Noda[2], Satoshi Gondaira[3], Ikuo Uchida[4] and Rikio Kirisawa[4]

[1]Department of Mycobacterium Reference and Research, Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association, Japan
[2]Environment Health Sciences, Graduate School of Veterinary Science, Rakuno Gakuen University, Japan
[3]Laboratory of Animal Health, School of Veterinary Medicine, Rakuno Gakuen University, Japan
[4]Laboratory of Veterinary Bacteriology, Department of Pathobiology, School of Veterinary Medicine, Rakuno Gakuen University, Japan

Abstract

Background: An excessive demand for N95 respirators occurred during the SARS-CoV-2 pandemic. Therefore, health care workers were obligated to reuse N95 respirators, which were intended to be disposable.

Aim: The primary objective of this study was to establish a standard procedure for safe disinfection or sterilization that does not affect the performance of an N95 respirator.

Methods: As disinfection or sterilization methods, immersion in 70% ethanol, 0.1% hypochlorous acid, 0.3% peracetic acid, 0.2% alkyldiaminoethylglycine hydrochloride aqueous solution, hypochlorous acid water, or plant mineral-activated water, autoclaving, pasteurization and hydrogen peroxide plasma sterilization were used. After sterilization/disinfection, the filtration capacity of each N95 respirator was examined.

Findings: The performance changes in the N95 respirator caused by each sterilization/disinfection method differed for each manufacturer's product. Seventy percent ethanol, 0.1% sodium hypochlorite aqueous solution, 0.3% peracetic acid aqueous solution, autoclaving, hypochlorous acid water, and plant mineral-activated water significantly deteriorated the performance of N95 respirators. Performance degradation (increased permeability) was observed in 0.2% alkyldiaminoethylglycine hydrochloride aqueous solution and hydrogen peroxide plasma sterilization, and the permeation performance significantly deteriorated by 50–70% in all N95 respirators tested. Only pasteurization resulted in no deterioration in performance, even after five repeated sterilizations.

Conclusion: Verification of sterilization/disinfection methods for the reuse of N95 respirators has shown that the currently recommended hydrogen peroxide plasma sterilization is inadequate as it increases permeability by more than 50% with a single treatment. In this study, pasteurization was found to be the optimal sterilization method.

***Corresponding author(s)**

Satoshi Mitarai, Department of Mycobacterium Reference and Research, the Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association, 3-1-24 Matsuyama, Kiyose, Tokyo 204-8533 Japan

Tel: +814-249-357-11 (ext. 395)
Fax: +814-249-246-00
Email: mitarai@jata.or.jp

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- Sterilization
- Disinfection
- Performance degradation
- COVID-19

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画像診断学（Veterinary Diagnostic Imaging）

Kiwamu Hanazono

Associate Professor

准教授　華園　究

I. 筆頭または責任著者　＜First or Corresponding Author＞

1) Evaluation of renal function in dogs using pulsed Doppler ultrasonography.
   Ito T, **Hanazono K**, Miyoshi K, Endoh D.
   Open Vet J 14:3449–3459. 2024. doi: 10.5455/OVJ.2024.v14.i12.29

II.　その他　＜Others＞

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Evaluation of renal function in dogs using pulsed Doppler ultrasonography

Takami Ito, Kiwamu Hanazono*, Kenjirou Miyoshi and Daiji Endoh

School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan

ABSTRACT

Background: In human medicine, efforts have been made to evaluate venous blood flow in the kidneys to diagnose renal disease and estimate renal function. In dogs, previous studies have predicted renal function using the resistive index (RI) and pulsatility index (PI), which are derived from renal arterial blood flow velocity assessed via pulsed Doppler ultrasonography. However, to date, no study has been conducted on renal venous blood flow velocity in dogs.
Aim: To investigate the relationship between renal venous blood flow velocity and renal function.
Methods: Ten normal beagle dogs underwent blood tests and glomerular filtration rate (GFR) measurements. Pulsed Doppler ultrasonography was performed under sedation to measure the maximum venous flow velocity (Vmax), minimum venous flow velocity (Vmin), and venous impedance index in the renal and interlobular veins. The RI and PI were calculated from the renal and interlobular arteries.
Results: Vmax and Vmin of the renal vein were negatively correlated with GFR in both kidneys. No significant correlations were found between other measures and GFR. These results suggest a relationship between GFR and venous flow velocity in the renal veins assessed using pulsed Doppler ultrasonography.
Conclusion: These findings demonstrate the potential of this methodology as a new tool for predicting abnormalities in the renal venous blood flow and renal congestion in dogs. Further large-scale studies and comparisons between healthy dogs and dogs with impaired renal function are needed to validate this relationship.
Keywords: Doppler ultrasonography, Glomerular filtration rate, Renal venous blood flow velocity, Beagle dogs.

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最終責任者 Kiwamu Hanazono (Corresponding Author)

獣医麻酔学（Veterinary Anesthesiology）

Takaharu Itami

Associate Professor

准教授　伊丹　貴晴

I. 筆頭または責任著者　＜First or Corresponding Author＞

1）Cardiorespiratory effects of intramuscular alfaxalone combined with low-dose medetomidine and butorphanol in dogs anesthetized with sevoflurane.
Kato K, **Itami T**, Oyama N, Yamashita K.
Open Vet J 14:1251–1258. 2024. doi: 10.5455/OVJ.2024.v14.i5.20.

2）The anti-inflammatory effects of Fuzapladib in an endotoxemic porcine model.
Sugita C, **Itami T**, Miyasho T, Chen IY, Hirokawa T, Tsukui H, Kato M, Shibuya M, Sano Y, Kato K, Yamashita K.
J Vet Med Sci 86:1145–1155. 2024. doi: 10.1292/jvms.24-0190.

II.　その他　＜Others＞

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Cardiorespiratory effects of intramuscular alfaxalone combined with low-dose medetomidine and butorphanol in dogs anesthetized with sevoflurane

Keiko Kato, Takaharu Itami*, Norihiko Oyama and Kazuto Yamashita

Department of Companion Animal Clinical Sciences, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan

Abstract

Background: The intramuscular (IM) administration of 7.5–10 mg/kg of alfaxalone produces anesthetic effects that enable endotracheal intubation with mild cardiorespiratory depression in dogs. However, the effects of IM co-administration of medetomidine, butorphanol, and alfaxalone on cardiorespiratory function under inhalation anesthesia have not been studied.

Aim: To assess the cardiorespiratory function following the IM co-administration of 5 μg/kg of medetomidine, 0.3 mg/kg of butorphanol, and 2.5 mg/kg of alfaxalone (MBA) in dogs anesthetized with sevoflurane.

Methods: Seven intact healthy Beagles (three males and four females, aged 3–6 years old and weighing 10.0–18.1 kg) anesthetized with a predetermined minimum alveolar concentration (MAC) of sevoflurane were included in this study. The baseline cardiorespiratory variable values were recorded using the thermodilution method with a pulmonary artery catheter after stabilization for 15 minutes at 1.3 times their individual sevoflurane MAC. The cardiorespiratory variables were measured again following the IM administration of MBA. Data are expressed as median [interquartile range] and compared with the corresponding baseline values using the Friedman test and Sheff's method. A $p < 0.05$ was considered statistically significant.

Results: The intramuscular administration of MBA transiently decreased the cardiac index [baseline: 3.46 (3.18–3.69), 5 minutes: 1.67 (1.57–1.75) l/minute/m^2 : $p < 0.001$], respiratory frequency, and arterial pH. In contrast, it increased the systemic vascular resistance index [baseline: 5,367 (3,589–6,617), 5 minutes:10,197 (9,955–15,005) dynes second/cm^5/m^2 : $p = 0.0092$], mean pulmonary arterial pressure, and arterial partial pressure of carbon dioxide.

Conclusion: The intramuscular administration of MBA in dogs anesthetized with sevoflurane transiently decreased cardiac output due to vasoconstriction. Although spontaneous breathing was maintained, MBA administration resulted in respiratory acidosis due to hypoventilation. Thus, it is important to administer MBA with caution to dogs with insufficient cardiovascular function. In addition, ventilatory support is recommended.

Keywords: Alfaxalone, Medetomidine, Butorphanol, Dog, Cardiorespiratory effects.

***Corresponding Author:** Takaharu Itami. Department of Companion Animal Clinical Sciences, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan. Email: *t-itami@rakuno.ac.jp*

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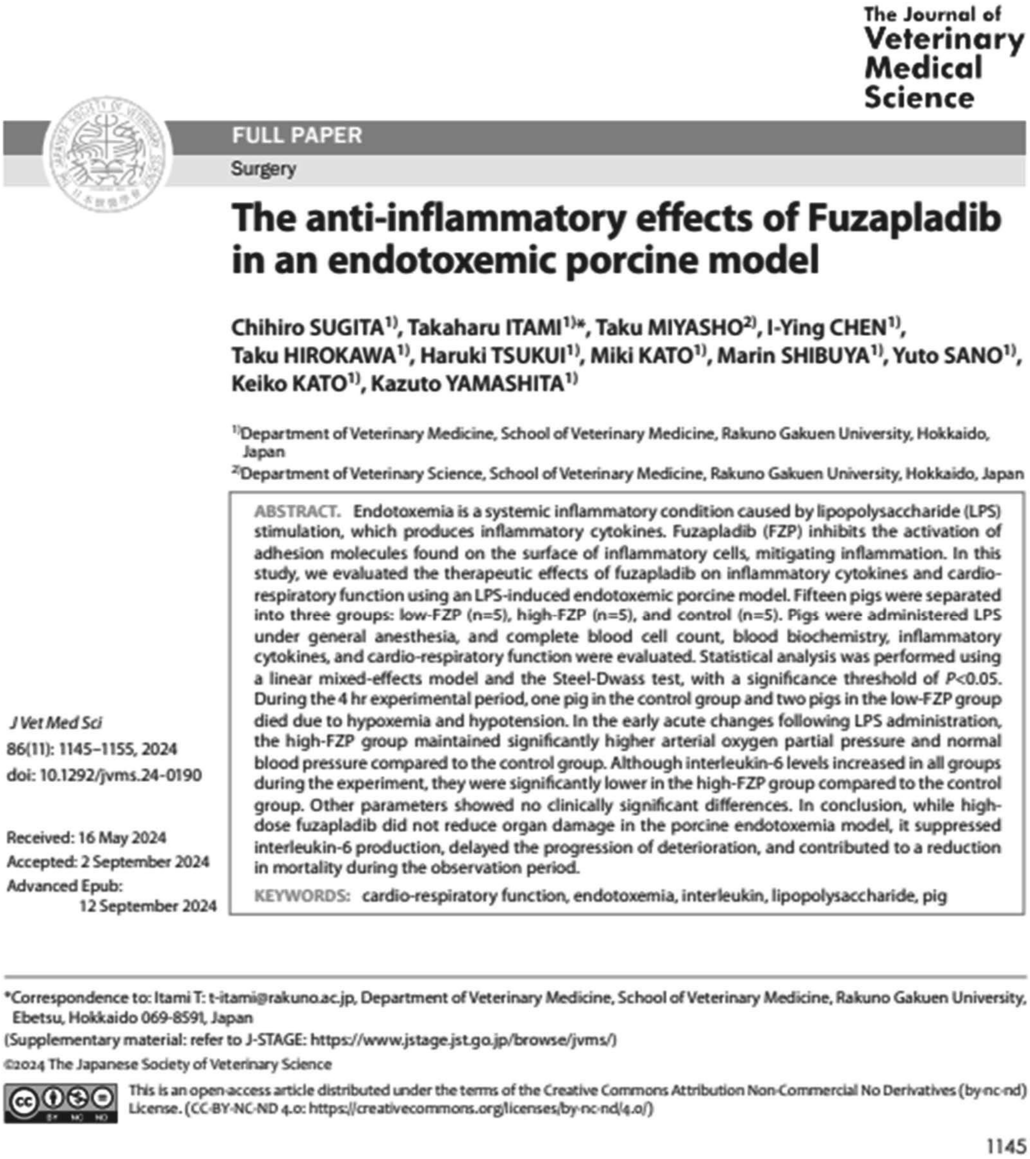

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FULL PAPER
Surgery

The anti-inflammatory effects of Fuzapladib in an endotoxemic porcine model

Chihiro SUGITA[1], Takaharu ITAMI[1]*, Taku MIYASHO[2], I-Ying CHEN[1], Taku HIROKAWA[1], Haruki TSUKUI[1], Miki KATO[1], Marin SHIBUYA[1], Yuto SANO[1], Keiko KATO[1], Kazuto YAMASHITA[1]

[1]Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Hokkaido, Japan
[2]Department of Veterinary Science, School of Veterinary Medicine, Rakuno Gakuen University, Hokkaido, Japan

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ABSTRACT. Endotoxemia is a systemic inflammatory condition caused by lipopolysaccharide (LPS) stimulation, which produces inflammatory cytokines. Fuzapladib (FZP) inhibits the activation of adhesion molecules found on the surface of inflammatory cells, mitigating inflammation. In this study, we evaluated the therapeutic effects of fuzapladib on inflammatory cytokines and cardio-respiratory function using an LPS-induced endotoxemic porcine model. Fifteen pigs were separated into three groups: low-FZP (n=5), high-FZP (n=5), and control (n=5). Pigs were administered LPS under general anesthesia, and complete blood cell count, blood biochemistry, inflammatory cytokines, and cardio-respiratory function were evaluated. Statistical analysis was performed using a linear mixed-effects model and the Steel-Dwass test, with a significance threshold of $P<0.05$. During the 4 hr experimental period, one pig in the control group and two pigs in the low-FZP group died due to hypoxemia and hypotension. In the early acute changes following LPS administration, the high-FZP group maintained significantly higher arterial oxygen partial pressure and normal blood pressure compared to the control group. Although interleukin-6 levels increased in all groups during the experiment, they were significantly lower in the high-FZP group compared to the control group. Other parameters showed no clinically significant differences. In conclusion, while high-dose fuzapladib did not reduce organ damage in the porcine endotoxemia model, it suppressed interleukin-6 production, delayed the progression of deterioration, and contributed to a reduction in mortality during the observation period.

KEYWORDS: cardio-respiratory function, endotoxemia, interleukin, lipopolysaccharide, pig

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*Correspondence to: Itami T: t-itami@rakuno.ac.jp, Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8591, Japan

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最終責任者　Takaharu Itami (Corresponding Author)

伴侶動物内科学（Companion Animal Internal Medicine）

Hiroshi Ohta

Associate Professor

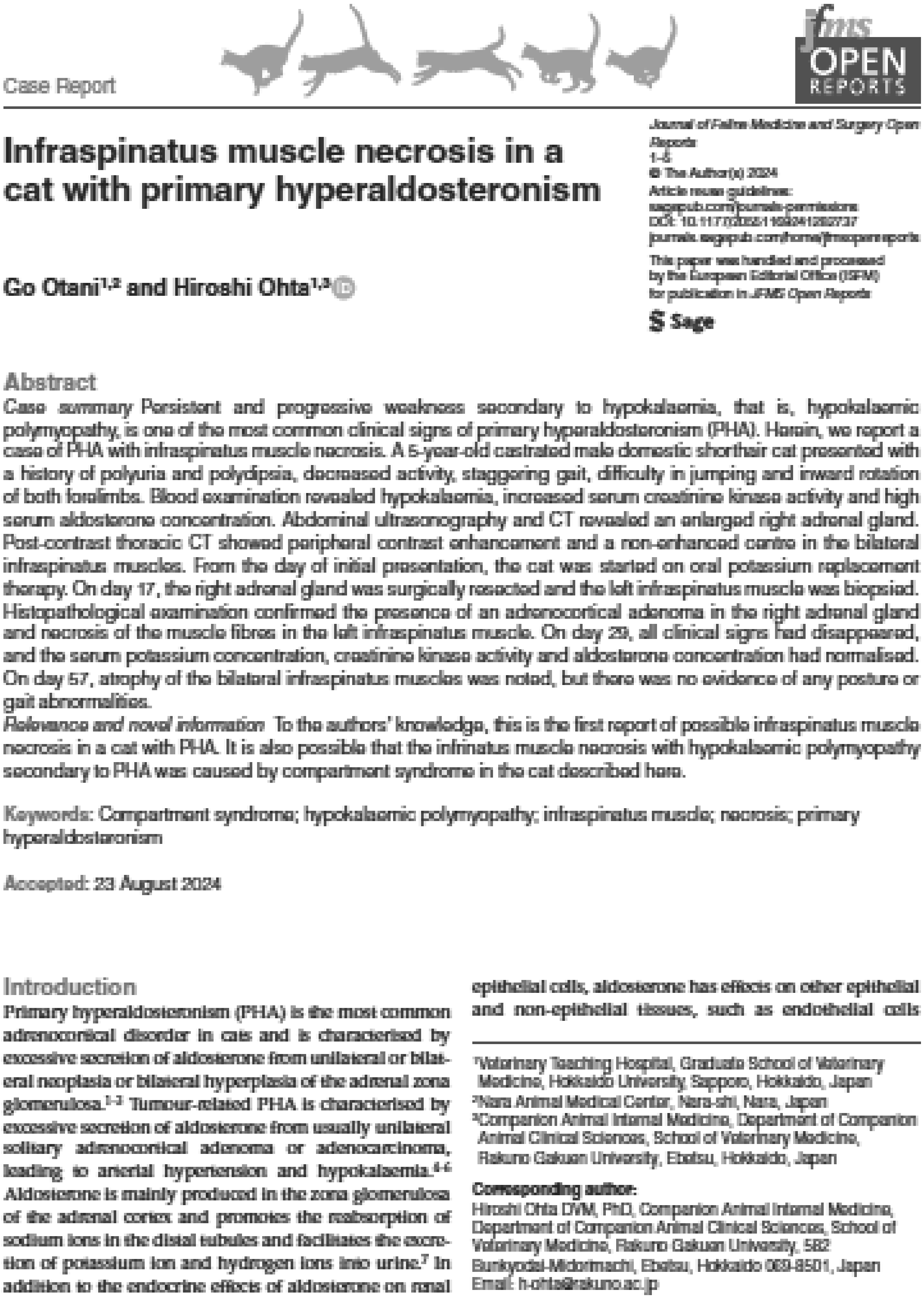
准教授　大田　寛

I. 筆頭または責任著者　＜First or Corresponding Author＞

1）Infraspinatus muscle necrosis in a cat with primary hyperaldosteronism.
Otani G, **Ohta H**.
JFMS Open Reports 10:20551169241282737. 2024.
doi: 10.1177/20551169241282737.

II.　その他＜Others＞

1) Management of acute-onset pancreatitis in dogs: a Narrative Review.
Lim SY, Cridge H, Twedt DC, **Ohta H**, Nuruki T, Steiner JM.
J Am Vet Med Assoc 262:1231–1240. 2024. doi: 10.2460/javma.24.02.0107.
2) Comparison of chemotherapy outcomes between normal and high serum cortisol concentration in dogs with lymphoma.
Yamazaki H, Bunbai K, Deguchi T, Tamura M, **Ohota H**.
J Vet Intern Med 38:1651–1658. 2024. doi: 10.1111/jvim.17044.



Case Report

Infraspinatus muscle necrosis in a cat with primary hyperaldosteronism

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Sage

Go Otani[1,2] and Hiroshi Ohta[1,3]

Abstract

Case summary Persistent and progressive weakness secondary to hypokalaemia, that is, hypokalaemic polymyopathy, is one of the most common clinical signs of primary hyperaldosteronism (PHA). Herein, we report a case of PHA with infraspinatus muscle necrosis. A 5-year-old castrated male domestic shorthair cat presented with a history of polyuria and polydipsia, decreased activity, staggering gait, difficulty in jumping and inward rotation of both forelimbs. Blood examination revealed hypokalaemia, increased serum creatinine kinase activity and high serum aldosterone concentration. Abdominal ultrasonography and CT revealed an enlarged right adrenal gland. Post-contrast thoracic CT showed peripheral contrast enhancement and a non-enhanced centre in the bilateral infraspinatus muscles. From the day of initial presentation, the cat was started on oral potassium replacement therapy. On day 17, the right adrenal gland was surgically resected and the left infraspinatus muscle was biopsied. Histopathological examination confirmed the presence of an adrenocortical adenoma in the right adrenal gland and necrosis of the muscle fibres in the left infraspinatus muscle. On day 29, all clinical signs had disappeared, and the serum potassium concentration, creatinine kinase activity and aldosterone concentration had normalised. On day 57, atrophy of the bilateral infraspinatus muscles was noted, but there was no evidence of any posture or gait abnormalities.
Relevance and novel information To the authors' knowledge, this is the first report of possible infraspinatus muscle necrosis in a cat with PHA. It is also possible that the infrinatus muscle necrosis with hypokalaemic polymyopathy secondary to PHA was caused by compartment syndrome in the cat described here.

Keywords: Compartment syndrome; hypokalaemic polymyopathy; infraspinatus muscle; necrosis; primary hyperaldosteronism

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Introduction

Primary hyperaldosteronism (PHA) is the most common adrenocortical disorder in cats and is characterised by excessive secretion of aldosterone from unilateral or bilateral neoplasia or bilateral hyperplasia of the adrenal zona glomerulosa.[1–3] Tumour-related PHA is characterised by excessive secretion of aldosterone from usually unilateral solitary adrenocortical adenoma or adenocarcinoma, leading to arterial hypertension and hypokalaemia.[4–6] Aldosterone is mainly produced in the zona glomerulosa of the adrenal cortex and promotes the reabsorption of sodium ions in the distal tubules and facilitates the excretion of potassium ion and hydrogen ions into urine.[7] In addition to the endocrine effects of aldosterone on renal epithelial cells, aldosterone has effects on other epithelial and non-epithelial tissues, such as endothelial cells

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[1]Veterinary Teaching Hospital, Graduate School of Veterinary Medicine, Hokkaido University, Sapporo, Hokkaido, Japan
[2]Nara Animal Medical Center, Nara-shi, Nara, Japan
[3]Companion Animal Internal Medicine, Department of Companion Animal Clinical Sciences, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

Corresponding author:
Hiroshi Ohta DVM, PhD, Companion Animal Internal Medicine, Department of Companion Animal Clinical Sciences, School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyodai-Midorimachi, Ebetsu, Hokkaido 069-8501, Japan
Email: h-ohta@rakuno.ac.jp

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最終責任者　Hiroshi Ohta (Corresponding Author)

JAVMA AVMA

Management of acute-onset pancreatitis in dogs: a Narrative Review

Sue Yee Lim, DVM, PhD[1¶]; Harry Cridge, MVB, MS, DACVIM[2¶]; David C. Twedt, DVM, DACVIM[3];
Hiroshi Ohta, DVM, PhD, AiCVIM[4]; Takaomi Nuruki, DVM[5]; Jörg M. Steiner, Dr med vet, PhD, DACVIM, DECVIM[1*]

[1]Gastrointestinal Laboratory, Department of Small Animal Clinical Sciences, School of Veterinary Medicine and Biomedical Sciences, Texas A&M University, College Station, TX
[2]Department of Small Animal Clinical Sciences, College of Veterinary Medicine, Michigan State University, East Lansing, MI
[3]Department of Clinical Sciences, College of Veterinary Medicine and Biomedical Science, Colorado State University, Fort Collins, CO
[4]Companion Animal Internal Medicine, Department of Companion Animal Clinical Sciences, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan
[5]TRVA Animal Medical Center, Setagaya City, Tokyo, Japan

¶Co-first authors

*Corresponding author: Dr. Steiner (jsteiner@cvm.tamu.edu)

ABSTRACT
Acute-onset pancreatitis (AP) is common in dogs and presents diagnostic as well as management challenges. Until recently, the management of AP in dogs was based mainly on supportive and symptomatic care. Identification and management of a possible cause of the disease is important, but the majority of cases are considered to be idiopathic. Fluid therapy that is tailored to the patient's needs is crucial to provide adequate hydration while preventing overhydration. Antiemetics are required to control vomiting and fluid loss and aid in early nutritional support. Recognition and management of complications is also crucial. Furthermore, analgesics for abdominal pain are very important. More recently, pharmaceutical modification of the inflammatory cascade has gained interest and the first specific therapeutic agent for the treatment of AP, fuzapladib sodium, has been shown to have a reasonable expectation of effectiveness in a pilot study. This drug has been licensed for the treatment of clinical signs of AP in dogs in Japan and also has achieved FDA conditional approval in the US. Antibiotics should not be used indiscriminately but are indicated for patients with aspiration pneumonia, gastrointestinal bacterial translocation, or evidence of another bacterial infection. Proton pump inhibitors and plasma are not routinely prescribed in pancreatitis unless specifically indicated. Nonsteroidal anti-inflammatory drugs should be avoided. Corticosteroid therapy, once thought to be contraindicated, may have some beneficial effects, as shown in a single retrospective study. However, further studies are required before their routine use can be recommended. Finally, a surgical approach is rarely indicated.

Keywords: management, acute, narrative, review, pancreatitis

Introduction

Pancreatitis is common in dogs and can be either acute or chronic, with some cases showing evidence of both patterns of disease, which most likely represents acute on chronic disesase.[1,2] Acute pancreatitis is histologically associated with neutrophilic infiltration and, in severe cases, pancreatic necrosis. Acute pancreatitis is potentially reversible.[1] In contrast, chronic pancreatitis is associated with lymphocytic plasmacytic infiltration and irreversible changes with acinar atrophy and fibrosis.[1] One histopathologic study[1] reported that almost two-thirds of pancreatitis cases are chronic. Clinically, the differentiation of acute and chronic pancreatitis is not possible, but chronic cases are commonly subclinical to mild and often remain undiagnosed. Acute pancreatitis is associated with an acute onset and worsening of clinical signs and, if severe, systemic complications and significant morbidity and mortality. The clinical differentiation between acute and chronic pancreatitis is difficult and requires histopathological confirmation. The designation acute-onset pancreatitis (AP), which refers to cases in which clinical signs appear suddenly, is the preferred designation.

Diagnosis of pancreatitis is challenging, but there is general agreement that optimal diagnosis is achieved by integrating clinical, imaging, and clinicopathologic findings. Measuring the concentration of pancreatic lipase in serum has been reported to represent the most sensitive and specific clinicopathologic parameter for the diagnosis of AP in the dog.[3]

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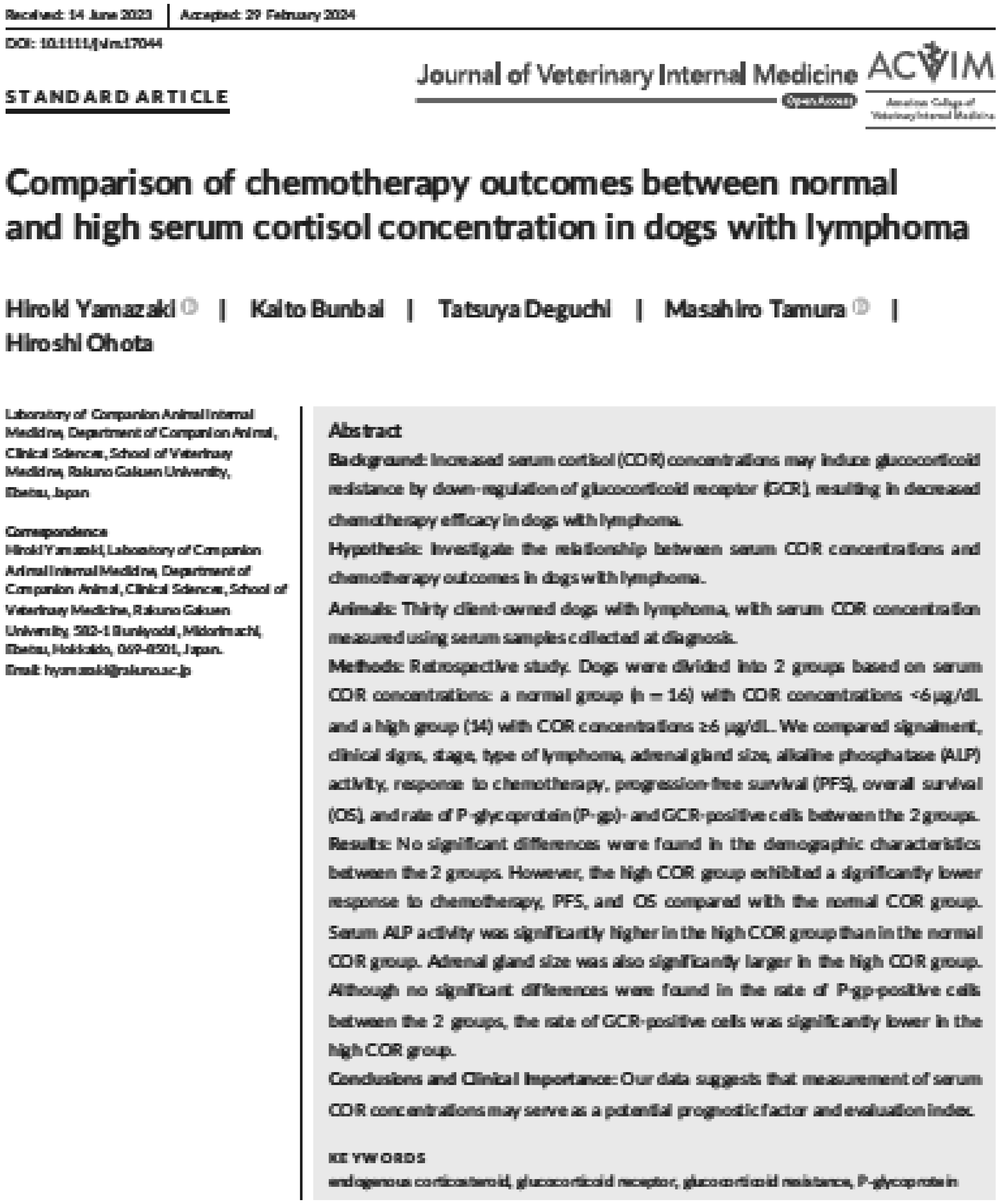
最終責任者　Jörg M. Steiner (Corresponding Author)



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STANDARD ARTICLE

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Comparison of chemotherapy outcomes between normal and high serum cortisol concentration in dogs with lymphoma

Hiroki Yamazaki | Kaito Bunbai | Tatsuya Deguchi | Masahiro Tamura | Hiroshi Ohota

Laboratory of Companion Animal Internal Medicine, Department of Companion Animal, Clinical Sciences, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan

Correspondence
Hiroki Yamazaki, Laboratory of Companion Animal Internal Medicine, Department of Companion Animal, Clinical Sciences, School of Veterinary Medicine, Rakuno Gakuen University, 582-1 Bunkyodai, Midorimachi, Ebetsu, Hokkaido, 069-8501, Japan.
Email: hyamazaki@rakuno.ac.jp

Abstract

Background: Increased serum cortisol (COR) concentrations may induce glucocorticoid resistance by down-regulation of glucocorticoid receptor (GCR), resulting in decreased chemotherapy efficacy in dogs with lymphoma.

Hypothesis: Investigate the relationship between serum COR concentrations and chemotherapy outcomes in dogs with lymphoma.

Animals: Thirty client-owned dogs with lymphoma, with serum COR concentration measured using serum samples collected at diagnosis.

Methods: Retrospective study. Dogs were divided into 2 groups based on serum COR concentrations: a normal group ($n = 16$) with COR concentrations <6 μg/dL and a high group (14) with COR concentrations ≥ 6 μg/dL. We compared signalment, clinical signs, stage, type of lymphoma, adrenal gland size, alkaline phosphatase (ALP) activity, response to chemotherapy, progression-free survival (PFS), overall survival (OS), and rate of P-glycoprotein (P-gp)- and GCR-positive cells between the 2 groups.

Results: No significant differences were found in the demographic characteristics between the 2 groups. However, the high COR group exhibited a significantly lower response to chemotherapy, PFS, and OS compared with the normal COR group. Serum ALP activity was significantly higher in the high COR group than in the normal COR group. Adrenal gland size was also significantly larger in the high COR group. Although no significant differences were found in the rate of P-gp-positive cells between the 2 groups, the rate of GCR-positive cells was significantly lower in the high COR group.

Conclusions and Clinical Importance: Our data suggests that measurement of serum COR concentrations may serve as a potential prognostic factor and evaluation index.

KEYWORDS
endogenous corticosteroid, glucocorticoid receptor, glucocorticoid resistance, P-glycoprotein

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最終責任者　Hiroki Yamazaki (Corresponding Author)

獣医臨床病理学（Veterinary Clinicopathology）

Minoru Okamoto

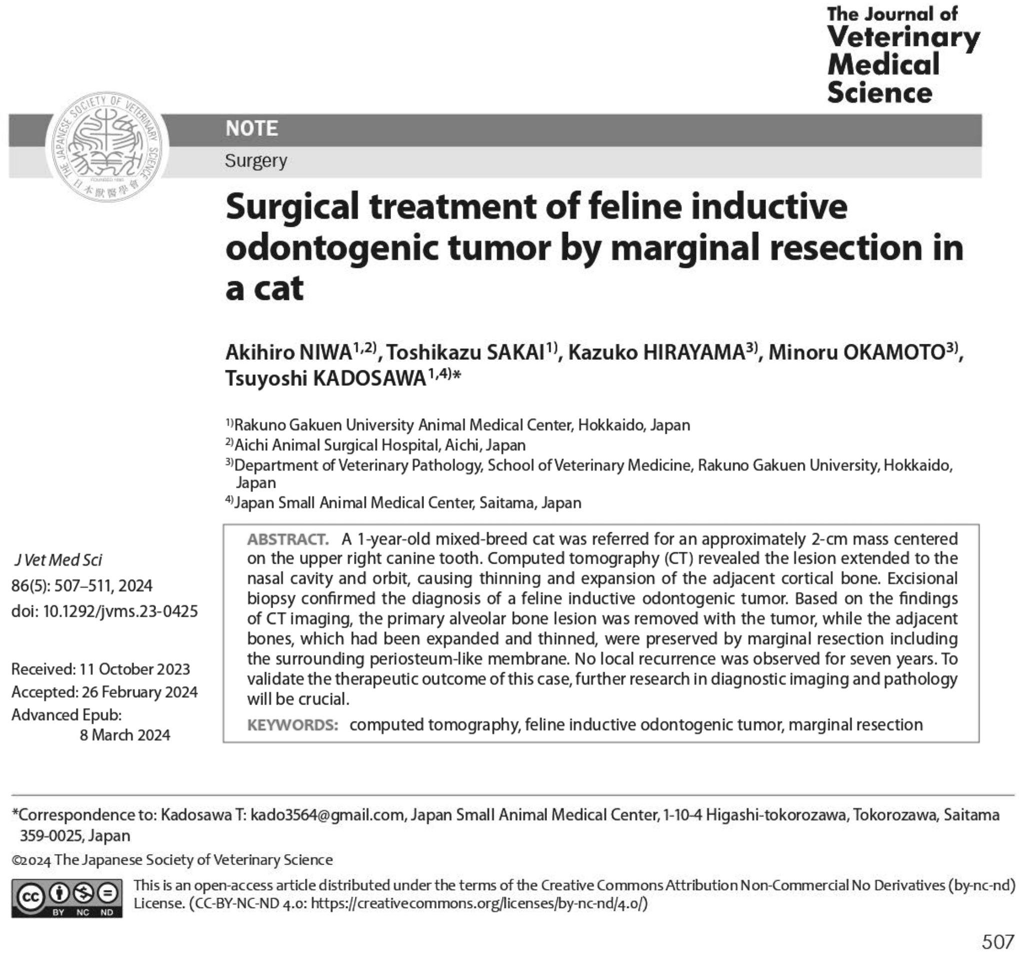
Associate Professor

准教授　岡本　実

I. 筆頭または責任著者　＜First or Corresponding Author＞

II.　その他　＜Others＞

1）Surgical treatment of feline inductive odontogenic tumor by marginal resection in a cat.
Niwa A, Sakai T, Hirayama K, **Okamoto M**, Kadosawa T.
J Vet Med Sci 86:507–511. 2024. doi: 10.1292/jvms.23-0425..



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NOTE

Surgery

Surgical treatment of feline inductive odontogenic tumor by marginal resection in a cat

Akihiro NIWA[1,2], Toshikazu SAKAI[1], Kazuko HIRAYAMA[3], Minoru OKAMOTO[3], Tsuyoshi KADOSAWA[1,4]*

[1]Rakuno Gakuen University Animal Medical Center, Hokkaido, Japan
[2]Aichi Animal Surgical Hospital, Aichi, Japan
[3]Department of Veterinary Pathology, School of Veterinary Medicine, Rakuno Gakuen University, Hokkaido, Japan
[4]Japan Small Animal Medical Center, Saitama, Japan

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ABSTRACT. A 1-year-old mixed-breed cat was referred for an approximately 2-cm mass centered on the upper right canine tooth. Computed tomography (CT) revealed the lesion extended to the nasal cavity and orbit, causing thinning and expansion of the adjacent cortical bone. Excisional biopsy confirmed the diagnosis of a feline inductive odontogenic tumor. Based on the findings of CT imaging, the primary alveolar bone lesion was removed with the tumor, while the adjacent bones, which had been expanded and thinned, were preserved by marginal resection including the surrounding periosteum-like membrane. No local recurrence was observed for seven years. To validate the therapeutic outcome of this case, further research in diagnostic imaging and pathology will be crucial.

KEYWORDS: computed tomography, feline inductive odontogenic tumor, marginal resection

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*Correspondence to: Kadosawa T: kado3564@gmail.com, Japan Small Animal Medical Center, 1-10-4 Higashi-tokorozawa, Tokorozawa, Saitama 359-0025, Japan

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最終責任者　Tsuyoshi Kadosawa (Corresponding Author)

獣医臨床病理学（Veterinary Clinicopathology）

Nao Tsuzuki

Associate Professor

准教授 都築 直

I. 筆頭または責任著者 ＜First or Corresponding Author＞

II. その他＜Others＞

1）Quantitative analysis of the skull in the Japanese wolf (Canis lupus hodophilax) using CT.
Suzuki C, Sasaki M, **Tsuzuki N**, Kayano, Yamada K, Ishiguro, Suzuki S, Taru H, Matsuda W, Endo H, Kikuchi T, Kikuchi K, Kitamura N.
J Vet Med Sci 86:440–450. 2024. doi: 10.1292/jvms.22-0070.

2）IgG Subtype Response against Virulence-Associated Protein A in Foals Naturally Infected with Rhodococcus equi.
Mizuguchi Y, **Tsuzuki N**, Ebana MD, Suzuki Y, Kakuda T.
Vet Sci 11:422. 2024. doi: 10.3390/vetsci11090422

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FULL PAPER
Wildlife Science

Quantitative analysis of the skull in the Japanese wolf (*Canis lupus hodophilax*) using CT

Chihiro SUZUKI1), Motoki SASAKI1)*, Nao TSUZUKI1), Mitsunori KAYANO1), Kazutaka YAMADA2), Naotaka ISHIGURO3), Satoshi SUZUKI4), Hajime TARU4), Wataru MATSUDA5), Hideki ENDO6), Tomoaki KIKUCHI7), Kaoru KIKUCHI8), Nobuo KITAMURA1)

1)Obihiro University of Agriculture and Veterinary Medicine, Hokkaido, Japan
2)Azabu University, Kanagawa, Japan
3)The Graduate University for Advanced Studies, Miura, Kanagawa, Japan
4)Kanagawa Prefectural Museum of Natural History, Kanagawa, Japan
5)Oyodo-cho Town Official Board of Education, Nara, Japan
6)The University Museum, The University of Tokyo, Tokyo, Japan
7)Hokkaido Chuo Agricultural Mutual Aid Association, Hokkaido, Japan
8)Kikuchi Veterinary Clinic, Iwate, Japan

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ABSTRACT. In this study using computed tomography (CT), the volumes of the internal cranial cavities, such as the braincase, frontal sinus and tympanic cavity, and the ratio of the volume of each cavity to the skull volume in Japanese wolves were quantified, and CT images of the frontal sinus were observed. The results were then compared with those of other wolf subspecies, including Akita, a dog breed, to clarify the characteristics of the internal cranial cavities in Japanese wolves. The present study revealed that the Japanese wolf had a relatively larger braincase volume and a relatively smaller frontal sinus volume than the wolf ssp. (a group of wild wolf subspecies except the Japanese wolf) and Akita. Moreover, the relative and absolute tympanic cavity volumes of the Japanese wolf and Akita were significantly smaller than those of the wolf ssp. In the CT image or macroscopic observations, the frontal sinuses of the wolf ssp. and Akita were relatively well developed to the caudal and dorsal directions, respectively, compared with that of the Japanese wolf, and the tympanic cavity of the wolf ssp. was more largely swelled ventrally and medially than that of other groups.

KEYWORDS: braincase, CT, frontal sinus, Japanese wolf, tympanic cavity

The gray wolf or wolf (*Canis lupus* Linnaeus, 1758), which is the largest canids, inhabits the Eurasian and North American continents and the North Pole [32, 36]. Dogs (*C. l. familiaris*), classified as subspecies of wolves, were domesticated from wild wolves by humans 15,000 years ago [41, 46]; however, the place of domestication remains controversial. A study on the genetic diversity with mitochondrial DNA (mtDNA) information suggested a Southeast Asian origin for domestication [41], whereas the single nucleotide polymorphism (SNP) genotyping array analysis suggested a simultaneous origin in several areas worldwide [53].

The Japanese wolf (*C. l. hodophilax*) is one of the subspecies of gray wolves and inhabited Honshu, Shikoku and Kyushu islands. Japanese wolves have a distinct mtDNA haplotype and are able to be genetically distinguished from other gray wolves [20, 22–24, 34, 35]. A recent phylogenetic study using the nuclear DNA (nDNA) extracted from nine Japanese wolves suggested that Japanese wolves are genetically separated from other wolves, including ancient wolves [14]. It is also possible to distinguish Japanese wolves from other subspecies by common morphological characters. For example, most Japanese wolves have a rostral alar foramen separated by a bony septum and a horizontal plate of the palatine bone with an anterior notch (Fig. 1) [15, 17, 18, 37–39, 51]. Regarding skull size, that of Japanese wolves is smaller than that of most other subspecies [17].

In the Meiji era (1868–1912), infectious diseases, such as rabies, introduced from overseas spread among Japanese wolves. In addition, with the development of the livestock industry in Japan, the extermination of Japanese wolves was recommended as they attacked livestock [10, 15, 54]. As a result, the population of the Japanese wolf decreased and a male wolf caught at Higashi Yoshino

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*Correspondence to: Sasaki M: sasakim@obihiro.ac.jp, Obihiro University of Agriculture and Veterinary Medicine, Inada, Obihiro, Hokkaido 080-8555, Japan

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veterinary sciences

MDPI

Article

IgG Subtype Response against Virulence-Associated Protein A in Foals Naturally Infected with *Rhodococcus equi*

Yuya Mizuguchi [1], Nao Tsuzuki [2], Marina Dee Ebana [3], Yasunori Suzuki [3] and Tsutomu Kakuda [3,*]

[1] Mitsuishi Animal Medical Center, Hokkaido 059-3105, Japan; yuuya_mizuguchi_p1@nosai-do.or.jp
[2] Department of Veterinary Medicine, Rakuno Gakuen University, Hokkaido 069-8501, Japan; n-tsuzuki@rakuno.ac.jp
[3] Laboratory of Animal Hygiene, Faculty of Veterinary Medicine, School of Veterinary Medicine, Kitasato University, Aomori 034-8628, Japan; vm19022@st.kitasato-u.ac.jp (M.D.E.); ysuzuki@vmas.kitasato-u.ac.jp (Y.S.)
* Correspondence: kakuda@vmas.kitasato-u.ac.jp; Tel.: +81-176-24-9458

Simple Summary: *Rhodococcus equi* infection causes life-threatening bacterial pneumonia in foals, resulting in significant economic losses to equine farms. Due to the lack of an effective vaccine, infected foals receive intensive antibiotic treatment. However, the emergence of antibiotic-resistant bacteria in recent years has become problematic. Thus, appropriate use of antibiotics is required. Horses that die from *R. equi* infection tend to show specific patterns of IgG subtype responses. Therefore, this study focused on qualitative differences in antibody responses to *R. equi* between resistant and susceptible foals as a means of predicting *R. equi* susceptibility. These findings may be useful in predicting which foals require treatment.

Abstract: *Rhodococcus equi* is an intracellular bacterium that causes suppurative pneumonia in foals. T-helper (Th) 1 cells play an important role in the protective response against *R. equi*. In mice and humans, the directionality of IgG switching reflects the polarization of Th-cell responses, but this has not been fully elucidated in horses. In this 4-year study, we classified *R. equi*-infected foals into surviving and non-surviving group and investigated differences in IgG subclass response to virulence-associated protein A, the main virulence factor of *R. equi*, between the groups. IgGa, IgGb, and IgG(T) titers were significantly higher in the non-surviving group compared with the surviving group. The titers of IgGa and IgG(T), IgGb and IgG(T), and IgGa and IgGb, respectively, were positively correlated, and the IgG(T)/IgGb ratio in the non-surviving group was significantly higher than that in the surviving group. The IgG(T) titer tended to increase more than the IgGa and IgGb titers in the non-surviving group compared with the surviving group. Our findings suggest that the IgG(T) bias in IgG subclass responses reflects the immune status, which exacerbates *R. equi* infection.

Keywords: *Rhodococcus equi*; prognosis; IgG subtype; polarization of Th-cell response

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1. Introduction

Rhodococcus equi (*R. equi*) causes suppurative pneumonia in foals aged 1–5 months, leading to severe economic losses in horse-farming areas worldwide each year [1–3]. *R. equi* is widely distributed in soil, and the rate of infection is high on farms with high levels of contamination [4]. Because there is no effective vaccine, clinically affected foals are diagnosed early and treated with antibiotics [5].

R. equi is a Gram-positive intracellular bacterium that survives and multiplies within the phagosomes of macrophages [6]. It harbors a virulence plasmid that encodes for virulence-associated protein A (VapA), which is secreted within the macrophage phagosome to prevent decreased intravesicular pH, facilitating *R. equi* survival [7,8]. Although humoral immune responses have been reported to induce protective effects by producing specific antibodies, cellular immune responses are considered of primary importance for

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最終責任者 Tsutomu Kakuda (Corresponding Author)

伴侶動物内科学（Companion Animal Internal Medicine）

Hiroki Yamazaki

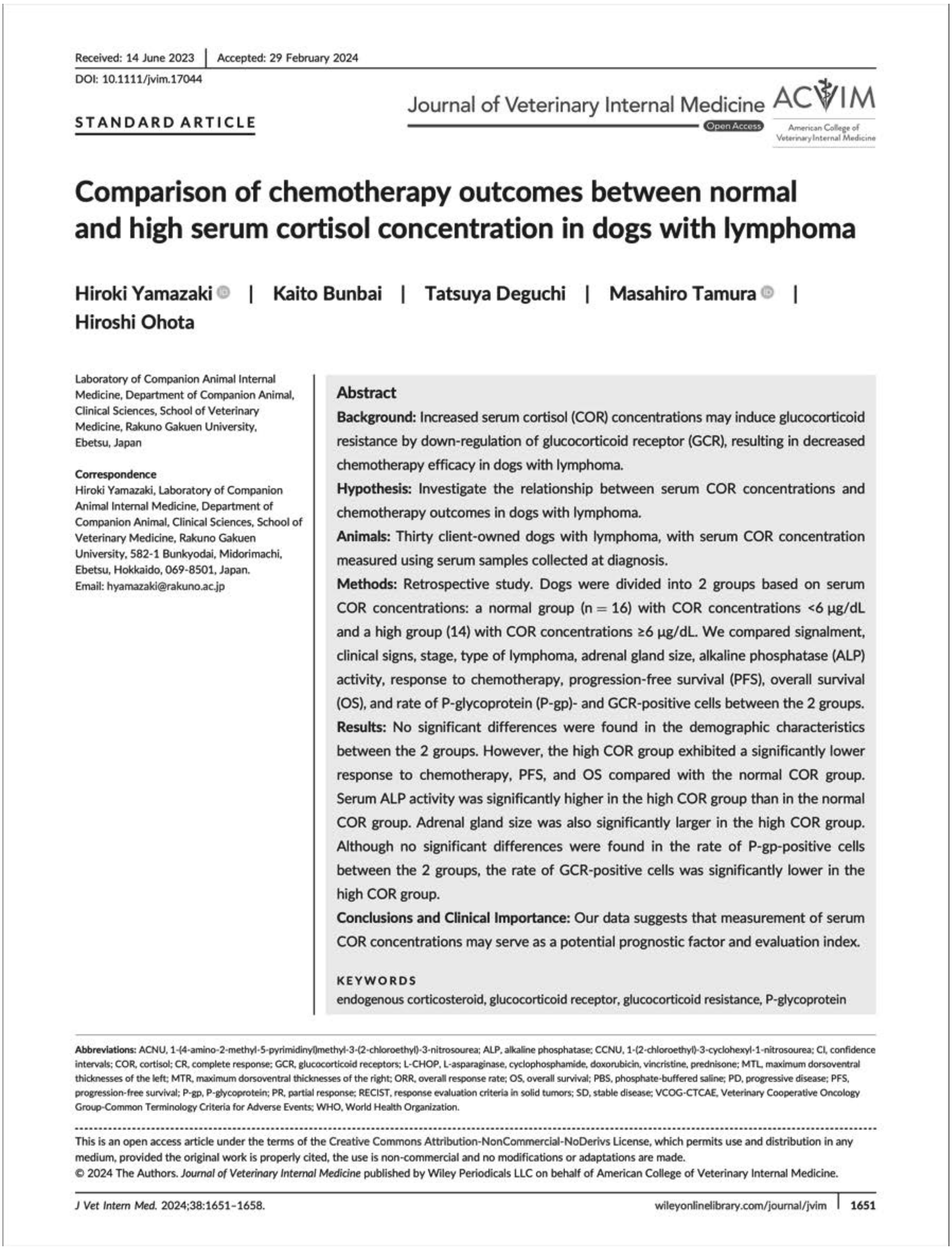
Associate Professor

准教授　山﨑　裕毅

I. 筆頭または責任著者　＜First or Corresponding Author＞

1) Comparison of chemotherapy outcomes between normal and high serum cortisol concentration in dogs with lymphoma.
Yamazaki H, Bunbai K, Deguchi T, Tamura M, Ohota H.
J Vet Intern Med 38:1651–1658. 2024. doi: 10.1111/jvim.17044.
2) Influence of changes in gut microbiota and metabolites on postoperative late complications following gastrointestinal resection.
Yamazaki H, Hanasaki Y, Himura Y, Sakai T, Torisu S.
J Pet Anim Nutr 27: *in press.* 2024.

II. その他 ＜Others＞



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Comparison of chemotherapy outcomes between normal and high serum cortisol concentration in dogs with lymphoma

Hiroki Yamazaki | **Kaito Bunbai** | **Tatsuya Deguchi** | **Masahiro Tamura** | **Hiroshi Ohota**

Laboratory of Companion Animal Internal Medicine, Department of Companion Animal, Clinical Sciences, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan

Correspondence
Hiroki Yamazaki, Laboratory of Companion Animal Internal Medicine, Department of Companion Animal, Clinical Sciences, School of Veterinary Medicine, Rakuno Gakuen University, 582-1 Bunkyodai, Midorimachi, Ebetsu, Hokkaido, 069-8501, Japan.
Email: hyamazaki@rakuno.ac.jp

Abstract

Background: Increased serum cortisol (COR) concentrations may induce glucocorticoid resistance by down-regulation of glucocorticoid receptor (GCR), resulting in decreased chemotherapy efficacy in dogs with lymphoma.

Hypothesis: Investigate the relationship between serum COR concentrations and chemotherapy outcomes in dogs with lymphoma.

Animals: Thirty client-owned dogs with lymphoma, with serum COR concentration measured using serum samples collected at diagnosis.

Methods: Retrospective study. Dogs were divided into 2 groups based on serum COR concentrations: a normal group ($n = 16$) with COR concentrations <6 μg/dL and a high group (14) with COR concentrations ≥6 μg/dL. We compared signalment, clinical signs, stage, type of lymphoma, adrenal gland size, alkaline phosphatase (ALP) activity, response to chemotherapy, progression-free survival (PFS), overall survival (OS), and rate of P-glycoprotein (P-gp)- and GCR-positive cells between the 2 groups.

Results: No significant differences were found in the demographic characteristics between the 2 groups. However, the high COR group exhibited a significantly lower response to chemotherapy, PFS, and OS compared with the normal COR group. Serum ALP activity was significantly higher in the high COR group than in the normal COR group. Adrenal gland size was also significantly larger in the high COR group. Although no significant differences were found in the rate of P-gp-positive cells between the 2 groups, the rate of GCR-positive cells was significantly lower in the high COR group.

Conclusions and Clinical Importance: Our data suggests that measurement of serum COR concentrations may serve as a potential prognostic factor and evaluation index.

KEYWORDS
endogenous corticosteroid, glucocorticoid receptor, glucocorticoid resistance, P-glycoprotein

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Abbreviations: ACNU, 1-(4-amino-2-methyl-5-pyrimidinyl)methyl-3-(2-chloroethyl)-3-nitrosourea; ALP, alkaline phosphatase; CCNU, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea; CI, confidence intervals; COR, cortisol; CR, complete response; GCR, glucocorticoid receptors; L-CHOP, L-asparaginase, cyclophosphamide, doxorubicin, vincristine, prednisone; MTL, maximum dorsoventral thicknesses of the left; MTR, maximum dorsoventral thicknesses of the right; ORR, overall response rate; OS, overall survival; PBS, phosphate-buffered saline; PD, progressive disease; PFS, progression-free survival; P-gp, P-glycoprotein; PR, partial response; RECIST, response evaluation criteria in solid tumors; SD, stable disease; VCOG-CTCAE, Veterinary Cooperative Oncology Group-Common Terminology Criteria for Adverse Events; WHO, World Health Organization.

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Original Paper

Influence of changes in gut microbiota and metabolites on postoperative late complications following gastrointestinal resection.

Hiroki Yamazaki[1], Yoshi Hanasaki[2], Yuri Himura[2],
Toshikazu Sakai[3], Shidow Torisu[3]

[1]Laboratory of Companion Animal Internal, Medicine, Department of Companion Animal Clinical Sciences, School of Veterinary Medicine, Rakuno Gakuen University, 582-1 Bunkyodai-Midorimachi, Ebetsu, Hokkaido, 069-8501, JAPAN
[2]School of Medicine Department of Medical Science and Graduate School of Medicine. Osaka Metropolitan University, 1-4-3 Asahi-machi, Abeno-ku, Osaka-shi, Osaka 545-8585, Japan
[3]Laboratory of Companion Animal Surgery, Department of Companion, Animal Clinical Sciences, School of Veterinary Medicine, Rakuno Gakuen University, 582-1 Bunkyodai-Midorimachi, Ebetsu, Hokkaido, 069-8501, JAPAN

Abstract：We evaluated gut microbiota and metabolite concentrations using fecal samples from dogs that had undergone gastrointestinal resection to explore the distinctive post-surgery effects. Analyses of the 16S rRNA gene sequences and metabolomes were conducted on fecal samples from 4 healthy dogs, 4 dogs with inflammatory bowel disease (IBD), and 16 dogs that had gastrointestinal resections. The resected dogs exhibited a reduction in α-diversity compared to their pre-resection levels, leading to significant changes such as a decrease in the Firmicutes and Bacteroidetes phyla, and an increase in the Proteobacteria phylum. Concentrations of short-chain fatty acids (SCFAs) were significantly lower after gastroduodenectomy, and bile acids (BAs) concentrations were significantly higher after ileectomy, compared to pre-resection levels. These effects varied according to the resection site, and 4 of the 16 resected dogs showed marked changes in their intestinal environment, resembling the gut conditions found in IBD, and ultimately developed enteritis, a condition considered to be a late complication. Our findings reveal characteristic changes in gut microbiota and metabolites following gastrointestinal resections, and suggest that the decrease in SCFAs and the increase in BAs may be associated with late complications. This assessment method using fecal samples may serve as a novel approach to predicting late complications after gastrointestinal resections.

Keywords：Dog, Gastrointestinal Resection, Late Complications, Gut Microbiota, Intestinal Metabolites

Introduction

Obesity, defined as the excessive accumulation of body fat, is caused by an energy imbalance when the dietary intake exceeds energy expenditure. Obesity in humans increases the risk of developing various diseases, including diabetes, hypertension, dyslipidemia including hyperlipidemia, cardiovascular disease, and coronary artery disease[3,16,19,21]. Hyperlipidemia is a condition of high blood cholesterol, triglycerides, and other lipids. The onset of hyperlipidemia is caused by obesity due to lifestyle disturbances, such as overeating and lack of exercise, resulting in abnormal lipoprotein cholesterol values. Lipoprotein particles, lipid-protein through the bloodstream from sites of absorption and synthesis to systemic use. Obesity results in increased low-density lipoprotein (LDL) levels and decreased high-density lipoprotein (HDL) levels[9,8,12]. In humans, high levels of LDL accelerate the development of coronary artery disease due to lipid accumulation in blood vessel walls[3,4]. Similar to humans, obese cats develop hyperlipidemia with insulin resistance and abnormal lipoprotein cholesterol fractions[10,11,13]. On the other hand, fewer studies of lipoprotein cholesterol in cats than in humans because the occurrence of atherosclerosis due to hyperlipidemia is rare in cats[1,6]. Also, most reports on lipoprotein cholesterol levels in cats have used experimental models

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最終責任者　Hiroki Yamazaki (First Author and Corresponding Author)

伴侶動物内科学（Companion Animal Internal Medicine）

Tatsuya Deguchi

Lecturer

講師　出口　辰弥

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Ⅱ. その他＜Others＞

1）Comparison of chemotherapy outcomes between normal and high serum cortisol concentration in dogs with lymphoma.
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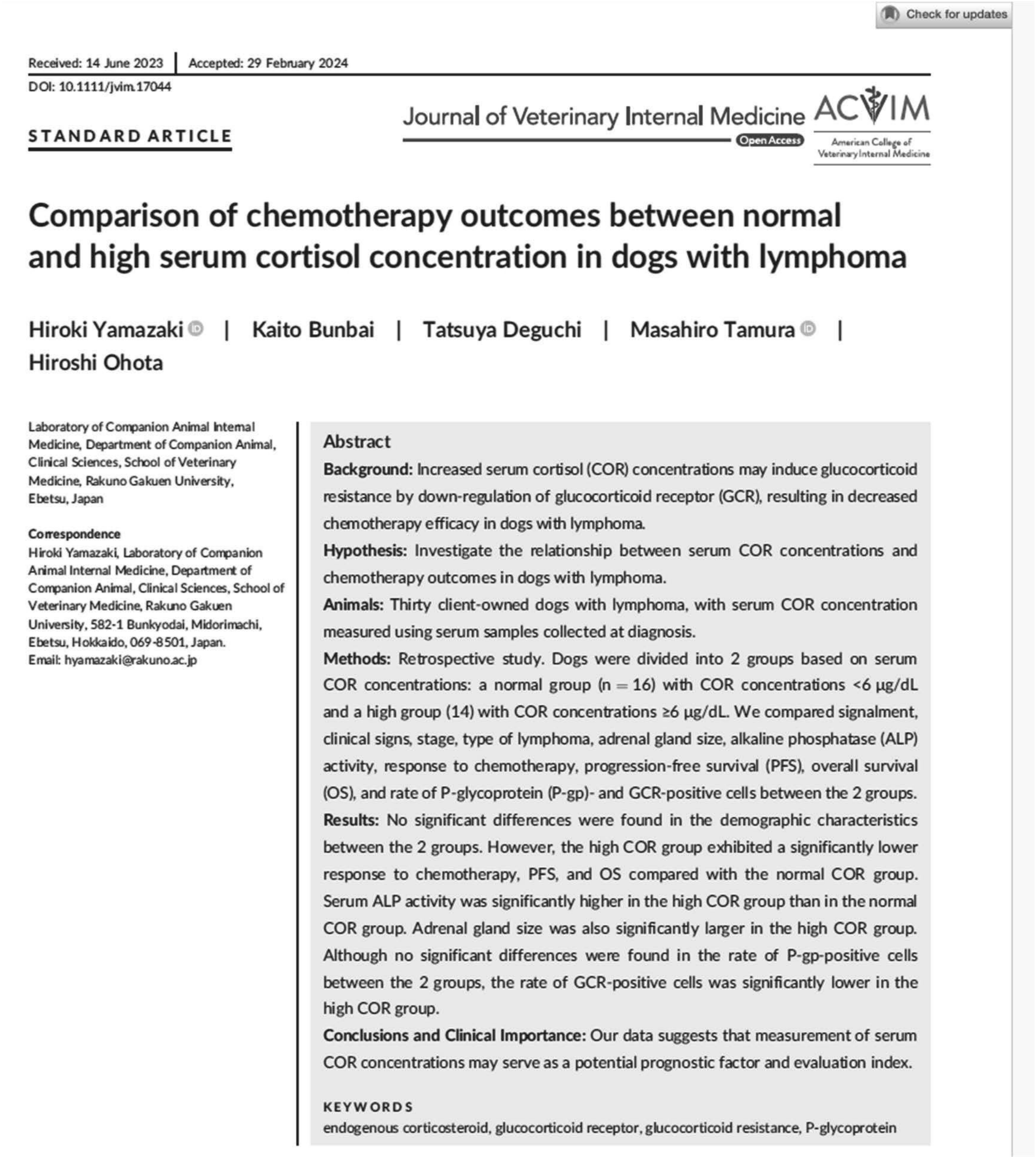

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STANDARD ARTICLE

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Comparison of chemotherapy outcomes between normal and high serum cortisol concentration in dogs with lymphoma

Hiroki Yamazaki | Kaito Bunbai | Tatsuya Deguchi | Masahiro Tamura | Hiroshi Ohota

Laboratory of Companion Animal Internal Medicine, Department of Companion Animal, Clinical Sciences, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan

Correspondence
Hiroki Yamazaki, Laboratory of Companion Animal Internal Medicine, Department of Companion Animal, Clinical Sciences, School of Veterinary Medicine, Rakuno Gakuen University, 582-1 Bunkyodai, Midorimachi, Ebetsu, Hokkaido, 069-8501, Japan.
Email: hyamazaki@rakuno.ac.jp

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最終責任者　Hiroki Yamazaki (Corresponding Author)

獣医生化学（Veterinary Biochemistry）

Jumpei Fujiki

Lecturer

講師　藤木　純平

I. 筆頭または責任著者　＜First or Corresponding Author＞

1）Using phage to drive selections toward restoring antibiotic sensitivity in *Pseudomonas aeruginosa* via chromosomal deletions.
Fujiki J, Nakamura K, Ishiguro Y, Iwano H
Front Microbiol 15:1401234. 2024. doi: 10.3389/fmicb.2024.1401234.

2）DNA methylation of Ad4BP/SF-1 suppresses Cyp11a1 and StAR transcripts in C2C12 myoblasts.
Fujiki J, Maeda N, Yamaguchi K, Ohtsuki Y, Iwano H.
Mol Cell Endocrinol 593:112336. 2024. doi: 10.1016/j.mce.2024.112336.

II.　その他　＜Others＞

1）Innate immune response of bovine mammary epithelial cells in Mycoplasma bovis mastitis using an in vitro model of bovine mammary gland infection.
Imaizumi N, Gondaira S, Kamioka M, Sugiura T, Eguchi A, Nishi K, **Fujiki J**, Iwano H, Higuchi H.
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Wu C, **Fujiki J**, Mathieu J, Schwarz C, Cornell C, Alvarez PJJ.
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Ohara J, **Fujiki J**, Kinoshita M, Sudo K, Kawaguchi K, Inoue K, Naito Y, Moriyama K, Nakamura T, Iwano H, Sawa T.
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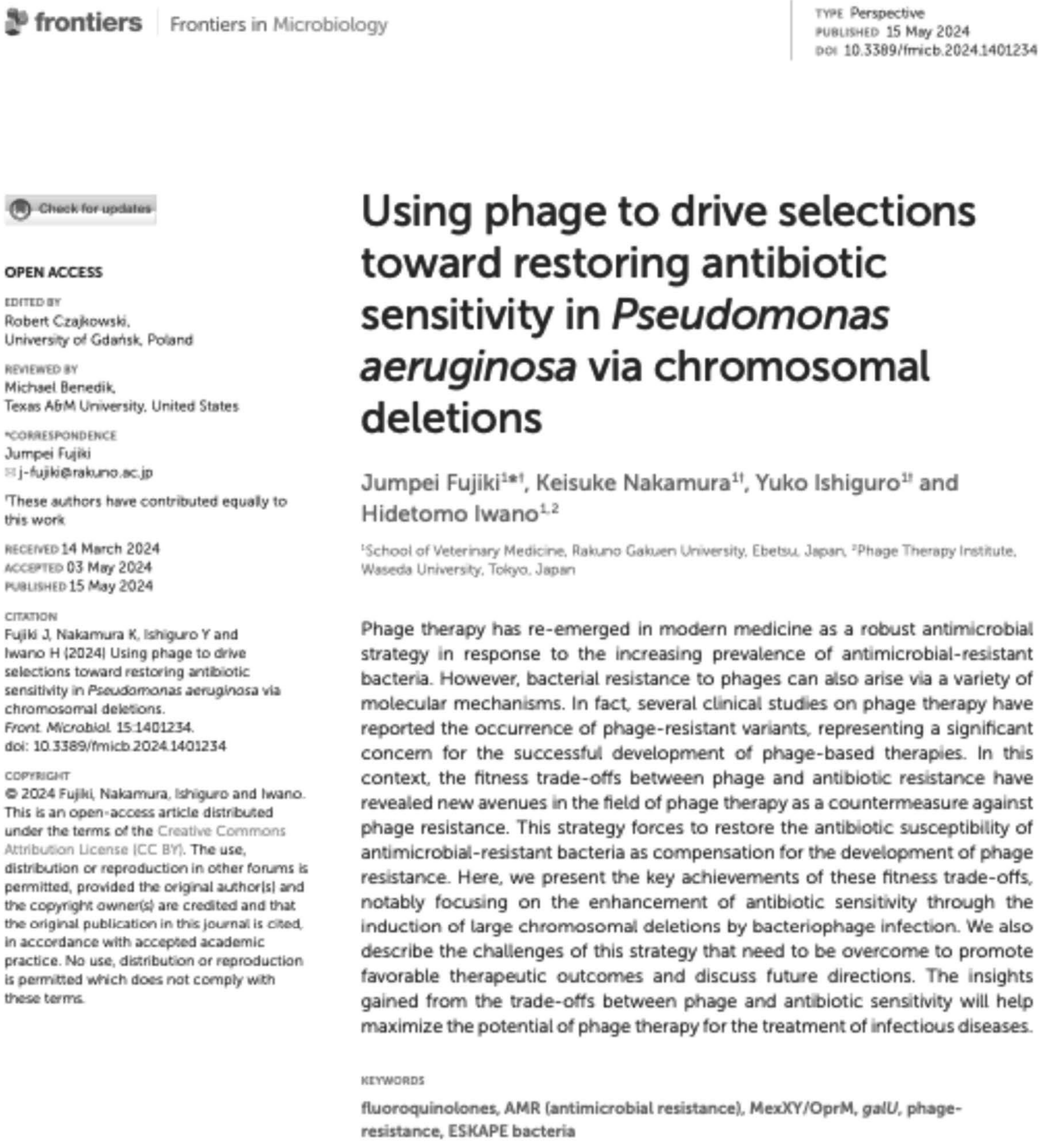

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Using phage to drive selections toward restoring antibiotic sensitivity in *Pseudomonas aeruginosa* via chromosomal deletions

Jumpei Fujiki[1*†], Keisuke Nakamura[1†], Yuko Ishiguro[1†] and Hidetomo Iwano[1,2]

[1]School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan, [2]Phage Therapy Institute, Waseda University, Tokyo, Japan

Phage therapy has re-emerged in modern medicine as a robust antimicrobial strategy in response to the increasing prevalence of antimicrobial-resistant bacteria. However, bacterial resistance to phages can also arise via a variety of molecular mechanisms. In fact, several clinical studies on phage therapy have reported the occurrence of phage-resistant variants, representing a significant concern for the successful development of phage-based therapies. In this context, the fitness trade-offs between phage and antibiotic resistance have revealed new avenues in the field of phage therapy as a countermeasure against phage resistance. This strategy forces to restore the antibiotic susceptibility of antimicrobial-resistant bacteria as compensation for the development of phage resistance. Here, we present the key achievements of these fitness trade-offs, notably focusing on the enhancement of antibiotic sensitivity through the induction of large chromosomal deletions by bacteriophage infection. We also describe the challenges of this strategy that need to be overcome to promote favorable therapeutic outcomes and discuss future directions. The insights gained from the trade-offs between phage and antibiotic sensitivity will help maximize the potential of phage therapy for the treatment of infectious diseases.

KEYWORDS

fluoroquinolones, AMR (antimicrobial resistance), MexXY/OprM, *galU*, phage-resistance, ESKAPE bacteria

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Robert Czajkowski,
University of Gdańsk, Poland

REVIEWED BY
Michael Benedik,
Texas A&M University, United States

*CORRESPONDENCE
Jumpei Fujiki
✉ j-fujiki@rakuno.ac.jp

†These authors have contributed equally to this work

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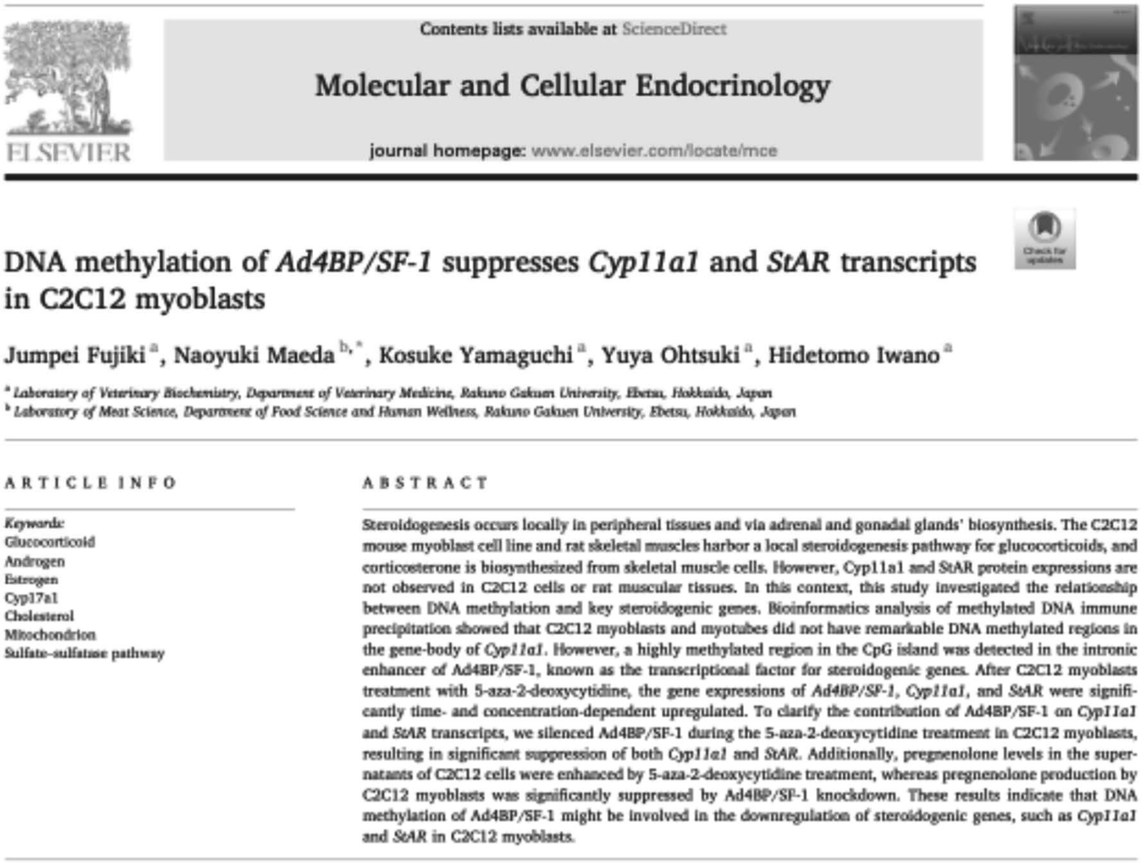

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Molecular and Cellular Endocrinology

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DNA methylation of *Ad4BP/SF-1* suppresses *Cyp11a1* and *StAR* transcripts in C2C12 myoblasts

Jumpei Fujiki[a], Naoyuki Maeda[b,*], Kosuke Yamaguchi[a], Yuya Ohtsuki[a], Hidetomo Iwano[a]

[a] *Laboratory of Veterinary Biochemistry, Department of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan*
[b] *Laboratory of Meat Science, Department of Food Science and Human Wellness, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan*

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ABSTRACT

Steroidogenesis occurs locally in peripheral tissues and via adrenal and gonadal glands' biosynthesis. The C2C12 mouse myoblast cell line and rat skeletal muscles harbor a local steroidogenesis pathway for glucocorticoids, and corticosterone is biosynthesized from skeletal muscle cells. However, Cyp11a1 and StAR protein expressions are not observed in C2C12 cells or rat muscular tissues. In this context, this study investigated the relationship between DNA methylation and key steroidogenic genes. Bioinformatics analysis of methylated DNA immune precipitation showed that C2C12 myoblasts and myotubes did not have remarkable DNA methylated regions in the gene-body of *Cyp11a1*. However, a highly methylated region in the CpG island was detected in the intronic enhancer of Ad4BP/SF-1, known as the transcriptional factor for steroidogenic genes. After C2C12 myoblasts treatment with 5-aza-2-deoxycytidine, the gene expressions of *Ad4BP/SF-1*, *Cyp11a1*, and *StAR* were significantly time- and concentration-dependent upregulated. To clarify the contribution of Ad4BP/SF-1 on *Cyp11a1* and *StAR* transcripts, we silenced Ad4BP/SF-1 during the 5-aza-2-deoxycytidine treatment in C2C12 myoblasts, resulting in significant suppression of both *Cyp11a1* and *StAR*. Additionally, pregnenolone levels in the supernatants of C2C12 cells were enhanced by 5-aza-2-deoxycytidine treatment, whereas pregnenolone production by C2C12 myoblasts was significantly suppressed by Ad4BP/SF-1 knockdown. These results indicate that DNA methylation of Ad4BP/SF-1 might be involved in the downregulation of steroidogenic genes, such as *Cyp11a1* and *StAR* in C2C12 myoblasts.

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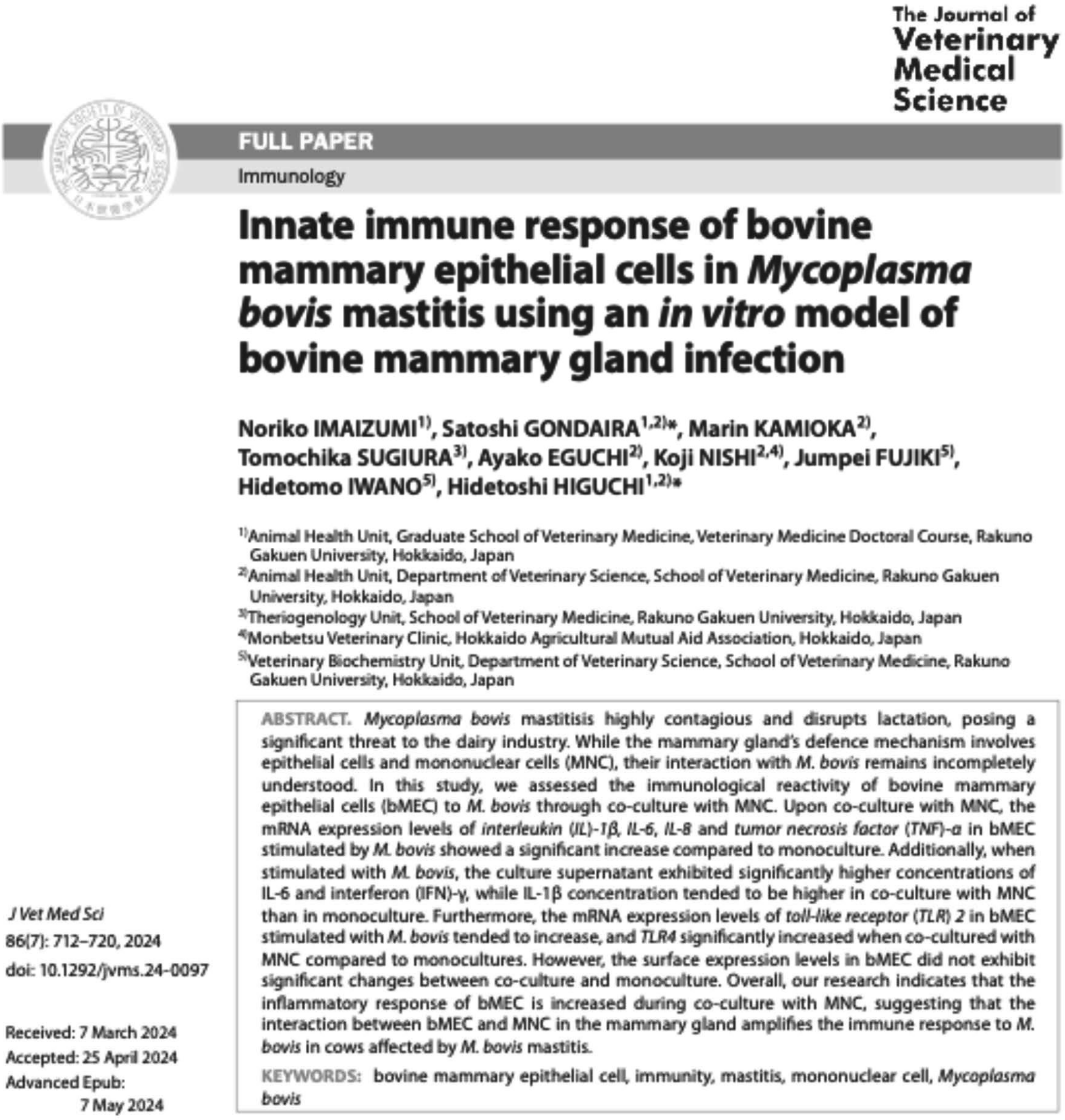

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FULL PAPER
Immunology

Innate immune response of bovine mammary epithelial cells in *Mycoplasma bovis* mastitis using an *in vitro* model of bovine mammary gland infection

Noriko IMAIZUMI[1)], Satoshi GONDAIRA[1,2)]*, Marin KAMIOKA[2)], Tomochika SUGIURA[3)], Ayako EGUCHI[2)], Koji NISHI[2,4)], Jumpei FUJIKI[5)], Hidetomo IWANO[5)], Hidetoshi HIGUCHI[1,2)]*

[1)]Animal Health Unit, Graduate School of Veterinary Medicine, Veterinary Medicine Doctoral Course, Rakuno Gakuen University, Hokkaido, Japan
[2)]Animal Health Unit, Department of Veterinary Science, School of Veterinary Medicine, Rakuno Gakuen University, Hokkaido, Japan
[3)]Theriogenology Unit, School of Veterinary Medicine, Rakuno Gakuen University, Hokkaido, Japan
[4)]Monbetsu Veterinary Clinic, Hokkaido Agricultural Mutual Aid Association, Hokkaido, Japan
[5)]Veterinary Biochemistry Unit, Department of Veterinary Science, School of Veterinary Medicine, Rakuno Gakuen University, Hokkaido, Japan

ABSTRACT. *Mycoplasma bovis* mastitisis highly contagious and disrupts lactation, posing a significant threat to the dairy industry. While the mammary gland's defence mechanism involves epithelial cells and mononuclear cells (MNC), their interaction with *M. bovis* remains incompletely understood. In this study, we assessed the immunological reactivity of bovine mammary epithelial cells (bMEC) to *M. bovis* through co-culture with MNC. Upon co-culture with MNC, the mRNA expression levels of *interleukin* (*IL*)-*1β*, *IL-6*, *IL-8* and *tumor necrosis factor* (*TNF*)-*α* in bMEC stimulated by *M. bovis* showed a significant increase compared to monoculture. Additionally, when stimulated with *M. bovis*, the culture supernatant exhibited significantly higher concentrations of IL-6 and interferon (IFN)-γ, while IL-1β concentration tended to be higher in co-culture with MNC than in monoculture. Furthermore, the mRNA expression levels of *toll-like receptor* (*TLR*) *2* in bMEC stimulated with *M. bovis* tended to increase, and *TLR4* significantly increased when co-cultured with MNC compared to monocultures. However, the surface expression levels in bMEC did not exhibit significant changes between co-culture and monoculture. Overall, our research indicates that the inflammatory response of bMEC is increased during co-culture with MNC, suggesting that the interaction between bMEC and MNC in the mammary gland amplifies the immune response to *M. bovis* in cows affected by *M. bovis* mastitis.

KEYWORDS: bovine mammary epithelial cell, immunity, mastitis, mononuclear cell, *Mycoplasma bovis*

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Bacteriophages | Full-Length Text

Phage-based biocontrol of *Porphyromonas gingivalis* through indirect targeting

Chuncheng Wu,[1] Jumpei Fujiki,[2] Jacques Mathieu,[1] Cory Schwarz,[1] Carolyn Cornell,[1] Pedro J. J. Alvarez[1]

AUTHOR AFFILIATIONS See affiliation list on p. 10.

ABSTRACT Bacteriophages offer an opportunity for chemical-free, precise control of problematic bacteria, but this approach can be limited when lytic phages are difficult to obtain for the target host. In such cases, phage-based targeting of cooperating or cross-feeding bacteria (e.g., *Streptococcus gordonii*) can be an effective approach to control the problematic bacteria (e.g., *Porphyromonas gingivalis*). Using a dual-species biofilm system, phage predation of *S. gordonii* (10^8 PFU-mL^{-1}) decreased the abundance of pathogenic *P. gingivalis* by >99% compared with no-treatment controls, while also inhibiting the production of cytotoxic metabolic end products (butyric and propionic acids). Phage treatment upregulated genes associated with interspecies co-adhesion (5- to 8-fold) and quorum sensing (10-fold) in residual *P. gingivalis*, which is conducive to increased potential to bind to *S. gordonii*. Counterintuitively, lower-titer phage applications (10^4 PFU-mL^{-1}) increased the production of extracellular polymeric substance (EPS) by 22% and biofilm biomass by 50%. This overproduction of EPS may contribute to the phenomenon where the biofilm separated into two distinct species layers, as observed by confocal laser scanning microscopy. Although more complex mixed-culture systems should be considered to delineate the merits and limitations of this novel biocontrol approach (which would likely require the use of phage cocktails), our results offer proof of concept that indirect phage-based targeting can expand the applicability of phage-based control of pathogenic bacteria for public health protection.

IMPORTANCE Lytic phages are valuable agents for targeted elimination of bacteria in diverse applications. Nevertheless, lytic phages are difficult to isolate for some target pathogens. We offer proof of concept that this limitation may be overcome via indirect phage targeting, which involves knocking out species that interact closely with and benefit the primary problematic target bacteria. Our target (*P. gingivalis*) only forms a periodontal pathogenic biofilm if the pioneer colonizer (*S. gordonii*) offers its surface for *P. gingivalis* to attach. Phage predation of the co-adhesive *S. gordonii* significantly reduced abundance of the target pathogen by >99%, decreased the total biofilm biomass by >44%, and suppressed its production of cytotoxic metabolic byproducts. Thus, this research extends the scope of phage-based biocontrol for public health protection.

KEYWORDS phage therapy, indirect targeting, pathogen control, biofilm, virulence

Interest in bacteriophages (phages) to selectively eliminate or suppress specific bacteria without using harmful chemicals is growing in many applications, including the food and agricultural industries, in corrosion control applications, and wastewater treatment (1–5). New technologies to manipulate microbiomes to suppress or enhance specific functions are desirable to address pressing public health challenges. Nonetheless, implementation of phage-based biocontrol strategies faces various potential obstacles, including: (1) Limited target access: diffusion limitations hinder the ability of

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Address correspondence to Pedro J. J. Alvarez, alvarez@rice.edu.

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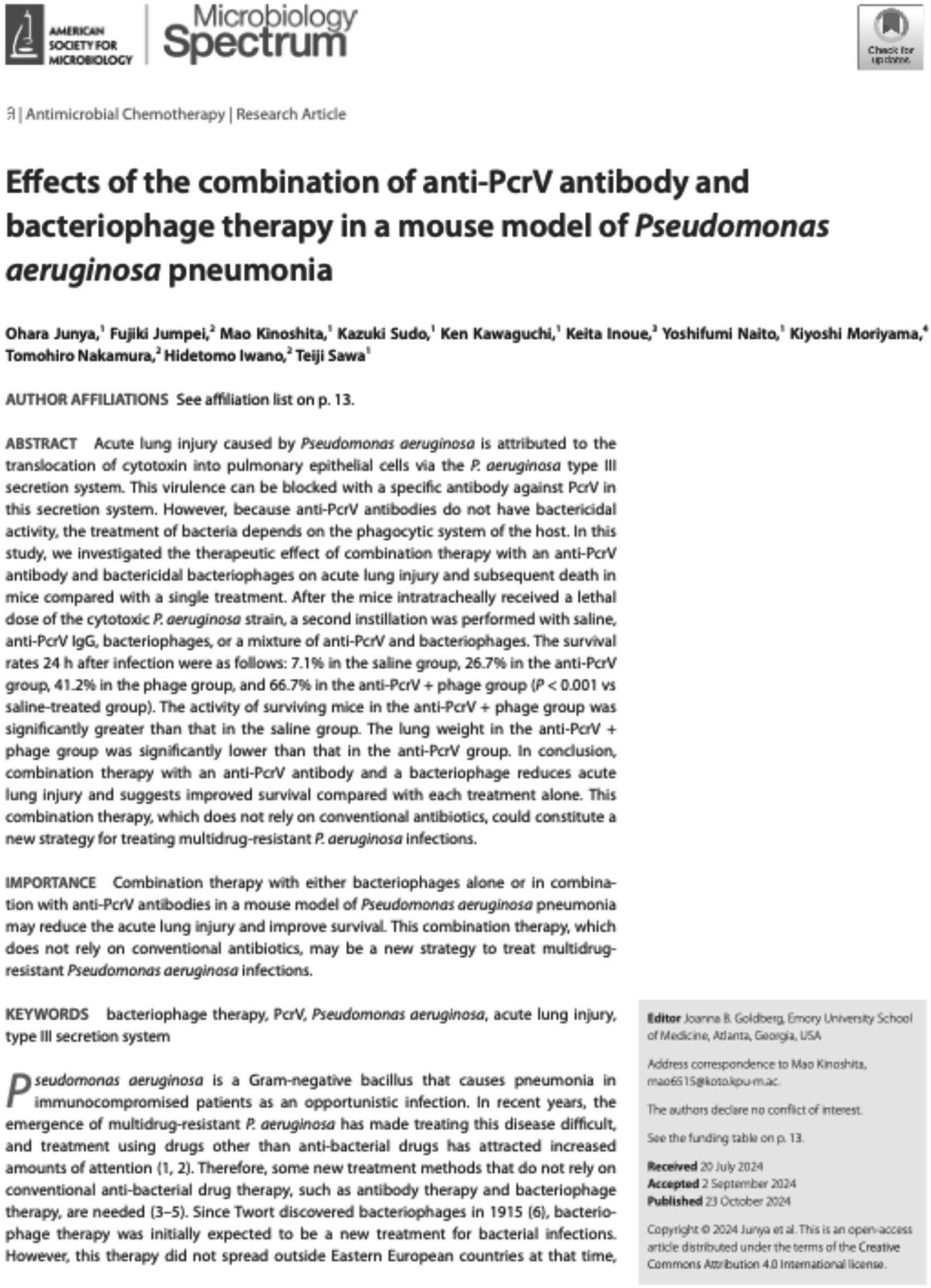

AMERICAN SOCIETY FOR MICROBIOLOGY | Microbiology Spectrum

Antimicrobial Chemotherapy | Research Article

Effects of the combination of anti-PcrV antibody and bacteriophage therapy in a mouse model of *Pseudomonas aeruginosa* pneumonia

Ohara Junya,[1] Fujiki Jumpei,[2] Mao Kinoshita,[1] Kazuki Sudo,[1] Ken Kawaguchi,[1] Keita Inoue,[2] Yoshifumi Naito,[1] Kiyoshi Moriyama,[4] Tomohiro Nakamura,[2] Hidetomo Iwano,[2] Teiji Sawa[1]

AUTHOR AFFILIATIONS See affiliation list on p. 13.

ABSTRACT Acute lung injury caused by *Pseudomonas aeruginosa* is attributed to the translocation of cytotoxin into pulmonary epithelial cells via the *P. aeruginosa* type III secretion system. This virulence can be blocked with a specific antibody against PcrV in this secretion system. However, because anti-PcrV antibodies do not have bactericidal activity, the treatment of bacteria depends on the phagocytic system of the host. In this study, we investigated the therapeutic effect of combination therapy with an anti-PcrV antibody and bactericidal bacteriophages on acute lung injury and subsequent death in mice compared with a single treatment. After the mice intratracheally received a lethal dose of the cytotoxic *P. aeruginosa* strain, a second instillation was performed with saline, anti-PcrV IgG, bacteriophages, or a mixture of anti-PcrV and bacteriophages. The survival rates 24 h after infection were as follows: 7.1% in the saline group, 26.7% in the anti-PcrV group, 41.2% in the phage group, and 66.7% in the anti-PcrV + phage group ($P < 0.001$ vs saline-treated group). The activity of surviving mice in the anti-PcrV + phage group was significantly greater than that in the saline group. The lung weight in the anti-PcrV + phage group was significantly lower than that in the anti-PcrV group. In conclusion, combination therapy with an anti-PcrV antibody and a bacteriophage reduces acute lung injury and suggests improved survival compared with each treatment alone. This combination therapy, which does not rely on conventional antibiotics, could constitute a new strategy for treating multidrug-resistant *P. aeruginosa* infections.

IMPORTANCE Combination therapy with either bacteriophages alone or in combination with anti-PcrV antibodies in a mouse model of *Pseudomonas aeruginosa* pneumonia may reduce the acute lung injury and improve survival. This combination therapy, which does not rely on conventional antibiotics, may be a new strategy to treat multidrug-resistant *Pseudomonas aeruginosa* infections.

KEYWORDS bacteriophage therapy, PcrV, *Pseudomonas aeruginosa*, acute lung injury, type III secretion system

Pseudomonas aeruginosa is a Gram-negative bacillus that causes pneumonia in immunocompromised patients as an opportunistic infection. In recent years, the emergence of multidrug-resistant *P. aeruginosa* has made treating this disease difficult, and treatment using drugs other than anti-bacterial drugs has attracted increased amounts of attention (1, 2). Therefore, some new treatment methods that do not rely on conventional anti-bacterial drug therapy, such as antibody therapy and bacteriophage therapy, are needed (3–5). Since Twort discovered bacteriophages in 1915 (6), bacteriophage therapy was initially expected to be a new treatment for bacterial infections. However, this therapy did not spread outside Eastern European countries at that time,

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Address correspondence to Mao Kinoshita, mao6515@koto.kpu-m.ac.

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最終責任者　Teiji Sawa (Corresponding Author)

食品衛生学（Food Microbiology and Food Safety）

Akira Fukuda

Lecture

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1）Transferable linezolid resistance genes (optrA and poxtA) in enterococci derived from livestock compost at Japanese farms.
Fukuda A, Nakajima C, Suzuki Y, Usui M.
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2）Low-frequency transmission and persistence of antimicrobial-resistant bacteria and genes from livestock to agricultural soil and crops through compost application.
Fukuda A, Suzuki M, Makita K, Usui M.
PLoS ONE 19:e301972. 2024. doi: 10.1371/journal.pone.0301972

3）Spreading ability of tet(X)-harboring plasmid and effect of tetracyclines as a selective pressure.
Fukuda A, Kozaki Y, Kürekci C, Suzuki Y, Nakajima C, Usui M.
Microbial Drug Resistance 30:489–501. 2024. doi: 10.1089/mdr.2024.011

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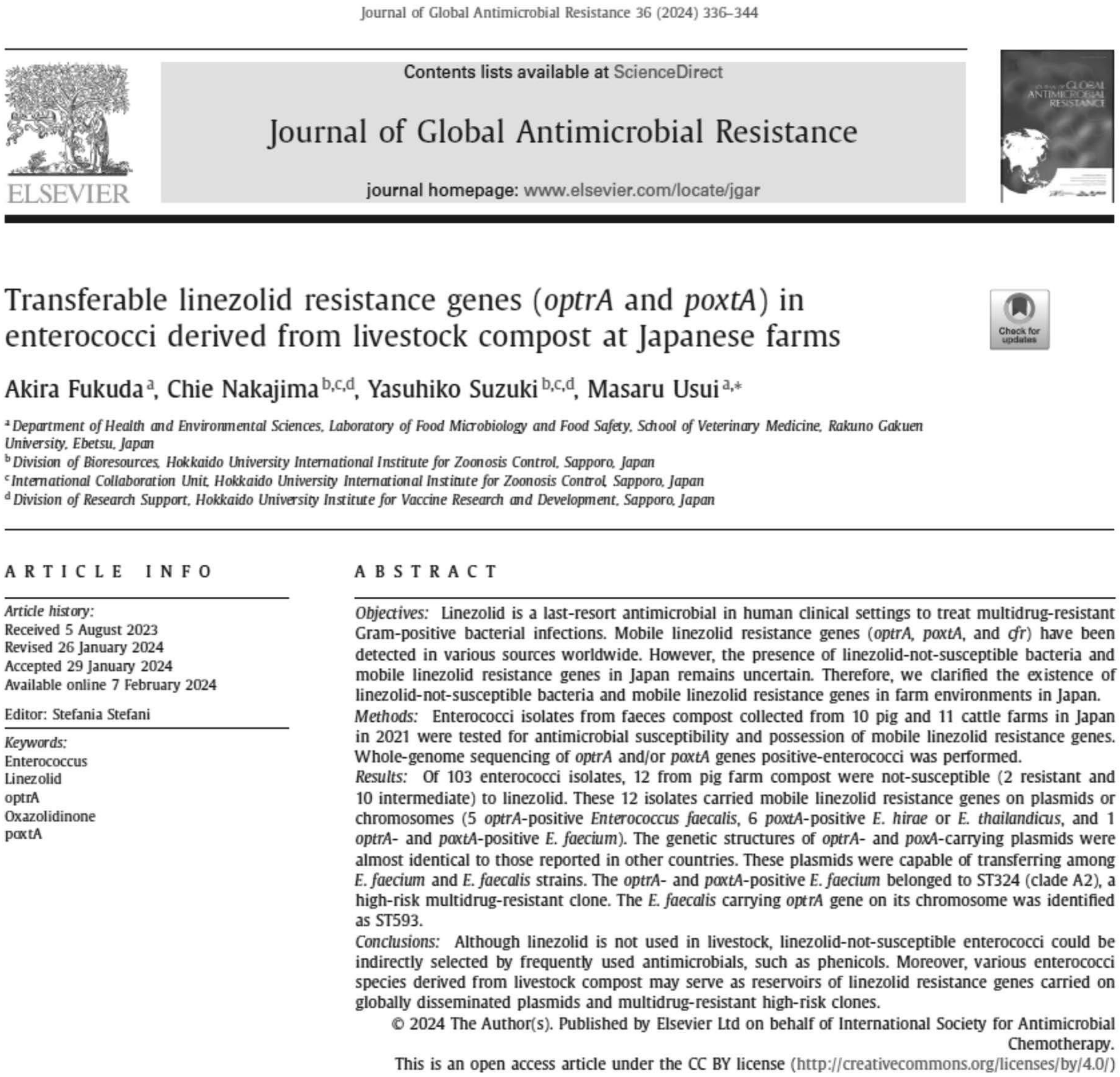

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Transferable linezolid resistance genes (*optrA* and *poxtA*) in enterococci derived from livestock compost at Japanese farms

Akira Fukuda[a], Chie Nakajima[b,c,d], Yasuhiko Suzuki[b,c,d], Masaru Usui[a,*]

[a] Department of Health and Environmental Sciences, Laboratory of Food Microbiology and Food Safety, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan
[b] Division of Bioresources, Hokkaido University International Institute for Zoonosis Control, Sapporo, Japan
[c] International Collaboration Unit, Hokkaido University International Institute for Zoonosis Control, Sapporo, Japan
[d] Division of Research Support, Hokkaido University Institute for Vaccine Research and Development, Sapporo, Japan

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ABSTRACT

Objectives: Linezolid is a last-resort antimicrobial in human clinical settings to treat multidrug-resistant Gram-positive bacterial infections. Mobile linezolid resistance genes (*optrA*, *poxtA*, and *cfr*) have been detected in various sources worldwide. However, the presence of linezolid-not-susceptible bacteria and mobile linezolid resistance genes in Japan remains uncertain. Therefore, we clarified the existence of linezolid-not-susceptible bacteria and mobile linezolid resistance genes in farm environments in Japan.

Methods: Enterococci isolates from faeces compost collected from 10 pig and 11 cattle farms in Japan in 2021 were tested for antimicrobial susceptibility and possession of mobile linezolid resistance genes. Whole-genome sequencing of *optrA* and/or *poxtA* genes positive-enterococci was performed.

Results: Of 103 enterococci isolates, 12 from pig farm compost were not-susceptible (2 resistant and 10 intermediate) to linezolid. These 12 isolates carried mobile linezolid resistance genes on plasmids or chromosomes (5 *optrA*-positive *Enterococcus faecalis*, 6 *poxtA*-positive *E. hirae* or *E. thailandicus*, and 1 *optrA*- and *poxtA*-positive *E. faecium*). The genetic structures of *optrA*- and *poxA*-carrying plasmids were almost identical to those reported in other countries. These plasmids were capable of transferring among *E. faecium* and *E. faecalis* strains. The *optrA*- and *poxtA*-positive *E. faecium* belonged to ST324 (clade A2), a high-risk multidrug-resistant clone. The *E. faecalis* carrying *optrA* gene on its chromosome was identified as ST593.

Conclusions: Although linezolid is not used in livestock, linezolid-not-susceptible enterococci could be indirectly selected by frequently used antimicrobials, such as phenicols. Moreover, various enterococci species derived from livestock compost may serve as reservoirs of linezolid resistance genes carried on globally disseminated plasmids and multidrug-resistant high-risk clones.

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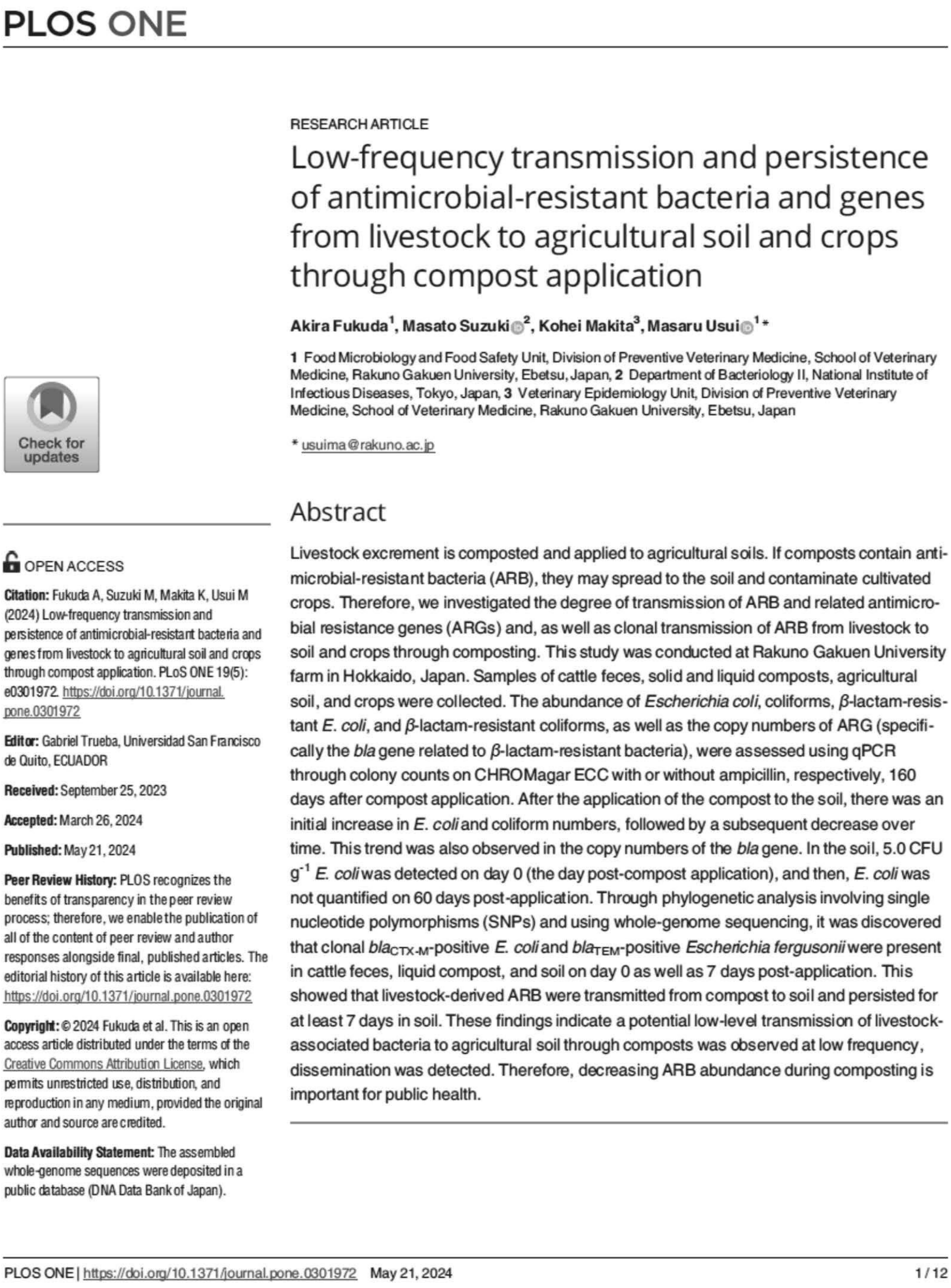

PLOS ONE

RESEARCH ARTICLE

Low-frequency transmission and persistence of antimicrobial-resistant bacteria and genes from livestock to agricultural soil and crops through compost application

Akira Fukuda[1], **Masato Suzuki**[2], **Kohei Makita**[3], **Masaru Usui**[1]*

1 Food Microbiology and Food Safety Unit, Division of Preventive Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan, **2** Department of Bacteriology II, National Institute of Infectious Diseases, Tokyo, Japan, **3** Veterinary Epidemiology Unit, Division of Preventive Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan

* usuima@rakuno.ac.jp

Abstract

Livestock excrement is composted and applied to agricultural soils. If composts contain antimicrobial-resistant bacteria (ARB), they may spread to the soil and contaminate cultivated crops. Therefore, we investigated the degree of transmission of ARB and related antimicrobial resistance genes (ARGs) and, as well as clonal transmission of ARB from livestock to soil and crops through composting. This study was conducted at Rakuno Gakuen University farm in Hokkaido, Japan. Samples of cattle feces, solid and liquid composts, agricultural soil, and crops were collected. The abundance of *Escherichia coli*, coliforms, β-lactam-resistant *E. coli*, and β-lactam-resistant coliforms, as well as the copy numbers of ARG (specifically the *bla* gene related to β-lactam-resistant bacteria), were assessed using qPCR through colony counts on CHROMagar ECC with or without ampicillin, respectively, 160 days after compost application. After the application of the compost to the soil, there was an initial increase in *E. coli* and coliform numbers, followed by a subsequent decrease over time. This trend was also observed in the copy numbers of the *bla* gene. In the soil, 5.0 CFU g^{-1} *E. coli* was detected on day 0 (the day post-compost application), and then, *E. coli* was not quantified on 60 days post-application. Through phylogenetic analysis involving single nucleotide polymorphisms (SNPs) and using whole-genome sequencing, it was discovered that clonal $bla_{\text{CTX-M}}$-positive *E. coli* and bla_{TEM}-positive *Escherichia fergusonii* were present in cattle feces, liquid compost, and soil on day 0 as well as 7 days post-application. This showed that livestock-derived ARB were transmitted from compost to soil and persisted for at least 7 days in soil. These findings indicate a potential low-level transmission of livestock-associated bacteria to agricultural soil through composts was observed at low frequency, dissemination was detected. Therefore, decreasing ARB abundance during composting is important for public health.

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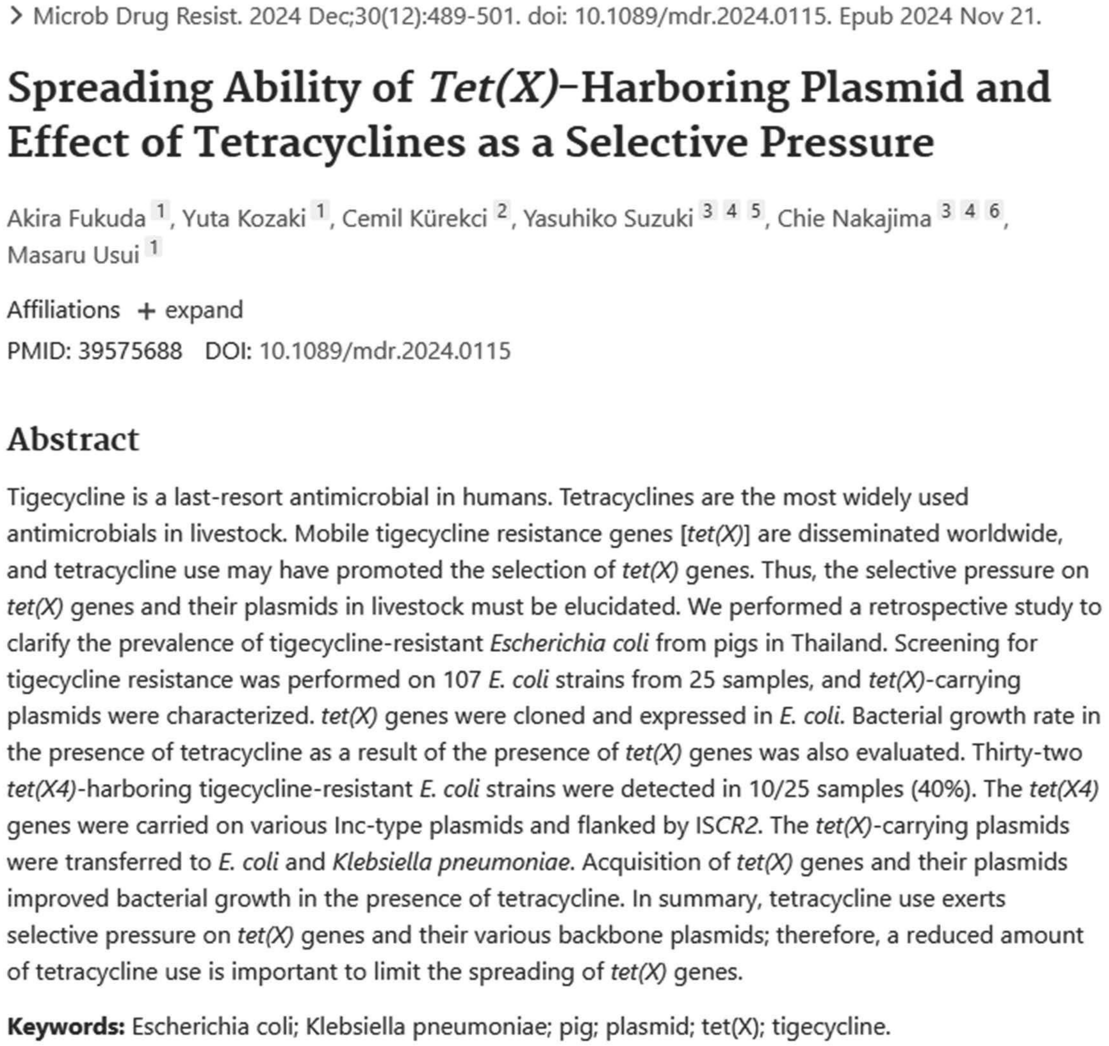

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Spreading Ability of *Tet(X)*-Harboring Plasmid and Effect of Tetracyclines as a Selective Pressure

Akira Fukuda [1], Yuta Kozaki [1], Cemil Kürekci [2], Yasuhiko Suzuki [3] [4] [5], Chie Nakajima [3] [4] [6], Masaru Usui [1]

Affiliations + expand

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Abstract

Tigecycline is a last-resort antimicrobial in humans. Tetracyclines are the most widely used antimicrobials in livestock. Mobile tigecycline resistance genes [*tet(X)*] are disseminated worldwide, and tetracycline use may have promoted the selection of *tet(X)* genes. Thus, the selective pressure on *tet(X)* genes and their plasmids in livestock must be elucidated. We performed a retrospective study to clarify the prevalence of tigecycline-resistant *Escherichia coli* from pigs in Thailand. Screening for tigecycline resistance was performed on 107 *E. coli* strains from 25 samples, and *tet(X)*-carrying plasmids were characterized. *tet(X)* genes were cloned and expressed in *E. coli*. Bacterial growth rate in the presence of tetracycline as a result of the presence of *tet(X)* genes was also evaluated. Thirty-two *tet(X4)*-harboring tigecycline-resistant *E. coli* strains were detected in 10/25 samples (40%). The *tet(X4)* genes were carried on various Inc-type plasmids and flanked by IS*CR2*. The *tet(X)*-carrying plasmids were transferred to *E. coli* and *Klebsiella pneumoniae*. Acquisition of *tet(X)* genes and their plasmids improved bacterial growth in the presence of tetracycline. In summary, tetracycline use exerts selective pressure on *tet(X)* genes and their various backbone plasmids; therefore, a reduced amount of tetracycline use is important to limit the spreading of *tet(X)* genes.

Keywords: Escherichia coli; Klebsiella pneumoniae; pig; plasmid; tet(X); tigecycline.

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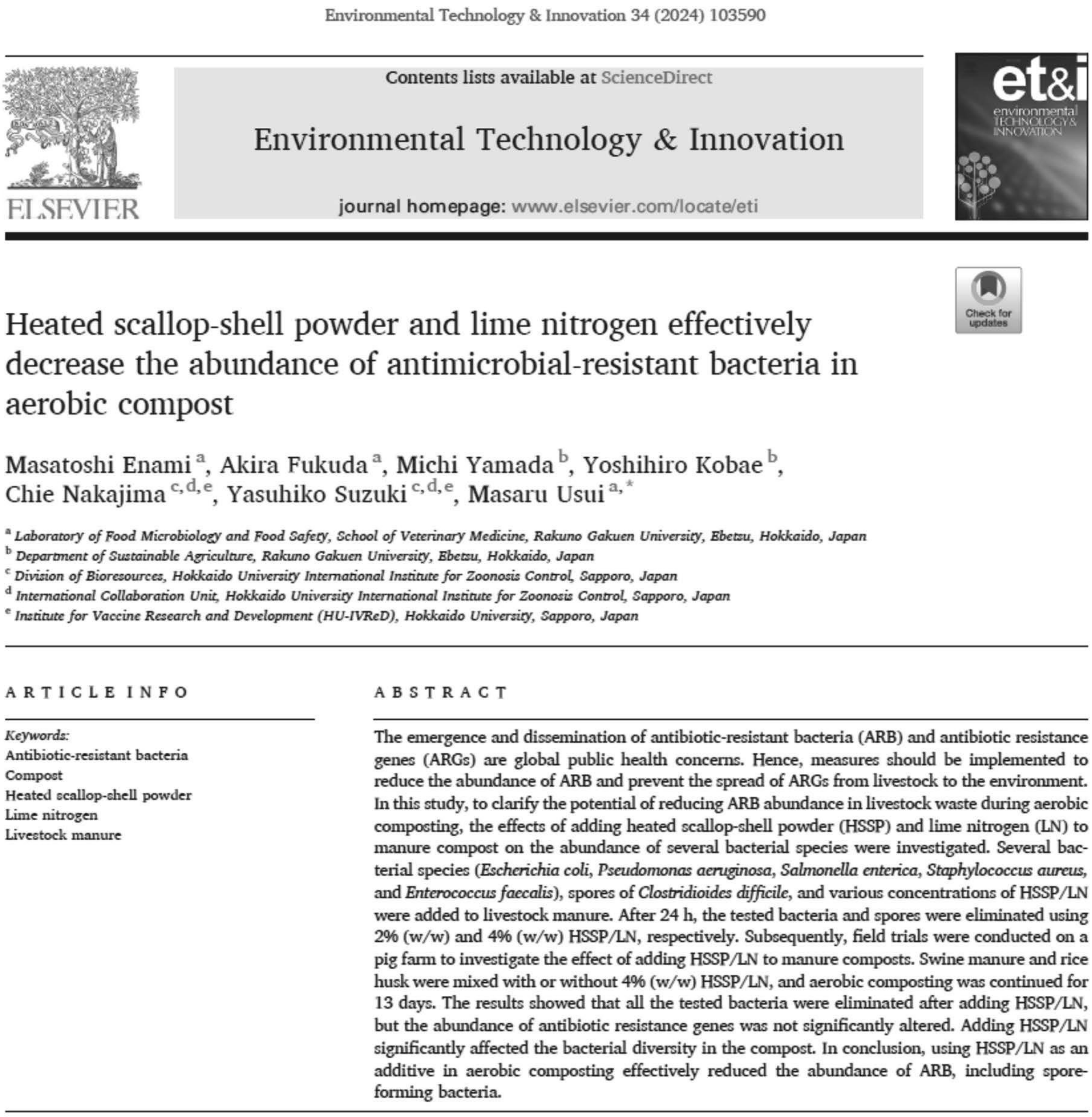

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Heated scallop-shell powder and lime nitrogen effectively decrease the abundance of antimicrobial-resistant bacteria in aerobic compost

Masatoshi Enami [a], Akira Fukuda [a], Michi Yamada [b], Yoshihiro Kobae [b], Chie Nakajima [c,d,e], Yasuhiko Suzuki [c,d,e], Masaru Usui [a,*]

[a] Laboratory of Food Microbiology and Food Safety, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan
[b] Department of Sustainable Agriculture, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan
[c] Division of Bioresources, Hokkaido University International Institute for Zoonosis Control, Sapporo, Japan
[d] International Collaboration Unit, Hokkaido University International Institute for Zoonosis Control, Sapporo, Japan
[e] Institute for Vaccine Research and Development (HU-IVReD), Hokkaido University, Sapporo, Japan

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ABSTRACT

The emergence and dissemination of antibiotic-resistant bacteria (ARB) and antibiotic resistance genes (ARGs) are global public health concerns. Hence, measures should be implemented to reduce the abundance of ARB and prevent the spread of ARGs from livestock to the environment. In this study, to clarify the potential of reducing ARB abundance in livestock waste during aerobic composting, the effects of adding heated scallop-shell powder (HSSP) and lime nitrogen (LN) to manure compost on the abundance of several bacterial species were investigated. Several bacterial species (*Escherichia coli, Pseudomonas aeruginosa, Salmonella enterica, Staphylococcus aureus,* and *Enterococcus faecalis*), spores of *Clostridioides difficile*, and various concentrations of HSSP/LN were added to livestock manure. After 24 h, the tested bacteria and spores were eliminated using 2% (w/w) and 4% (w/w) HSSP/LN, respectively. Subsequently, field trials were conducted on a pig farm to investigate the effect of adding HSSP/LN to manure composts. Swine manure and rice husk were mixed with or without 4% (w/w) HSSP/LN, and aerobic composting was continued for 13 days. The results showed that all the tested bacteria were eliminated after adding HSSP/LN, but the abundance of antibiotic resistance genes was not significantly altered. Adding HSSP/LN significantly affected the bacterial diversity in the compost. In conclusion, using HSSP/LN as an additive in aerobic composting effectively reduced the abundance of ARB, including spore-forming bacteria.

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Carbapenem and colistin-resistant hypervirulent *Klebsiella pneumoniae*: An emerging threat transcending the egyptian food chain

Rana Fahmi Sabala [a,b], Akira Fukuda [b], Chie Nakajima [c,d,e], Yasuhiko Suzuki [c,d,e], Masaru Usui [b,*], Mohamed Elhadidy [f,g,h,**]

[a] *Department of Food Hygiene and Control, Faculty of Veterinary Medicine, Mansoura University, Mansoura, Egypt*
[b] *Laboratory of Food Microbiology and Food Safety, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan*
[c] *Division of Bioresources, Hokkaido University International Institute for Zoonosis Control, Sapporo, Japan*
[d] *International Collaboration Unit, Hokkaido University International Institute for Zoonosis Control, Sapporo, Japan*
[e] *Division of Research Support, Hokkaido University Institute for Vaccine Research and Development, Sapporo, Japan*
[f] *Center for Genomics, Helmy Institute for Medical Sciences, Zewail City of Science and Technology, Giza, Egypt*
[g] *Biomedical Sciences Program, University of Science and Technology, Zewail City of Science and Technology, Giza, Egypt*
[h] *Department of Bacteriology, Mycology and Immunology, Faculty of Veterinary Medicine, Mansoura University, Mansoura, Egypt*

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ABSTRACT

Background: Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) is a great public health problem and is associated with many disease outbreaks and high mortality rates. Alarmingly, *K. pneumoniae* has been isolated from food in several recent studies. This study aimed to investigate the prevalence and characteristics of CRKP in food samples from Egypt.

Methods: A total of 311 food samples (including 116 minced meat, 92 chicken meat, 75 diced meat, and 28 mutton) were collected from local markets in Egypt and were screened for CRKP with the determination of their antimicrobial resistance profiles. The whole genome sequence was done for 23 CRKP isolates to clarify the relationship between CRKP from food and human cases in Egypt using the SNP core genome. The conjugation probability of the $bla_{\text{NDM-5}}$ harboring plasmid was identified using oriTfinder

Results: CRKP was isolated from 11% (35/311) of the samples, with 45.71% (16/35) of them showing resistance to colistin, one of the last-resort options for treating CRKP-mediated infections. In addition to the carbapenem and colistin resistance, the CRKP isolates frequently exhibited resistance to multiple antimicrobials including β-lactams, fluoroquinolones, aminoglycosides, tetracyclines, and chloramphenicol. In addition, most of the CRKP were potentially hypervirulent *K. pneumoniae* (HvKP) identified as phylogroup Kp1 and of high-risk groups as detected in STs reported in many human outbreaks globally, such as ST383 and ST147. The core-genome phylogeny showed similarities between the isolates from this study and those previously isolated from clinical human samples in Egypt. In addition, analysis of the plasmid on which bla_{NDM} is encoded revealed that several antimicrobial resistance genes such as $bla_{\text{OXA-9}}$, $bla_{\text{CTX-M-15}}$, *aac(6')-Ib*, *qnrS1*, and several virulence genes are encoded on the same plasmid.

Conclusions: This study is significant for food safety and public health and is important to further identify the change in the epidemiology of CRKP infections, especially the consumption of contaminated food products.

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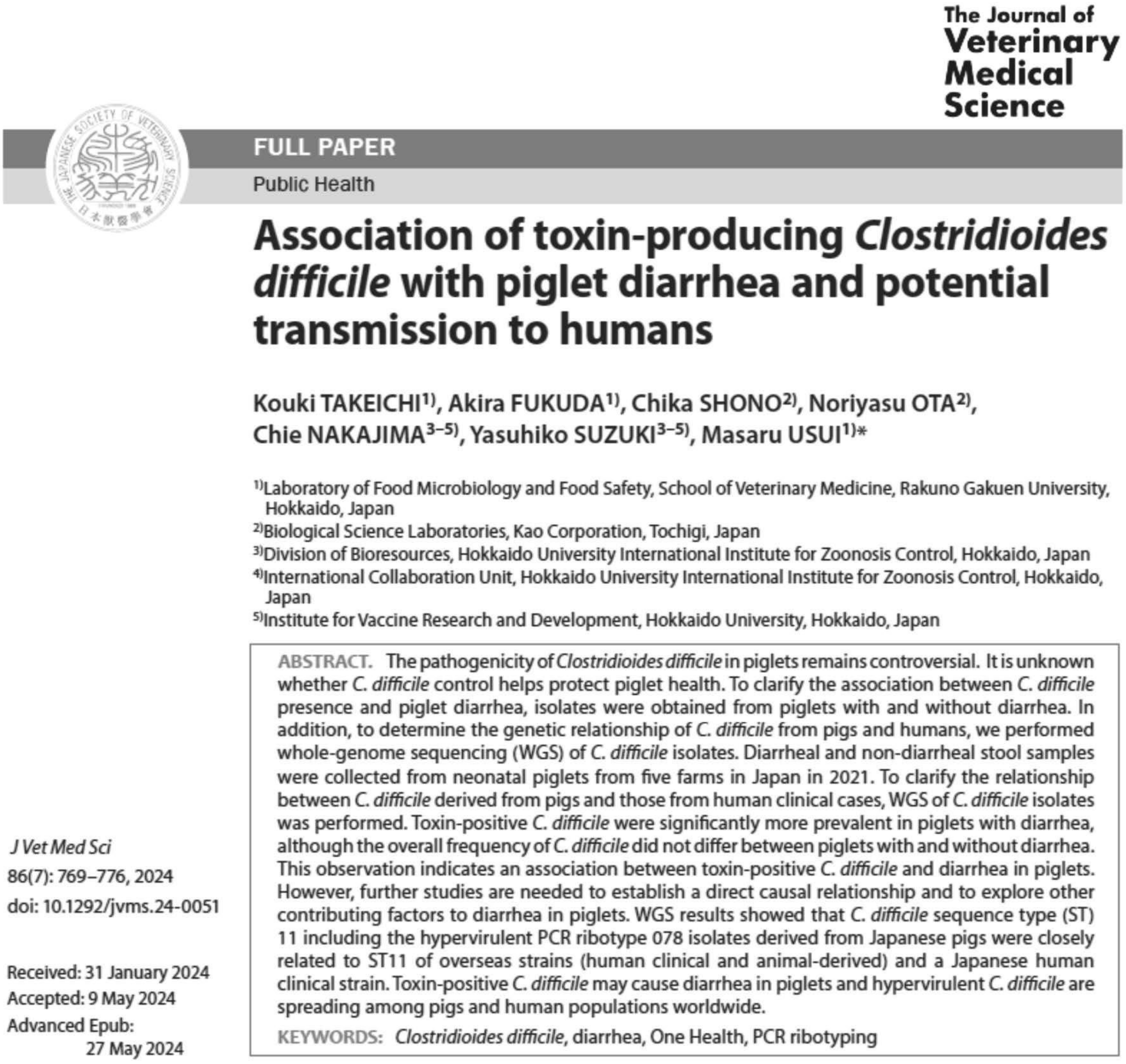

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FULL PAPER
Public Health

Association of toxin-producing *Clostridioides difficile* with piglet diarrhea and potential transmission to humans

Kouki TAKEICHI[1)], Akira FUKUDA[1)], Chika SHONO[2)], Noriyasu OTA[2)], Chie NAKAJIMA[3–5)], Yasuhiko SUZUKI[3–5)], Masaru USUI[1)]*

[1)]Laboratory of Food Microbiology and Food Safety, School of Veterinary Medicine, Rakuno Gakuen University, Hokkaido, Japan
[2)]Biological Science Laboratories, Kao Corporation, Tochigi, Japan
[3)]Division of Bioresources, Hokkaido University International Institute for Zoonosis Control, Hokkaido, Japan
[4)]International Collaboration Unit, Hokkaido University International Institute for Zoonosis Control, Hokkaido, Japan
[5)]Institute for Vaccine Research and Development, Hokkaido University, Hokkaido, Japan

ABSTRACT. The pathogenicity of *Clostridioides difficile* in piglets remains controversial. It is unknown whether *C. difficile* control helps protect piglet health. To clarify the association between *C. difficile* presence and piglet diarrhea, isolates were obtained from piglets with and without diarrhea. In addition, to determine the genetic relationship of *C. difficile* from pigs and humans, we performed whole-genome sequencing (WGS) of *C. difficile* isolates. Diarrheal and non-diarrheal stool samples were collected from neonatal piglets from five farms in Japan in 2021. To clarify the relationship between *C. difficile* derived from pigs and those from human clinical cases, WGS of *C. difficile* isolates was performed. Toxin-positive *C. difficile* were significantly more prevalent in piglets with diarrhea, although the overall frequency of *C. difficile* did not differ between piglets with and without diarrhea. This observation indicates an association between toxin-positive *C. difficile* and diarrhea in piglets. However, further studies are needed to establish a direct causal relationship and to explore other contributing factors to diarrhea in piglets. WGS results showed that *C. difficile* sequence type (ST) 11 including the hypervirulent PCR ribotype 078 isolates derived from Japanese pigs were closely related to ST11 of overseas strains (human clinical and animal-derived) and a Japanese human clinical strain. Toxin-positive *C. difficile* may cause diarrhea in piglets and hypervirulent *C. difficile* are spreading among pigs and human populations worldwide.

KEYWORDS: *Clostridioides difficile*, diarrhea, One Health, PCR ribotyping

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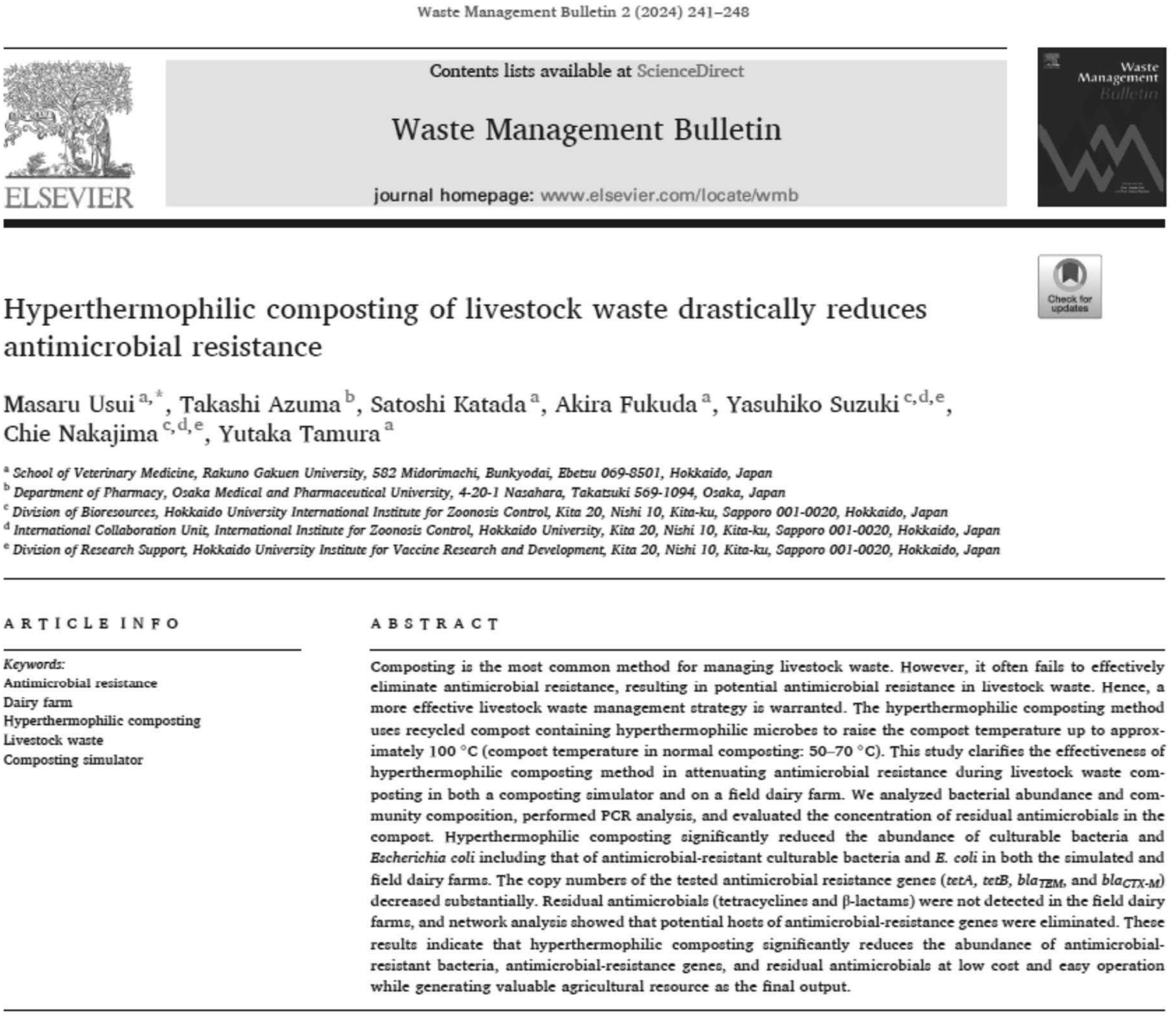

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Hyperthermophilic composting of livestock waste drastically reduces antimicrobial resistance

Masaru Usui [a,*], Takashi Azuma [b], Satoshi Katada [a], Akira Fukuda [a], Yasuhiko Suzuki [c,d,e], Chie Nakajima [c,d,e], Yutaka Tamura [a]

[a] *School of Veterinary Medicine, Rakuno Gakuen University, 582 Midorimachi, Bunkyodai, Ebetsu 069-8501, Hokkaido, Japan*
[b] *Department of Pharmacy, Osaka Medical and Pharmaceutical University, 4-20-1 Nasahara, Takatsuki 569-1094, Osaka, Japan*
[c] *Division of Bioresources, Hokkaido University International Institute for Zoonosis Control, Kita 20, Nishi 10, Kita-ku, Sapporo 001-0020, Hokkaido, Japan*
[d] *International Collaboration Unit, International Institute for Zoonosis Control, Hokkaido University, Kita 20, Nishi 10, Kita-ku, Sapporo 001-0020, Hokkaido, Japan*
[e] *Division of Research Support, Hokkaido University Institute for Vaccine Research and Development, Kita 20, Nishi 10, Kita-ku, Sapporo 001-0020, Hokkaido, Japan*

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Keywords:
Antimicrobial resistance
Dairy farm
Hyperthermophilic composting
Livestock waste
Composting simulator

ABSTRACT

Composting is the most common method for managing livestock waste. However, it often fails to effectively eliminate antimicrobial resistance, resulting in potential antimicrobial resistance in livestock waste. Hence, a more effective livestock waste management strategy is warranted. The hyperthermophilic composting method uses recycled compost containing hyperthermophilic microbes to raise the compost temperature up to approximately 100 °C (compost temperature in normal composting: 50–70 °C). This study clarifies the effectiveness of hyperthermophilic composting method in attenuating antimicrobial resistance during livestock waste composting in both a composting simulator and on a field dairy farm. We analyzed bacterial abundance and community composition, performed PCR analysis, and evaluated the concentration of residual antimicrobials in the compost. Hyperthermophilic composting significantly reduced the abundance of culturable bacteria and *Escherichia coli* including that of antimicrobial-resistant culturable bacteria and *E. coli* in both the simulated and field dairy farms. The copy numbers of the tested antimicrobial resistance genes (*tetA*, *tetB*, bla_{TEM}, and $bla_{CTX\text{-}M}$) decreased substantially. Residual antimicrobials (tetracyclines and β-lactams) were not detected in the field dairy farms, and network analysis showed that potential hosts of antimicrobial-resistance genes were eliminated. These results indicate that hyperthermophilic composting significantly reduces the abundance of antimicrobial-resistant bacteria, antimicrobial-resistance genes, and residual antimicrobials at low cost and easy operation while generating valuable agricultural resource as the final output.

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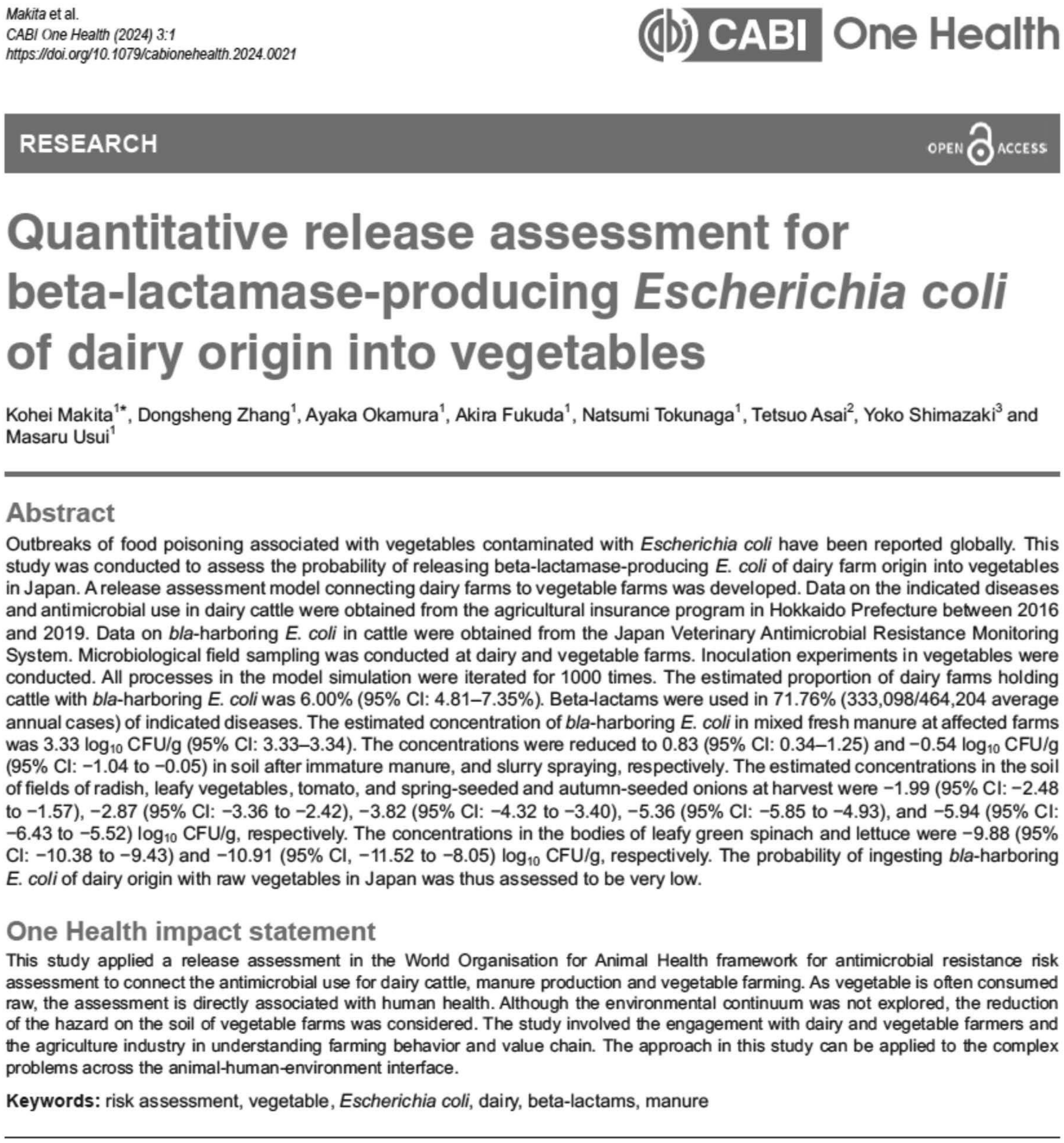

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CABI One Health

RESEARCH

OPEN ACCESS

Quantitative release assessment for beta-lactamase-producing *Escherichia coli* of dairy origin into vegetables

Kohei Makita[1*], Dongsheng Zhang[1], Ayaka Okamura[1], Akira Fukuda[1], Natsumi Tokunaga[1], Tetsuo Asai[2], Yoko Shimazaki[3] and Masaru Usui[1]

Abstract

Outbreaks of food poisoning associated with vegetables contaminated with *Escherichia coli* have been reported globally. This study was conducted to assess the probability of releasing beta-lactamase-producing *E. coli* of dairy farm origin into vegetables in Japan. A release assessment model connecting dairy farms to vegetable farms was developed. Data on the indicated diseases and antimicrobial use in dairy cattle were obtained from the agricultural insurance program in Hokkaido Prefecture between 2016 and 2019. Data on *bla*-harboring *E. coli* in cattle were obtained from the Japan Veterinary Antimicrobial Resistance Monitoring System. Microbiological field sampling was conducted at dairy and vegetable farms. Inoculation experiments in vegetables were conducted. All processes in the model simulation were iterated for 1000 times. The estimated proportion of dairy farms holding cattle with *bla*-harboring *E. coli* was 6.00% (95% CI: 4.81–7.35%). Beta-lactams were used in 71.76% (333,098/464,204 average annual cases) of indicated diseases. The estimated concentration of *bla*-harboring *E. coli* in mixed fresh manure at affected farms was 3.33 $\log_{10}$ CFU/g (95% CI: 3.33–3.34). The concentrations were reduced to 0.83 (95% CI: 0.34–1.25) and −0.54 $\log_{10}$ CFU/g (95% CI: −1.04 to −0.05) in soil after immature manure, and slurry spraying, respectively. The estimated concentrations in the soil of fields of radish, leafy vegetables, tomato, and spring-seeded and autumn-seeded onions at harvest were −1.99 (95% CI: −2.48 to −1.57), −2.87 (95% CI: −3.36 to −2.42), −3.82 (95% CI: −4.32 to −3.40), −5.36 (95% CI: −5.85 to −4.93), and −5.94 (95% CI: −6.43 to −5.52) $\log_{10}$ CFU/g, respectively. The concentrations in the bodies of leafy green spinach and lettuce were −9.88 (95% CI: −10.38 to −9.43) and −10.91 (95% CI, −11.52 to −8.05) $\log_{10}$ CFU/g, respectively. The probability of ingesting *bla*-harboring *E. coli* of dairy origin with raw vegetables in Japan was thus assessed to be very low.

One Health impact statement

This study applied a release assessment in the World Organisation for Animal Health framework for antimicrobial resistance risk assessment to connect the antimicrobial use for dairy cattle, manure production and vegetable farming. As vegetable is often consumed raw, the assessment is directly associated with human health. Although the environmental continuum was not explored, the reduction of the hazard on the soil of vegetable farms was considered. The study involved the engagement with dairy and vegetable farmers and the agriculture industry in understanding farming behavior and value chain. The approach in this study can be applied to the complex problems across the animal-human-environment interface.

Keywords: risk assessment, vegetable, *Escherichia coli*, dairy, beta-lactams, manure

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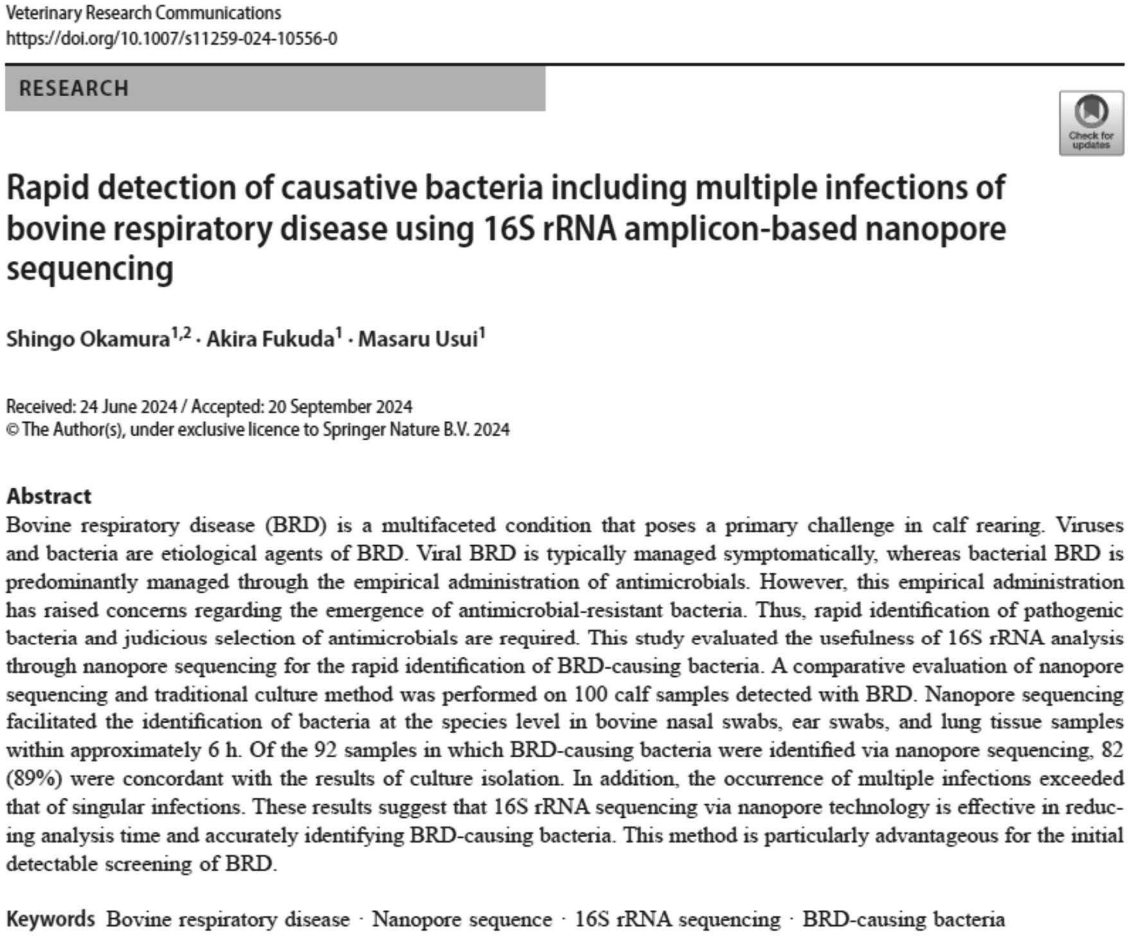

Veterinary Research Communications
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RESEARCH

Rapid detection of causative bacteria including multiple infections of bovine respiratory disease using 16S rRNA amplicon-based nanopore sequencing

Shingo Okamura[1,2] · Akira Fukuda[1] · Masaru Usui[1]

Received: 24 June 2024 / Accepted: 20 September 2024

Abstract

Bovine respiratory disease (BRD) is a multifaceted condition that poses a primary challenge in calf rearing. Viruses and bacteria are etiological agents of BRD. Viral BRD is typically managed symptomatically, whereas bacterial BRD is predominantly managed through the empirical administration of antimicrobials. However, this empirical administration has raised concerns regarding the emergence of antimicrobial-resistant bacteria. Thus, rapid identification of pathogenic bacteria and judicious selection of antimicrobials are required. This study evaluated the usefulness of 16S rRNA analysis through nanopore sequencing for the rapid identification of BRD-causing bacteria. A comparative evaluation of nanopore sequencing and traditional culture method was performed on 100 calf samples detected with BRD. Nanopore sequencing facilitated the identification of bacteria at the species level in bovine nasal swabs, ear swabs, and lung tissue samples within approximately 6 h. Of the 92 samples in which BRD-causing bacteria were identified via nanopore sequencing, 82 (89%) were concordant with the results of culture isolation. In addition, the occurrence of multiple infections exceeded that of singular infections. These results suggest that 16S rRNA sequencing via nanopore technology is effective in reducing analysis time and accurately identifying BRD-causing bacteria. This method is particularly advantageous for the initial detectable screening of BRD.

Keywords Bovine respiratory disease · Nanopore sequence · 16S rRNA sequencing · BRD-causing bacteria

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Crop contamination evaluation by antimicrobial-resistant bacteria via livestock waste compost-fertilized field soil

Yoshihiro Suzuki [a,*], Tomoyuki Horita [a], Emi Nishimura [b], Hui Xie [b], Soichiro Tamai [b], Ikuo Kobayashi [c], Akira Fukuda [d], Masaru Usui [d]

[a] *Department of Civil and Environmental Engineering, Faculty of Engineering, University of Miyazaki, Miyazaki 889-2192, Japan*
[b] *Department of Environment and Resource Sciences, Interdisciplinary Graduate School of Agriculture and Engineering, University of Miyazaki, Miyazaki 889-2192, Japan*
[c] *Sumiyoshi Livestock Science Station, Faculty of Agriculture, University of Miyazaki, Miyazaki 880-0192, Japan*
[d] *Laboratory of Food Microbiology and Food Safety, Department of Health and Environmental Sciences, School of Veterinary Medicine, Rakuno Gakuen University, Hokkaido 069-8501, Japan*

HIGHLIGHTS

- Ampicillin (AMP)-resistant *E. coli* was absent in all samples during the full survey.
- Numerous AMP-resistant coliforms were present in field solids and corn stems/roots.
- *Enterobacter bugandensis* and *E. asburiae* were the major AMP-resistant coliforms.
- AMP-resistant coliform spreading from fully matured compost to crops is unlikely.
- Use of fully matured compost is the most important for safe farm management.

GRAPHICAL ABSTRACT

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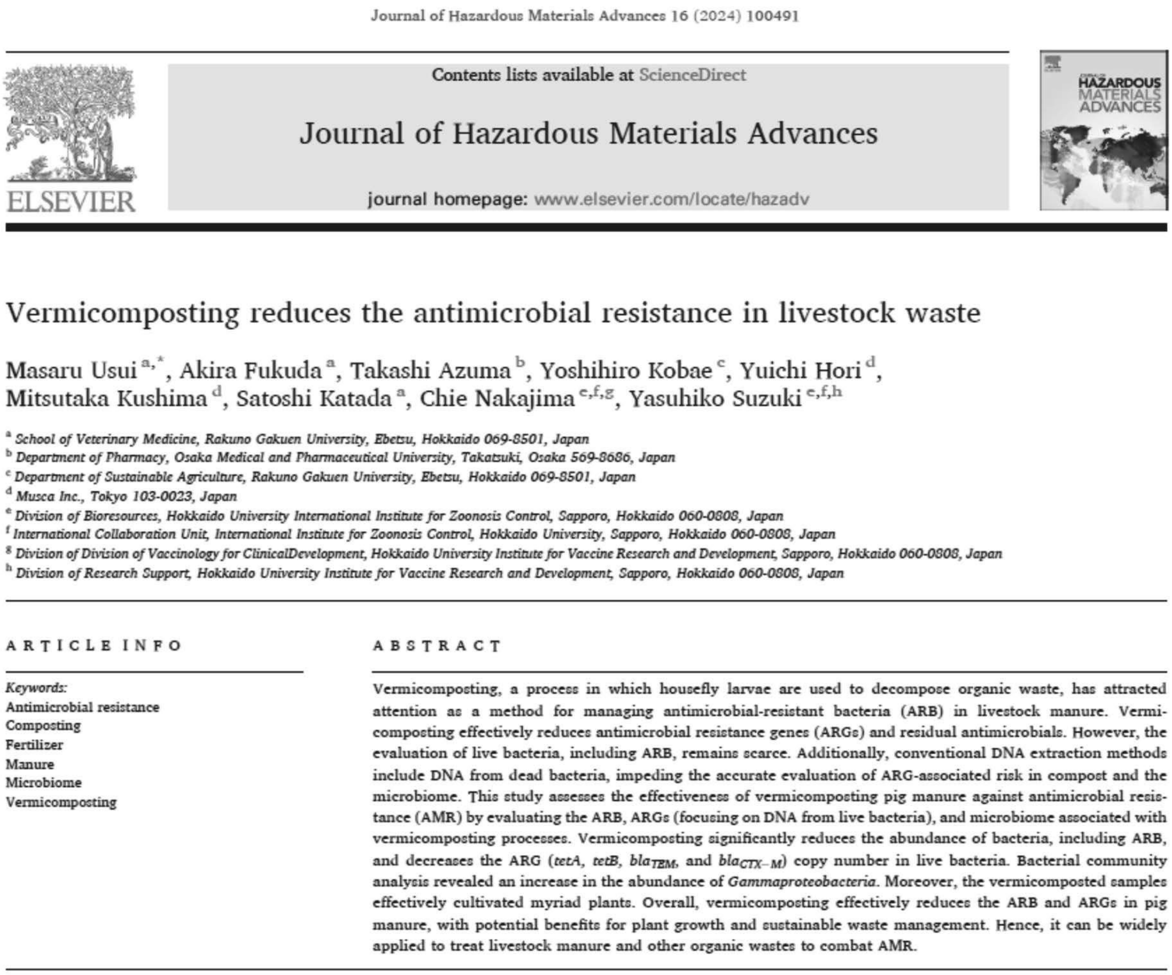

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Vermicomposting reduces the antimicrobial resistance in livestock waste

Masaru Usui [a,*], Akira Fukuda [a], Takashi Azuma [b], Yoshihiro Kobae [c], Yuichi Hori [d], Mitsutaka Kushima [d], Satoshi Katada [a], Chie Nakajima [e,f,g], Yasuhiko Suzuki [e,f,h]

[a] *School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan*
[b] *Department of Pharmacy, Osaka Medical and Pharmaceutical University, Takatsuki, Osaka 569-8686, Japan*
[c] *Department of Sustainable Agriculture, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan*
[d] *Musca Inc., Tokyo 103-0023, Japan*
[e] *Division of Bioresources, Hokkaido University International Institute for Zoonosis Control, Sapporo, Hokkaido 060-0808, Japan*
[f] *International Collaboration Unit, International Institute for Zoonosis Control, Hokkaido University, Sapporo, Hokkaido 060-0808, Japan*
[g] *Division of Division of Vaccinology for ClinicalDevelopment, Hokkaido University Institute for Vaccine Research and Development, Sapporo, Hokkaido 060-0808, Japan*
[h] *Division of Research Support, Hokkaido University Institute for Vaccine Research and Development, Sapporo, Hokkaido 060-0808, Japan*

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Keywords:
Antimicrobial resistance
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Microbiome
Vermicomposting

ABSTRACT

Vermicomposting, a process in which housefly larvae are used to decompose organic waste, has attracted attention as a method for managing antimicrobial-resistant bacteria (ARB) in livestock manure. Vermicomposting effectively reduces antimicrobial resistance genes (ARGs) and residual antimicrobials. However, the evaluation of live bacteria, including ARB, remains scarce. Additionally, conventional DNA extraction methods include DNA from dead bacteria, impeding the accurate evaluation of ARG-associated risk in compost and the microbiome. This study assesses the effectiveness of vermicomposting pig manure against antimicrobial resistance (AMR) by evaluating the ARB, ARGs (focusing on DNA from live bacteria), and microbiome associated with vermicomposting processes. Vermicomposting significantly reduces the abundance of bacteria, including ARB, and decreases the ARG (*tetA*, *tetB*, bla_{TEM}, and bla_{CTX-M}) copy number in live bacteria. Bacterial community analysis revealed an increase in the abundance of *Gammaproteobacteria*. Moreover, the vermicomposted samples effectively cultivated myriad plants. Overall, vermicomposting effectively reduces the ARB and ARGs in pig manure, with potential benefits for plant growth and sustainable waste management. Hence, it can be widely applied to treat livestock manure and other organic wastes to combat AMR.

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最終責任者　Masaru Usui (Corresponding Author)

医動物学（Parasitology and Zoology）

Takahiro Ishizaki

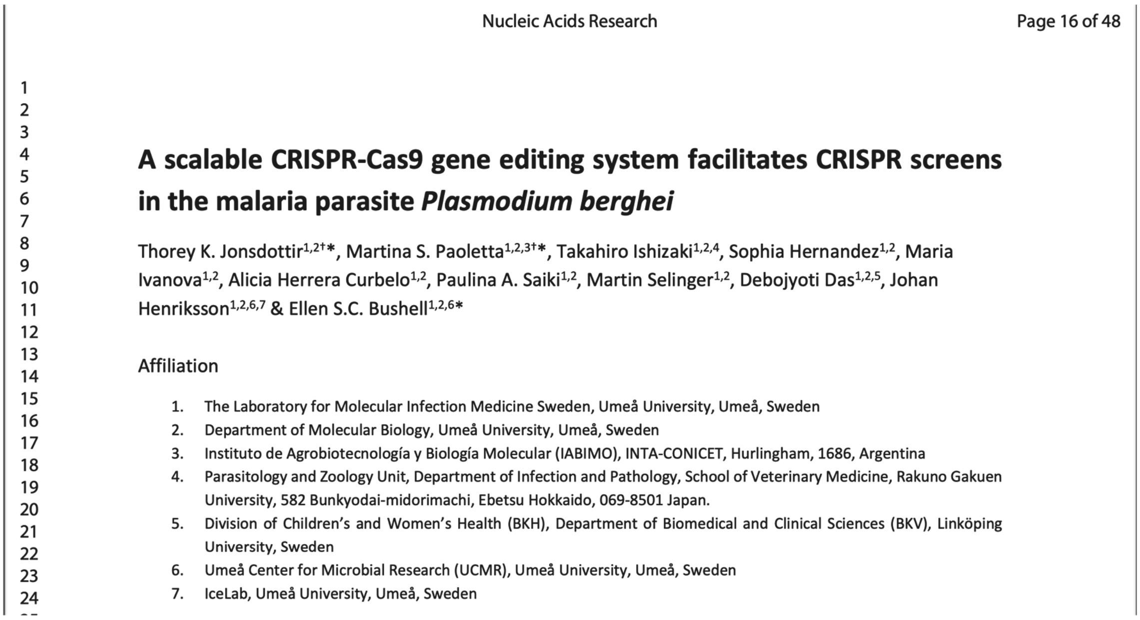
Lecturer

講師　石﨑　隆弘

I. 筆頭または責任著者　＜First or Corresponding Author＞

II.　その他　＜Others＞

1）A scalable CRISPR-Cas9 gene editing system facilitates CRISPR screens in the malaria parasite *Plasmodium berghei*.
Jonsdottir TK, Paoletta MS, **Ishizaki T**, Hernandez S, Ivanova M, Curbelo AH, Saiki PA, Selinger M, Das D, Henriksson J, Bushell ESC.
Nucleic Acids Res 52: *in press*. 2024.



Nucleic Acids Research

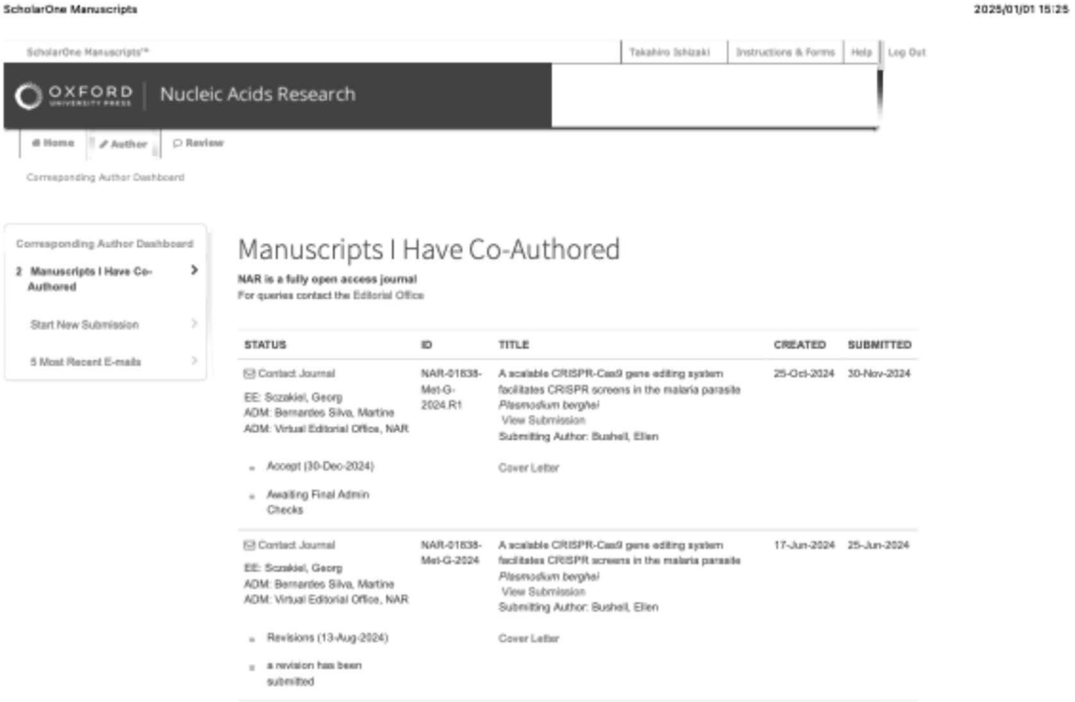
Page 16 of 48

A scalable CRISPR-Cas9 gene editing system facilitates CRISPR screens in the malaria parasite *Plasmodium berghei*

Thorey K. Jonsdottir^{1,2†}*, Martina S. Paoletta^{1,2,3†}*, Takahiro Ishizaki^{1,2,4}, Sophia Hernandez^{1,2}, Maria Ivanova^{1,2}, Alicia Herrera Curbelo^{1,2}, Paulina A. Saiki^{1,2}, Martin Selinger^{1,2}, Debojyoti Das^{1,2,5}, Johan Henriksson^{1,2,6,7} & Ellen S.C. Bushell^{1,2,6}*

Affiliation

1. The Laboratory for Molecular Infection Medicine Sweden, Umeå University, Umeå, Sweden
2. Department of Molecular Biology, Umeå University, Umeå, Sweden
3. Instituto de Agrobiotecnología y Biología Molecular (IABIMO), INTA-CONICET, Hurlingham, 1686, Argentina
4. Parasitology and Zoology Unit, Department of Infection and Pathology, School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyodai-midorimachi, Ebetsu Hokkaido, 069-8501 Japan.
5. Division of Children's and Women's Health (BKH), Department of Biomedical and Clinical Sciences (BKV), Linköping University, Sweden
6. Umeå Center for Microbial Research (UCMR), Umeå University, Umeå, Sweden
7. IceLab, Umeå University, Umeå, Sweden



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Contact Journal EE: Sczakiel, Georg ADM: Bernardes Silva, Martine ADM: Virtual Editorial Office, NAR Accept (30-Dec-2024) Awaiting Final Admin Checks	NAR-01838-Met-G-2024.R1	A scalable CRISPR-Cas9 gene editing system facilitates CRISPR screens in the malaria parasite *Plasmodium berghei* View Submission Submitting Author: Bushell, Ellen Cover Letter	25-Oct-2024	30-Nov-2024
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最終責任者　Ellen S.C. Bushell (Corresponding Author)

獣医疫学（Veterinary Epidemiology）

Ryota Matsuyama

Lecturer

講師　松山　亮太

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1）Estimating the impact of sarcoptic mange epidemic on the population size of wild raccoon dogs (*Nyctereutes procyonoides*) from wildlife rescue data.
Matsuyama R, Kido N, Omori R.
Int J Parasitol Parasites Wildl 25:101010. 2024.
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2）Evaluating the impact of application of anaerobic bacterial fermentation enhancer on digital dermatitis.
Matsuyama R, Abe N, Sato A, Ishikura Y, Ishikawa T, Otake A, Watanabe R, Sunadome M, Makita K, Murakami K.
J Vet Med Sci 86:796–800. 2024. doi: 10.1292/jvms.23-0442.

II. その他　＜Others＞

1）SARS-CoV-2 Infection in School Settings, Okinawa Prefecture, Japan, 2021–2022.
Takayama Y, Shimakawa Y, **Matsuyama R**, Chowell G, Omori R, Nagamoto T, Yamamoto T, Mizumoto K.
Emerg Infect Dis 30:2343–2351. 2024. doi: 10.3201/eid3011.240638.

2）SARS-CoV-2 IgG seroprevalence in the Okinawa Main Island and remote islands in Okinawa, Japan, 2020-2021.
Takayama Y, Shimakawa Y, Aizawa Y, Butcher C, Chibana N, Collins M, Kamegai K, Kim TG, Koyama S, **Matsuyama R**, Matthews MM, Mori T, Nagamoto T, Narita M, Omori R, Shibata N, Shibata S, Shiiki S, Takakura S, Toyozato N, Tsuchiya H, Wolf M, Yamamoto T, Yokoyama S, Yonaha S, Mizumoto K.

Jpn J Infect Dis 77: *in press*. 2024. Epub ahead of print. 2024 Sep 30.
doi: 10.7883/yoken.JJID.2023.255.

3）Decisions and Influential Factors Regarding Class-Specific School Closures Against Seasonal Influenza Outbreak.
Masumoto Y, Kawasaki H, Tsunematsu M, **Matsuyama R**, Kakehashi M.
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Takayama Y, Xu YS, Shimakawa Y, Chowell G, Kozuka M, Omori R, **Matsuyama R**, Yamamoto T, Mizumoto K.
BMC Infect Dis 24:542. 2024. doi: 10.1186/s12879-024-09427-5

5）Identifying Effective Biosecurity Measures for Preventing the Introduction of Classical Swine Fever in Pig Farms in Japan: Under the Condition of Absence/Presence of Observable Infected Wild Boar.
Ukita M, **Matsuyama R**, Isoda N, Omori R, Yamamoto T, Makita K.
Transbound. Emerg Dis 1305664. 2024. doi: 10.1155/2024/1305664

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Estimating the impact of sarcoptic mange epidemic on the population size of wild raccoon dogs (*Nyctereutes procyonoides*) from wildlife rescue data

Ryota Matsuyama [a,*,1], Nobuhide Kido [b,2], Ryosuke Omori [c,**,1]

[a] *School of Veterinary Medicine, Rakuno Gakuen University, 582 Midorimachi, Bunkyodai, Ebetsu, 069-0836, Japan*
[b] *Kanazawa Zoological Gardens, 5-15-1, Kamariyahigashi, Kanazawa-ku, Yokohama, 236-0042, Japan*
[c] *International Institute for Zoonosis Control, Hokkaido University, Kita-20, Nishi-10, Kita-Ku, Sapporo, 001-0020, Japan*

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Keywords:
Sarcoptic mange
Population dynamics
Raccoon dog
State-space model
Wildlife rescue

ABSTRACT

The impact of infectious diseases on host populations is often not quantified because it is difficult to observe the host population and infectious disease dynamics. To address this problem, we developed a state-space model to simultaneously estimate host population and disease dynamics using wildlife rescue data. Using this model, we aimed to quantify the impact of sarcoptic mange on a Japanese raccoon dog population by estimating the change in their relative population size. We classified the status of rescued raccoon dogs into four categories: i) rescued due to infection with mange, ii) rescued due to traffic accidents without mange, iii) rescued due to traffic accidents with mange, and iv) rescued due to causes other than traffic accidents or mange. We modelled the observation process for each category and fitted the model to the reported number of raccoon dogs rescued between 1990 and 2010 at three wildlife rescue facilities in Kanagawa Prefecture, Japan. The mortality rate induced by mange was estimated to be 1.09 (95% credible interval (CI): 0.47–1.72) per year. The estimated prevalence of sarcoptic mange ranged between 4 and 80% in the study period. When a substantial prevalence of mange was observed (1995–2002), the host population size decreased by 91.2% (95% credible intervals: 86.3–94.7). We show that the impact of infectious disease outbreak on the wildlife population can be estimated from the time-series data of wildlife rescue events due to multiple causes. Our estimates suggest that sarcoptic mange triggered a substantial decrease in the Japanese wild raccoon dog populations.

1. Introduction

Estimating population size of wildlife is important in the context of their conservation and management. Furthermore, the population size of wildlife should be measured for disease control to estimate the probability of transmission in the case that the wildlife is involved as a host species (Artois et al., 2009; Sweetapple and Nugent, 2018). Several factors affect the change in the population size of wildlife; as one of them, outbreaks of infectious diseases affect host population size (McCallum and Dobson, 1995; De Castro and Bolker, 2005; Salkeld et al., 2023). As a classical example, a large population crash of wild or introduced free-ranging rabbits was observed owing to an outbreak of the myxoma virus in the US, European countries, and Australia (Fenner, 1953; Alves et al., 2019). In addition, numerous emerging infectious diseases caused a decline in the population size of endangered species and important species as a disease reservoir, such as white nose syndrome in little brown myotises (*Myotis lucifugus*) (Frick et al., 2010), canine distemper in lions (*Panthera leo*) (Roelke-Parker et al., 1996), African swine fever in wild boar (*Sus scrofa*) (Morelle et al., 2020), and peste des petits ruminants in saiga antelopes (*Saiga tatarica*) (Pruvot et al., 2020). The impact on host population size by infectious disease outbreak should be elucidated qualitatively and quantitatively.

Sarcoptic mange (hereinafter, mange) is one of the diseases that can give influence on host population. Mange is caused by the pathogenic mite *Sarcoptes scabiei* (Pence and Ueckermann, 2002). *S. scabiei* is maintained in a multi-mammalian host system (Alasaad et al., 2013; Matsuyama et al., 2019) and detected from more than 140 mammalian species (Escobar et al., 2022). In particular, mange is associated with

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* Corresponding author.
** Corresponding author.
E-mail addresses: r-matsuyama@rakuno.ac.jp (R. Matsuyama), omori@czc.hokudai.ac.jp (R. Omori).
[1] Ryota Matsuyama and Ryosuke Omori contributed equally to this work.
[2] Present address: M.S.K Inc. Dai3-Tendai Building 2F 4-9-1, Higashienokicho, Shinjuku-ku, Tokyo 162-0807, Japan.

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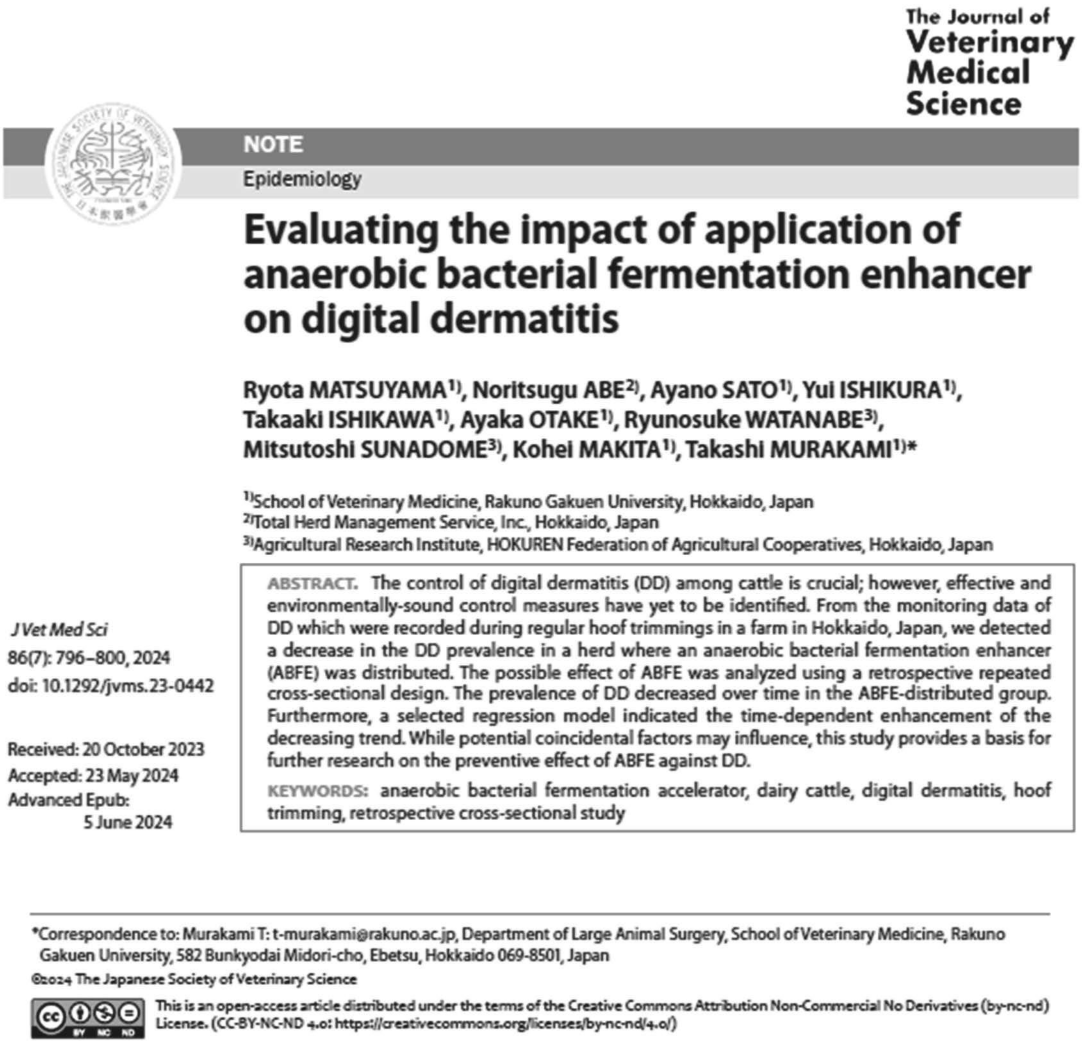

The Journal of
Veterinary
Medical
Science

NOTE

Epidemiology

Evaluating the impact of application of anaerobic bacterial fermentation enhancer on digital dermatitis

Ryota MATSUYAMA[1], Noritsugu ABE[2], Ayano SATO[1], Yui ISHIKURA[1], Takaaki ISHIKAWA[1], Ayaka OTAKE[1], Ryunosuke WATANABE[3], Mitsutoshi SUNADOME[3], Kohei MAKITA[1], Takashi MURAKAMI[1]*

[1]School of Veterinary Medicine, Rakuno Gakuen University, Hokkaido, Japan
[2]Total Herd Management Service, Inc., Hokkaido, Japan
[3]Agricultural Research Institute, HOKUREN Federation of Agricultural Cooperatives, Hokkaido, Japan

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ABSTRACT. The control of digital dermatitis (DD) among cattle is crucial; however, effective and environmentally-sound control measures have yet to be identified. From the monitoring data of DD which were recorded during regular hoof trimmings in a farm in Hokkaido, Japan, we detected a decrease in the DD prevalence in a herd where an anaerobic bacterial fermentation enhancer (ABFE) was distributed. The possible effect of ABFE was analyzed using a retrospective repeated cross-sectional design. The prevalence of DD decreased over time in the ABFE-distributed group. Furthermore, a selected regression model indicated the time-dependent enhancement of the decreasing trend. While potential coincidental factors may influence, this study provides a basis for further research on the preventive effect of ABFE against DD.

KEYWORDS: anaerobic bacterial fermentation accelerator, dairy cattle, digital dermatitis, hoof trimming, retrospective cross-sectional study

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*Correspondence to: Murakami T: t-murakami@rakuno.ac.jp, Department of Large Animal Surgery, School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyodai Midori-cho, Ebetsu, Hokkaido 069-8501, Japan

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最終責任者　Takashi Murakami (Corresponding Author)

SARS-CoV-2 Infection in School Settings, Okinawa Prefecture, Japan, 2021–2022

Yoshihiro Takayama, Yusuke Shimakawa, Ryota Matsuyama, Gerardo Chowell,
Ryosuke Omori, Tetsuharu Nagamoto, Taro Yamamoto, Kenji Mizumoto

During the COVID-19 pandemic, widespread school closures were implemented globally based on the assumption that transmission among children in the school environment is common. However, evidence regarding secondary infection rates by school type and level of contact is lacking. Our study estimated the frequency of SARS-CoV-2 infection in school settings by examining the positivity rate according to school type and level of contact by using data from a large-scale school-based PCR project conducted in Okinawa, Japan, during 2021–2022. Our results indicate that, despite detection of numerous positive cases, the average number of secondary infections remained relatively low at ≈0.5 cases across all types of schools. Considering the profound effects of prolonged closures on educational access, balancing public health benefits against potential long-term effects on children is crucial.

During the COVID-19 pandemic, many countries implemented extensive school closures from nurseries to high schools to reduce infection transmission within schools and curb community spread. School closures have proven effective against highly transmissible diseases (*1–3*). Closures may target specific classrooms, grades, or entire schools when positive cases are confirmed, and, in some instances, regional closures are enacted to contain outbreaks or curb epidemic spread.

During school closures, the shift to online learning places new demands on both students and teachers, particularly those unfamiliar with digital teaching methods. In addition, the cost of acquiring necessary online learning devices falls on families, posing a financial barrier for some. The prolonged closures during the COVID-19 pandemic have resulted in substantial learning setbacks; students lost ≈1.5 school years by the end of 2021. This lapse has led to a concerning rise in learning poverty; 70% of 10-year-olds cannot read and comprehend simple stories, especially in East Asia, South Asia, the Middle East, and Latin America (*4*). Face-to-face learning not only maximizes educational opportunities but also plays a crucial role in preventing the exacerbation of poverty issues. Moreover, the closure of nurseries and elementary schools has substantial socioeconomic effects, frequently necessitating parental leave to care for children (*5*).

The rationale for school closures rests on the assumption of high child-to-child transmission within schools. Both schools and households, where persons gather in close proximity for extended periods, are identified as high-risk settings for transmission (*6*). Some studies have suggested that reducing classroom sizes or increasing the distance between student seats can effectively reduce transmission rates (*7*). However, large-scale research on the extent of COVID-19 transmission among students, who now exhibit increased hygiene awareness and mask usage compared with prepandemic times, remains limited. Moreover, detailed data on the actual number of secondary infections that occur when positive cases occur in schools are scarce.

Author affiliations: Okinawa Chubu Hospital, Uruma, Japan (Y. Takayama); Okinawa Prefecture Epidemiological Statistics and Analysis Committee, Naha-shi, Japan (Y. Takayama, Y. Shimakawa, R. Matusuyama, R. Omori, T. Nagamoto, K. Mizumoto); Institute of Tropical Medicine Department of International Health and Medical Anthropology, Nagasaki University, Nagasaki, Japan (Y. Takayama, T. Yamamoto); Institut Pasteur, Université Paris Cité, Paris, France (Y. Shimakawa); Pasteur International Unit at Kumamoto University/National Center for Global Health and Medicine, Tokyo, Japan (Y. Shimakawa) Rakuno Gakuen Univerisity, Ebetsu, Japan (R. Matsuyama); Georgia State University School of Public Health, Atlanta, Georgia, USA (G. Chowell); International Institute for Zoonosis Control, Hokkaido University, Sapporo, Japan (R. Omori); Kyoto University Graduate School of Advanced Integrated Studies in Human Survivability, Kyoto, Japan (K. Mizumoto)

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最終責任者　Kenji Mizumoto (Corresponding Author)

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SARS-CoV-2 IgG seroprevalence in the Okinawa Main Island and remote islands in Okinawa, Japan, 2020-2021.

Yoshihiro Takayama, Yusuke Shimakawa, Yoshiaki Aizawa,
Christian Butcher, Naomi Chibana, Mary Collins, Kohei Kamegai,
Tae Gyun Kim, Satoshi Koyama, Ryota Matsuyama, Melissa M.Matthews,
Tomoari Mori, Tetsuharu Nagamoto, Masashi Narita, Ryosuke Omori,
Noriko Shibata, Satoshi Shibata, Souichi Shiiki, Shunichi Takakura,
Naoki Toyozato, Hiroyuki Tsuchiya, Matthias Wolf, Taro Yamamoto,
Shuhei Yokoyama, Sho Yonaha, and Kenji Mizumoto

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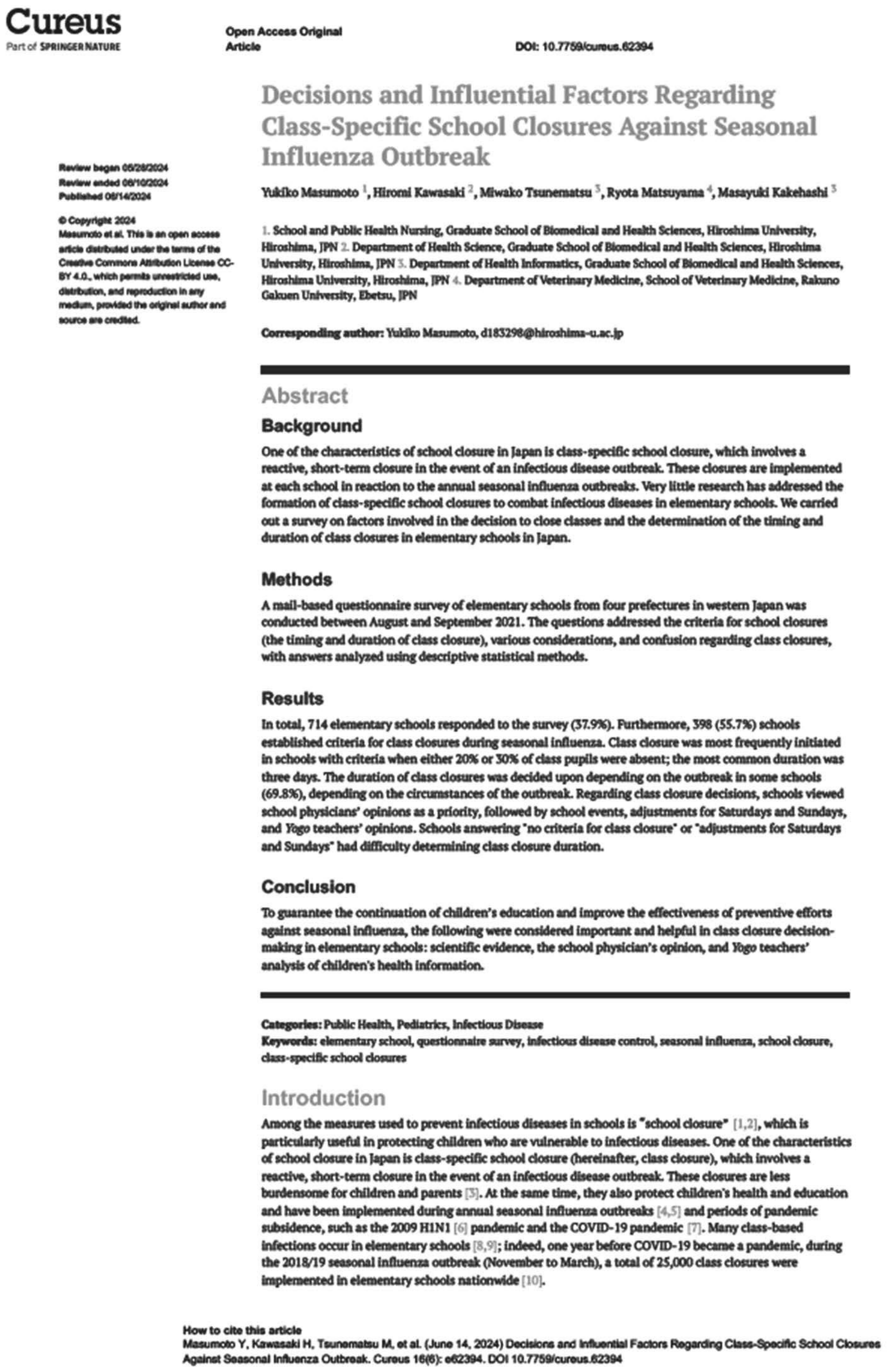

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Decisions and Influential Factors Regarding Class-Specific School Closures Against Seasonal Influenza Outbreak

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Yukiko Masumoto [1], Hiromi Kawasaki [2], Miwako Tsunematsu [3], Ryota Matsuyama [4], Masayuki Kakehashi [3]

1. School and Public Health Nursing, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, JPN 2. Department of Health Science, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, JPN 3. Department of Health Informatics, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, JPN 4. Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, JPN

Corresponding author: Yukiko Masumoto, d183298@hiroshima-u.ac.jp

Abstract

Background

One of the characteristics of school closure in Japan is class-specific school closure, which involves a reactive, short-term closure in the event of an infectious disease outbreak. These closures are implemented at each school in reaction to the annual seasonal influenza outbreaks. Very little research has addressed the formation of class-specific school closures to combat infectious diseases in elementary schools. We carried out a survey on factors involved in the decision to close classes and the determination of the timing and duration of class closures in elementary schools in Japan.

Methods

A mail-based questionnaire survey of elementary schools from four prefectures in western Japan was conducted between August and September 2021. The questions addressed the criteria for school closures (the timing and duration of class closure), various considerations, and confusion regarding class closures, with answers analyzed using descriptive statistical methods.

Results

In total, 714 elementary schools responded to the survey (37.9%). Furthermore, 398 (55.7%) schools established criteria for class closures during seasonal influenza. Class closure was most frequently initiated in schools with criteria when either 20% or 30% of class pupils were absent; the most common duration was three days. The duration of class closures was decided upon depending on the outbreak in some schools (69.8%), depending on the circumstances of the outbreak. Regarding class closure decisions, schools viewed school physicians' opinions as a priority, followed by school events, adjustments for Saturdays and Sundays, and *Yogo* teachers' opinions. Schools answering "no criteria for class closure" or "adjustments for Saturdays and Sundays" had difficulty determining class closure duration.

Conclusion

To guarantee the continuation of children's education and improve the effectiveness of preventive efforts against seasonal influenza, the following were considered important and helpful in class closure decision-making in elementary schools: scientific evidence, the school physician's opinion, and *Yogo* teachers' analysis of children's health information.

Categories: Public Health, Pediatrics, Infectious Disease
Keywords: elementary school, questionnaire survey, infectious disease control, seasonal influenza, school closure, class-specific school closures

Introduction

Among the measures used to prevent infectious diseases in schools is "school closure" [1,2], which is particularly useful in protecting children who are vulnerable to infectious diseases. One of the characteristics of school closure in Japan is class-specific school closure (hereinafter, class closure), which involves a reactive, short-term closure in the event of an infectious disease outbreak. These closures are less burdensome for children and parents [3]. At the same time, they also protect children's health and education and have been implemented during annual seasonal influenza outbreaks [4,5] and periods of pandemic subsidence, such as the 2009 H1N1 [6] pandemic and the COVID-19 pandemic [7]. Many class-based infections occur in elementary schools [8,9]; indeed, one year before COVID-19 became a pandemic, during the 2018/19 seasonal influenza outbreak (November to March), a total of 25,000 class closures were implemented in elementary schools nationwide [10].

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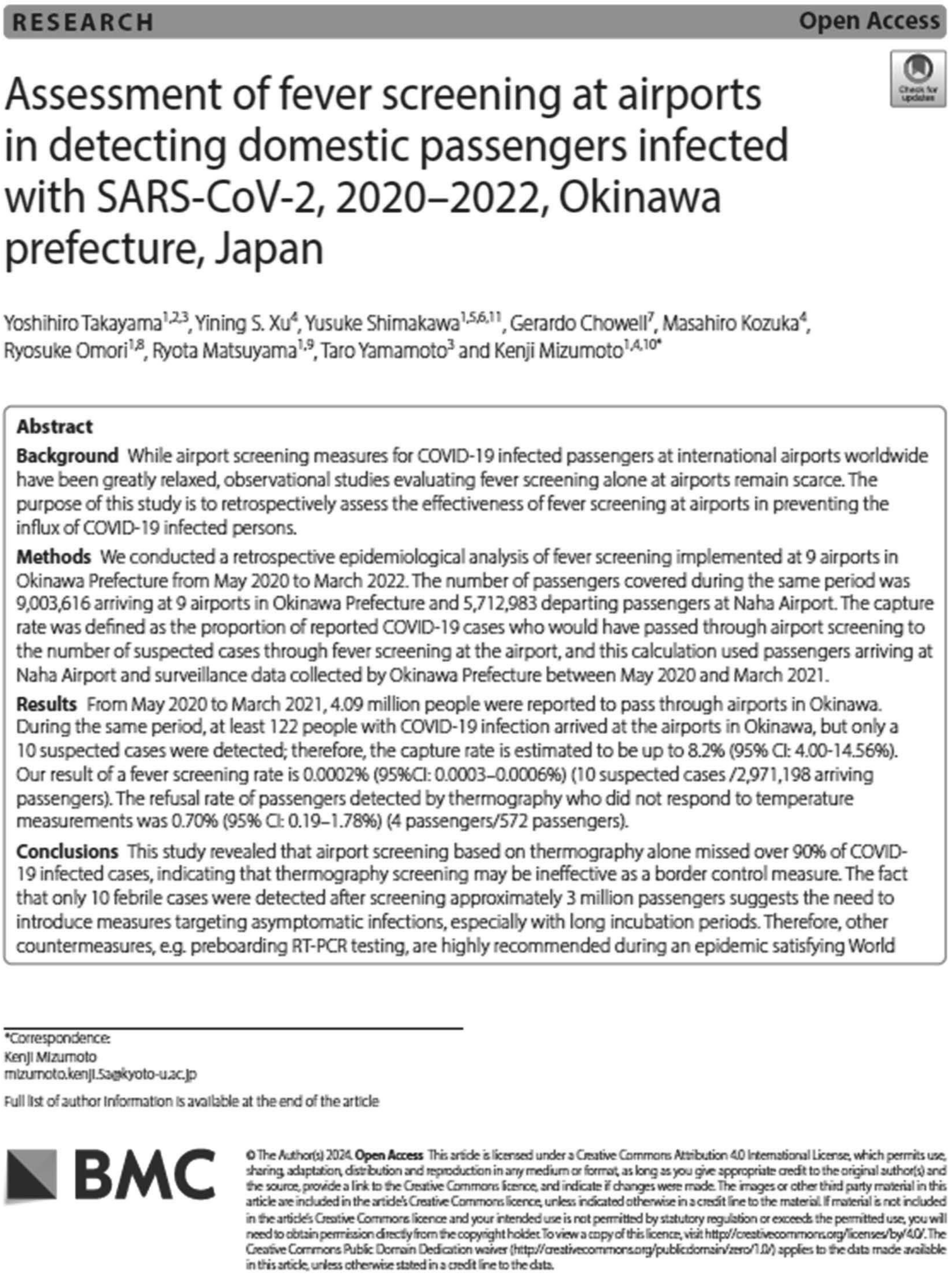
最終責任者　Yukiko Masumoto (Corresponding Author)



RESEARCH **Open Access**

Assessment of fever screening at airports in detecting domestic passengers infected with SARS-CoV-2, 2020–2022, Okinawa prefecture, Japan

Yoshihiro Takayama[1,2,3], Yining S. Xu[4], Yusuke Shimakawa[1,5,6,11], Gerardo Chowell[7], Masahiro Kozuka[4], Ryosuke Omori[1,8], Ryota Matsuyama[1,9], Taro Yamamoto[3] and Kenji Mizumoto[1,4,10*]

Abstract

Background While airport screening measures for COVID-19 infected passengers at international airports worldwide have been greatly relaxed, observational studies evaluating fever screening alone at airports remain scarce. The purpose of this study is to retrospectively assess the effectiveness of fever screening at airports in preventing the influx of COVID-19 infected persons.

Methods We conducted a retrospective epidemiological analysis of fever screening implemented at 9 airports in Okinawa Prefecture from May 2020 to March 2022. The number of passengers covered during the same period was 9,003,616 arriving at 9 airports in Okinawa Prefecture and 5,712,983 departing passengers at Naha Airport. The capture rate was defined as the proportion of reported COVID-19 cases who would have passed through airport screening to the number of suspected cases through fever screening at the airport, and this calculation used passengers arriving at Naha Airport and surveillance data collected by Okinawa Prefecture between May 2020 and March 2021.

Results From May 2020 to March 2021, 4.09 million people were reported to pass through airports in Okinawa. During the same period, at least 122 people with COVID-19 infection arrived at the airports in Okinawa, but only a 10 suspected cases were detected; therefore, the capture rate is estimated to be up to 8.2% (95% CI: 4.00-14.56%). Our result of a fever screening rate is 0.0002% (95%CI: 0.0003–0.0006%) (10 suspected cases /2,971,198 arriving passengers). The refusal rate of passengers detected by thermography who did not respond to temperature measurements was 0.70% (95% CI: 0.19–1.78%) (4 passengers/572 passengers).

Conclusions This study revealed that airport screening based on thermography alone missed over 90% of COVID-19 infected cases, indicating that thermography screening may be ineffective as a border control measure. The fact that only 10 febrile cases were detected after screening approximately 3 million passengers suggests the need to introduce measures targeting asymptomatic infections, especially with long incubation periods. Therefore, other countermeasures, e.g. preboarding RT-PCR testing, are highly recommended during an epidemic satisfying World

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*Correspondence:
Kenji Mizumoto
mizumoto.kenji.5a@kyoto-u.ac.jp
Full list of author information is available at the end of the article

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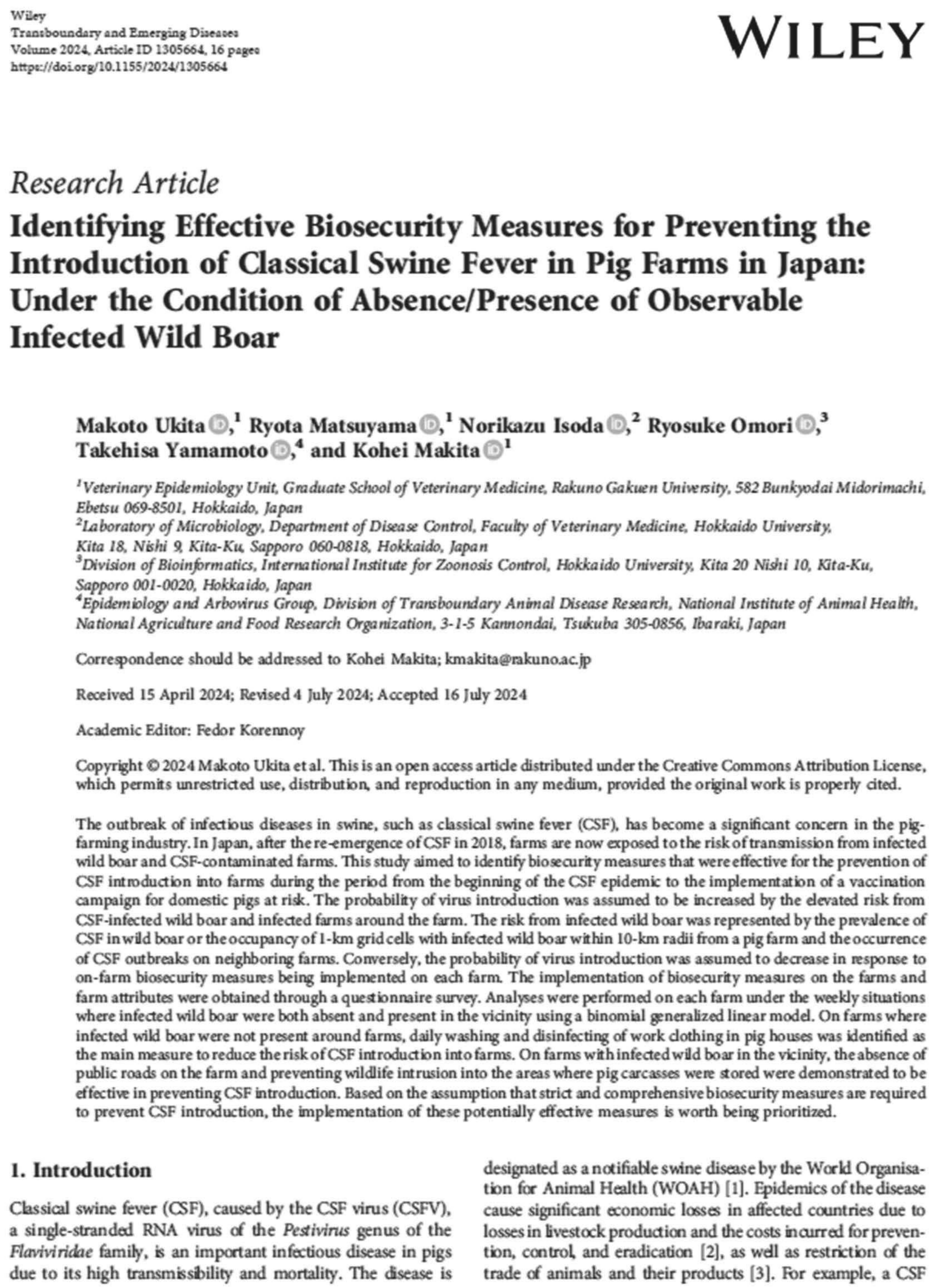
最終責任者　Kenji Mizumoto (Corresponding Author)



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Research Article

Identifying Effective Biosecurity Measures for Preventing the Introduction of Classical Swine Fever in Pig Farms in Japan: Under the Condition of Absence/Presence of Observable Infected Wild Boar

Makoto Ukita,[1] **Ryota Matsuyama**,[1] **Norikazu Isoda**,[2] **Ryosuke Omori**,[3]
Takehisa Yamamoto,[4] **and Kohei Makita**[1]

[1]*Veterinary Epidemiology Unit, Graduate School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyodai Midorimachi, Ebetsu 069-8501, Hokkaido, Japan*
[2]*Laboratory of Microbiology, Department of Disease Control, Faculty of Veterinary Medicine, Hokkaido University, Kita 18, Nishi 9, Kita-Ku, Sapporo 060-0818, Hokkaido, Japan*
[3]*Division of Bioinformatics, International Institute for Zoonosis Control, Hokkaido University, Kita 20 Nishi 10, Kita-Ku, Sapporo 001-0020, Hokkaido, Japan*
[4]*Epidemiology and Arbovirus Group, Division of Transboundary Animal Disease Research, National Institute of Animal Health, National Agriculture and Food Research Organization, 3-1-5 Kannondai, Tsukuba 305-0856, Ibaraki, Japan*

Correspondence should be addressed to Kohei Makita; kmakita@rakuno.ac.jp

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The outbreak of infectious diseases in swine, such as classical swine fever (CSF), has become a significant concern in the pig-farming industry. In Japan, after the re-emergence of CSF in 2018, farms are now exposed to the risk of transmission from infected wild boar and CSF-contaminated farms. This study aimed to identify biosecurity measures that were effective for the prevention of CSF introduction into farms during the period from the beginning of the CSF epidemic to the implementation of a vaccination campaign for domestic pigs at risk. The probability of virus introduction was assumed to be increased by the elevated risk from CSF-infected wild boar and infected farms around the farm. The risk from infected wild boar was represented by the prevalence of CSF in wild boar or the occupancy of 1-km grid cells with infected wild boar within 10-km radii from a pig farm and the occurrence of CSF outbreaks on neighboring farms. Conversely, the probability of virus introduction was assumed to decrease in response to on-farm biosecurity measures being implemented on each farm. The implementation of biosecurity measures on the farms and farm attributes were obtained through a questionnaire survey. Analyses were performed on each farm under the weekly situations where infected wild boar were both absent and present in the vicinity using a binomial generalized linear model. On farms where infected wild boar were not present around farms, daily washing and disinfecting of work clothing in pig houses was identified as the main measure to reduce the risk of CSF introduction into farms. On farms with infected wild boar in the vicinity, the absence of public roads on the farm and preventing wildlife intrusion into the areas where pig carcasses were stored were demonstrated to be effective in preventing CSF introduction. Based on the assumption that strict and comprehensive biosecurity measures are required to prevent CSF introduction, the implementation of these potentially effective measures is worth being prioritized.

1. Introduction

Classical swine fever (CSF), caused by the CSF virus (CSFV), a single-stranded RNA virus of the *Pestivirus* genus of the *Flaviviridae* family, is an important infectious disease in pigs due to its high transmissibility and mortality. The disease is designated as a notifiable swine disease by the World Organisation for Animal Health (WOAH) [1]. Epidemics of the disease cause significant economic losses in affected countries due to losses in livestock production and the costs incurred for prevention, control, and eradication [2], as well as restriction of the trade of animals and their products [3]. For example, a CSF

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最終責任者　Kohei Makita (Corresponding Author)

画像診断学（Veterinary Diagnostic Imaging）

Kenjirou Miyoshi

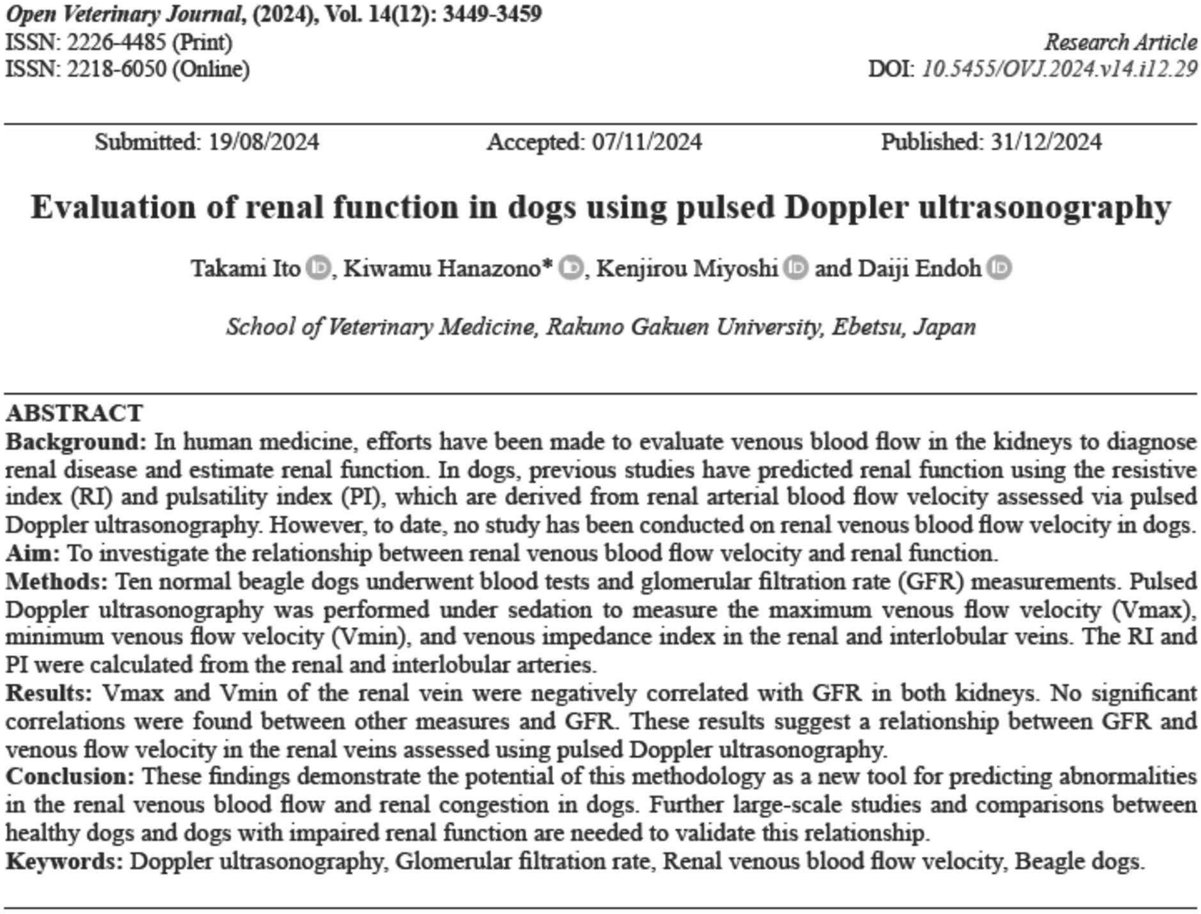
Lecturer

講師　三好健二郎

I. 筆頭または責任著者　＜First or Corresponding Author＞

II. **その他**＜Others＞

1) Evaluation of renal function in dogs using pulsed Doppler ultrasonography.
   Ito T, **Hanazono K**, Miyoshi K, Endoh D.
   Open Vet J 14:3449–3459. 2024. doi: 10.5455/OVJ.2024.v14.i12.29



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Evaluation of renal function in dogs using pulsed Doppler ultrasonography

Takami Ito, Kiwamu Hanazono*, Kenjirou Miyoshi and Daiji Endoh

School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan

ABSTRACT

Background: In human medicine, efforts have been made to evaluate venous blood flow in the kidneys to diagnose renal disease and estimate renal function. In dogs, previous studies have predicted renal function using the resistive index (RI) and pulsatility index (PI), which are derived from renal arterial blood flow velocity assessed via pulsed Doppler ultrasonography. However, to date, no study has been conducted on renal venous blood flow velocity in dogs.
Aim: To investigate the relationship between renal venous blood flow velocity and renal function.
Methods: Ten normal beagle dogs underwent blood tests and glomerular filtration rate (GFR) measurements. Pulsed Doppler ultrasonography was performed under sedation to measure the maximum venous flow velocity (Vmax), minimum venous flow velocity (Vmin), and venous impedance index in the renal and interlobular veins. The RI and PI were calculated from the renal and interlobular arteries.
Results: Vmax and Vmin of the renal vein were negatively correlated with GFR in both kidneys. No significant correlations were found between other measures and GFR. These results suggest a relationship between GFR and venous flow velocity in the renal veins assessed using pulsed Doppler ultrasonography.
Conclusion: These findings demonstrate the potential of this methodology as a new tool for predicting abnormalities in the renal venous blood flow and renal congestion in dogs. Further large-scale studies and comparisons between healthy dogs and dogs with impaired renal function are needed to validate this relationship.
Keywords: Doppler ultrasonography, Glomerular filtration rate, Renal venous blood flow velocity, Beagle dogs.

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最終責任者　Kiwamu Hanazono (Corresponding Author)

獣医生理学（Veterinary Physiology）

Taiki Moriya

Lecturer

講師　守屋　大樹

I. 筆頭または責任著者　＜First or Corresponding Author＞

II.　その他　＜Others＞

1) Sublingual immune cell clusters and dendritic cell distribution in the oral cavity.
Kusumoto Y, Ueda M, Hashimoto M, Takeuchi H, Okada N, Yamamoto J, Nishii A, Fujino A, Kurahashi A, Satoh M, Iwasa Y, Okamura K, Obazaki K, Kumagai R, Sakamoto N, Tanaka Y, Kamiya Y, Hoshida T, Kaisho T, Hemmi H, Katakai T, Honda T, Kikuta J, Kataoka K, Ikebuchi R, **Moriya T**, Adachi T, Watanabe T, Ishii M, Miyawaki A, Kabashima K, Chtanova T, Tomura M
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JCI insight

RESOURCE AND TECHNICAL ADVANCE

Sublingual immune cell clusters and dendritic cell distribution in the oral cavity

Yutaka Kusumoto,[1] Mizuki Ueda,[1] Mayuko Hashimoto,[1] Haruka Takeuchi,[1] Naoko Okada,[1] Junya Yamamoto,[1] Akiko Nishii,[1] Atsuki Fujino,[1] Akiho Kurahashi,[1] Momoka Satoh,[1] Yuki Iwasa,[1] Koki Okamura,[1] Karin Obazaki,[1] Ryoto Kumagai,[1] Naruya Sakamoto,[1] Yuto Tanaka,[1] Yukika Kamiya,[1] Tetsushi Hoshida,[2,3] Tsuneyasu Kaisho,[4] Hiroaki Hemmi,[4,5] Tomoya Katakai,[6] Tetsuya Honda,[7,8] Junichi Kikuta,[9] Kosuke Kataoka,[10] Ryoyo Ikebuchi,[1,11] Taiki Moriya,[1] Takahiro Adachi,[12] Takeshi Watanabe,[13] Masaru Ishii,[9] Atsushi Miyawaki,[2,3] Kenji Kabashima,[7] Tatyana Chtanova,[14,15] and Michio Tomura[1]

[1]Laboratory of Immunology, Faculty of Pharmacy, Osaka Ohtani University, Tondabayashi, Osaka, Japan. [2]Laboratory for Cell Function Dynamics, RIKEN Center for Brain Science, Wako, Saitama, Japan. [3]Biotechnological Optics Research Team, RIKEN Center for Advanced Photonics, Wako, Saitama, Japan. [4]Department of Immunology, Institute of Advanced Medicine, Wakayama Medical University, Graduate School of Medicine, Wakayama, Wakayama, Japan. [5]Laboratory of Immunology, Faculty of Veterinary Medicine, Okayama, University of Science, Imabari, Ehime, Japan. [6]Department of Immunology, Graduate School of Medical and Dental Sciences, Niigata University, Niigata, Niigata, Japan. [7]Department of Dermatology, Kyoto University, Graduate School of Medicine, Sakyo-ku, Kyoto, Japan. [8]Department of Dermatology, Hamamatsu University School of Medicine, Handayama, Hamamatsu, Japan. [9]Laboratory of Immunology and Cell Biology, Graduate school of Medicine, Osaka University, Suita, Osaka, Japan. [10]Department of Oral Health Science and Social Welfare, Graduate school of Oral Sciences, Tokushima University, Tokushima, Tokushima, Japan. [11]Research Fellow of Japan Society for the Promotion of Science, Japan. [12]Department of Precision Health, Medical Research Institute, Tokyo Medical and Dental University, Tokyo, Japan. [13]Laboratory of Immunology, Institute for Life and Medical Sciences, Kyoto University, Sakyo-ku, Kyoto, Japan. [14]School of Biotechnology and Biomolecular Sciences, Faculty of Science, University of New South Wales Sydney, Kensington, New South Wales, Australia. [15]Immunology Theme, Garvan Institute of Medical Research, Darlinghurst, New South Wales, Australia.

The oral mucosa is the first line of defense against pathogenic bacteria and plays a vital role in maintaining tolerance to food antigens and commensal bacteria. We used CD11c reporter mice to visualize dendritic cells (DCs), a key immune cell population, in the oral cavity. We identified differences in DC density in each oral tissue region. Sublingual immune cell clusters (SLICs) extended from the lamina propria to the epithelium, where DCs and T cells resided in close contact with each other and innate lymphoid cells. Targeted in situ photolabeling revealed that the SLICs comprised mostly $\text{CD11c}^+\text{CD11b}^+$ DCs and were enriched for cDC1s and Langerhans cells. Although the frequency of T cell subsets was similar within and outside the SLICs, tissue-resident memory T cells were significantly enriched within the clusters and cluster size increased in response to inflammation. Collectively, we found that SLICs form a unique microenvironment that facilitates T cell–DC interactions in the steady state and during inflammation. Since the oral mucosa is an important target for needle-free vaccination and sublingual immunotherapy to induce tolerogenic responses, the insight into the localized immunoregulation provided in this study may accelerate the development of these approaches.

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Introduction

The oral cavity is the first part of the digestive system that comes into contact with foreign antigens. Immune cells in the oral cavity form the first line of defense against pathogenic bacteria and maintain oral tolerance to food antigens and commensal bacteria (1, 2). They present potential targets for therapeutic regulation of systemic immune responses by painless needle-free vaccination and sublingual immunotherapy (SLIT) for type I allergic diseases (3–6). Dendritic cells (DCs) in peripheral tissues serve as sentinels for exogenous antigens, which they capture and present to T cells in the draining lymph nodes (dLNs) to initiate adaptive immune responses (7). DCs can also contact and directly stimulate T cells in peripheral

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最終責任者　Michio Tomura (Corresponding Author)

獣医薬理学（Veterinary Pharmacology）

Tatsuro Nakamura

Lecture

講師　中村　達朗

I. 筆頭または責任著者　＜First or Corresponding Author＞

II. その他　＜Others＞

1）Tyrosinase inhibition prevents non-coplanar polychlorinated biphenyls and polybrominated diphenyl ethers-induced hyperactivity in developing zebrafish: I nteraction between pigmentation and neurobehavior.
Tanaka Y, Shindo A, Dong W, **Nakamura T**, Ogura K, Nomiyama K, Teraoka H.
Neurotoxicol Teratol 104:107373. 2024. doi:10.1016/j.ntt.2024.107373.

2）Possible Shifts in the Genetic Diversity of Red-crowned Cranes (*Grus japonensis*) in Hokkaido, Japan: Indications of Continental Gene Flow.
Dong W, Tomita K, Sawada A, Hasebe M, Inoue M, Momose K, **Nakamura T**, Teraoka H.
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Tyrosinase inhibition prevents non-coplanar polychlorinated biphenyls and polybrominated diphenyl ethers-induced hyperactivity in developing zebrafish: Interaction between pigmentation and neurobehavior

Yasuaki Tanaka[a], Asako Shindo[a,b], Wenjing Dong[a], Tatsuro Nakamura[a], Kyoko Ogura[c], Kei Nomiyama[c], Hiroki Teraoka[a,*]

[a] *School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu 069-8501, Japan*
[b] *Department of Biological Sciences, Osaka University, Osaka 560-0043, Japan*
[c] *Center for Marine Environmental Studies (CMES), Ehime University, 2-5 Bunkyo-cho, Matsuyama, Ehime 790-8577, Japan*

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Zebrafish

ABSTRACT

Non-coplanar polychlorinated biphenyl (PCB) mixture Aroclor 1254 and polybrominated diphenyl ether (PBDE) BDE-47 are known to impede neurogenesis and neuronal development. We previously reported that exposure to PCB and PBDE leads to increased embryonic movement in zebrafish by decreasing dopamine levels. In this study, we studied the connection between the melanin and dopamine synthesis pathways in this context. Both genetic and chemical inhibition of tyrosinase, the rate-limiting enzyme in melanin synthesis, not only led to reduced pigmentation but also inhibit PCB/PBDE-induced embryonic hyperactivity. Furthermore, PCB and PBDE rarely affected tyrosinase expression in the potential pigment cells, suggesting that these compounds reduce dopamine through enzymatic regulation, including a competitive interaction for the substrate tyrosine. Our results provide new insights into the interactions between melanogenesis and dopaminergic neuronal activity, which may contribute to understanding the mechanisms underlying PCB/PBDE toxicity in developing organisms.

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最終責任者　Hiroki Teraoka (Corresponding Author)

animals

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Article

Possible Shifts in the Genetic Diversity of Red-crowned Cranes (*Grus japonensis*) in Hokkaido, Japan: Indications of Continental Gene Flow

Wenjing Dong [1], Kai Tomita [1], Akira Sawada [2], Makoto Hasebe [3], Masako Inoue [4], Kunikazu Momose [4], Tatsuro Nakamura [1] and Hiroki Teraoka [1,4,*]

[1] School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu 069-8501, Japan; dongwenjing_2015@163.com (W.D.); s21861114@g.rakuno.ac.jp (K.T.); t-naka@rakuno.ac.jp (T.N.)
[2] Faculty of Human Sciences, Waseda University, Tokorozawa 359-1192, Japan; akira.sawada.1312@gmail.com
[3] NPO Sarobetsu Eco Network, Toyotomi 098-4100, Japan; hasebe@sarobetsu.or.jp
[4] NPO Red-crowned Crane Conservancy, Kushiro 085-0036, Japan; masako@seagreen.ocn.ne.jp (M.I.); momosekunikazu@gmail.com (K.M.)
* Correspondence: hteraoka08@gmail.com or hteraoka@rakuno.ac.jp

Simple Summary: The red-crowned cranes consist of two populations: continental (Far East Eurasia) and island (Hokkaido, Japan) cranes. It was once thought that these two populations lived independently. Having recovered from near extinction more than a century ago, the island population in Hokkaido, Japan, now exhibits very low genetic diversity, raising concerns about potentially devastating effects from infectious diseases. In 2018, a possible mating between a continental male and an island female was observed in northern Hokkaido. This study investigates their offspring or their blood relatives by examining the major histocompatibility complex (MHC) in cranes from northern and southeastern Hokkaido between 2008 and 2022. We identified 58 MHC types based on nucleotide sequences. MHC types from the possible continental male were predominantly found in cranes from northern Hokkaido. Genetic analysis also suggested clear population differentiation between northern and southeastern Hokkaido. The results suggest that genetic traits from the continental population have been integrated into the Hokkaido cranes, particularly in the northern population. This genetic exchange may improve the disease resistance and environmental adaptability of the Hokkaido crane population, providing valuable insights for conservation efforts.

Abstract: Red-crowned cranes (*Grus japonensis*) consist of two distinct groups: the continental population and the island population. The island population, localized in Hokkaido, Japan, exhibits very low genetic diversity due to its rapid recovery from the brink of extinction. Our previous research in 2018 highlighted a possible mating between a male from the continental population, with the Gj5 haplotype, and a female from the island population, with the Gj2 haplotype, at Hitominuma Sawmp shore in northern Hokkaido. The present study attempted to unravel the distribution of their offspring by examining the major histocompatibility complex (MHC) of this mixed breeding pair compared with samples collected from cranes in northern and southeastern Hokkaido between 2008 and 2022. The analysis identified 55 MHC types, including 10 known types in a dataset of 89 crane samples, based on amino acid sequences. A total of 58 MHC types were recognized, based on nucleotide sequences, as there were many cases in which the same amino acid sequence had different nucleotide sequences. The five DNA types of MHC in the Hitominuma Swamp male were predominantly identified in eight cranes from northern Hokkaido and one chick from southeastern Hokkaido. In addition, population genetic analysis, based on insertion/deletion (InDel) polymorphisms, indicates distinct population differentiation between the northern and southeastern regions of Hokkaido. These results suggest that genetic contributions from the continental red-crowned crane population have already been integrated into the Hokkaido populations, with a more pronounced influence in northern Hokkaido.

Keywords: genetic diversity; *Grus japonensis*; Hokkaido; eastern Eurasia; MHC; Red-crowned crane

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最終責任者　Hiroki Teraoka (Corresponding Author)

獣医病理学（Veterinary Pathology）

Yuto Sano

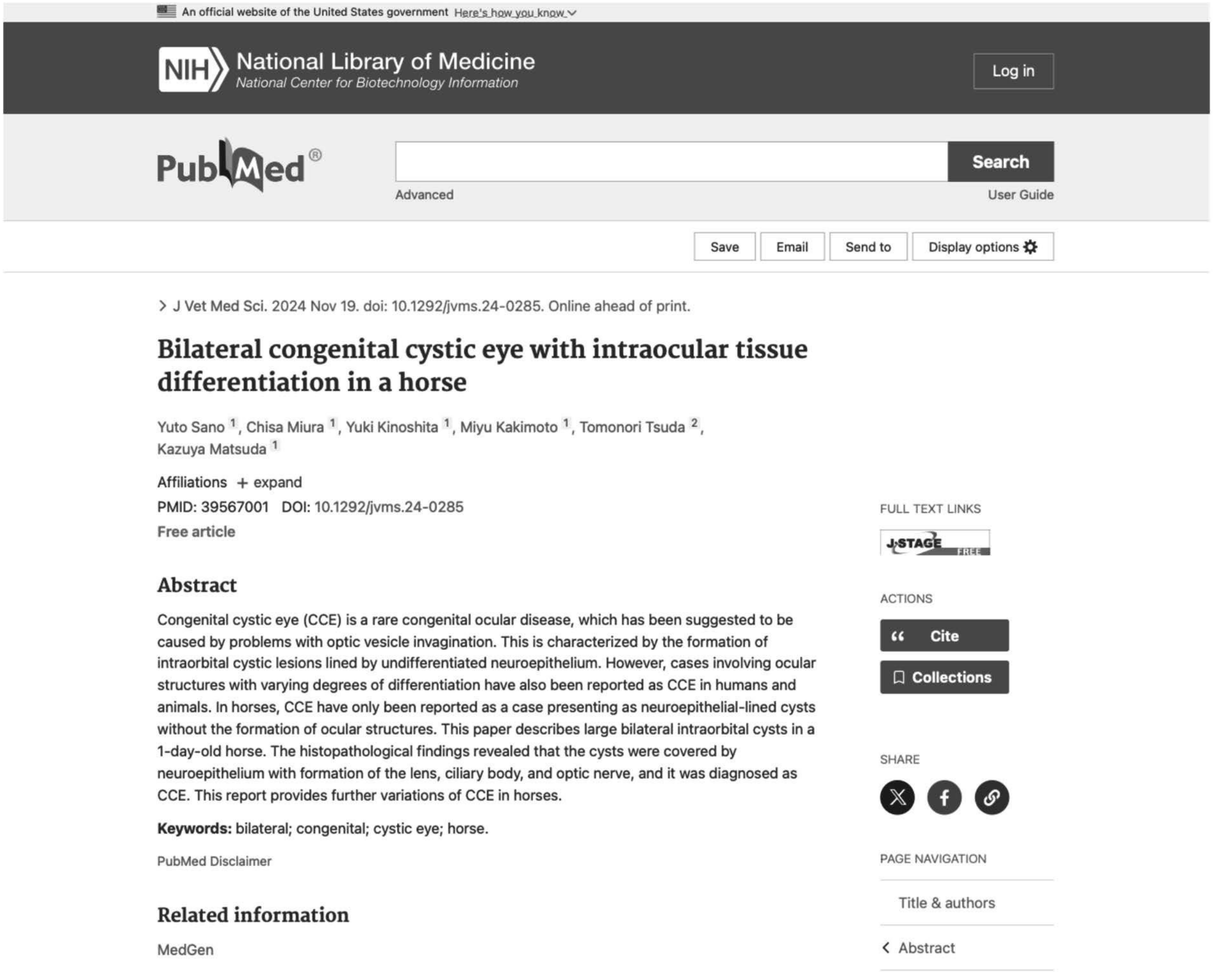
Lecturer

講師　佐野　悠人

Ⅰ. 筆頭または責任著者　＜First or Corresponding Author＞

1) Bilateral congenital cystic eye with intraocular tissue differentiation in a horse.
Sano Y, Miura C, Kinoshita Y, Kakimoto M, Tsuda T, Matsuda K.
J Vet Med Sci 86: *in press*. 2024. doi: 10.1292/jvms.24-0285. Online ahead of print.

Ⅱ. **その他**＜Others＞



> J Vet Med Sci. 2024 Nov 19. doi: 10.1292/jvms.24-0285. Online ahead of print.

Bilateral congenital cystic eye with intraocular tissue differentiation in a horse

Yuto Sano [1], Chisa Miura [1], Yuki Kinoshita [1], Miyu Kakimoto [1], Tomonori Tsuda [2], Kazuya Matsuda [1]

Affiliations + expand

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Free article

Abstract

Congenital cystic eye (CCE) is a rare congenital ocular disease, which has been suggested to be caused by problems with optic vesicle invagination. This is characterized by the formation of intraorbital cystic lesions lined by undifferentiated neuroepithelium. However, cases involving ocular structures with varying degrees of differentiation have also been reported as CCE in humans and animals. In horses, CCE have only been reported as a case presenting as neuroepithelial-lined cysts without the formation of ocular structures. This paper describes large bilateral intraorbital cysts in a 1-day-old horse. The histopathological findings revealed that the cysts were covered by neuroepithelium with formation of the lens, ciliary body, and optic nerve, and it was diagnosed as CCE. This report provides further variations of CCE in horses.

Keywords: bilateral; congenital; cystic eye; horse.

Related information

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最終責任著者　Yuto Sano (First Author/Corresponding Author)

生産動物外科学（Farm Animal Surgery）

Ayano Sato

Lecturer

講師　佐藤　綾乃

I. 筆頭または責任著者　＜First or Corresponding Author＞

1）Photogrammetric analysis of limb joint angles in cows with normal gait before and after hoof trimming.
Sato A, Kosenda K., Sugiura T., Murakami T.
J Dairy Sci 107:8523–8533. 2024. doi: 10.3168/jds.2023-24255

2）Comparing hoof dimensional measurements in cows based on 3D image creation and manual measurement
Murakami T, Ohtake A, Ishikawa T, **Sato A.**
Vet J 306:106193. 2024. doi: 10.1016/j.tvjl.2024.106193

II.　その他　＜Others＞

3）Use of a gum elastic bougie in a cat with severe upper airway stenosis. Evaluating the impact of application of anaerobic bacterial fermentation enhancer on digital dermatitis
Matsuyama R, Abe N, **Sato A**, Ishikura Y, Ishikawa T, Otake A, Watanabe R, Sunadome M, Makita K, Murakami T.
J Vet Med Sci 86: 796–800. 2024. doi: 10.1292/jvms.23-0442

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Photogrammetric analysis of limb joint angles in cows with normal gait before and after hoof trimming

A. Sato,* K. Kosenda, T. Sugiura, and T. Murakami
Department of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, 069-8501 Japan

ABSTRACT

The aim of this study was to evaluate the effect of hoof trimming on overall limb movements by comparing the changes in 8 limb joint angles 1 wk before and 1 wk after hoof trimming. Seventeen Holstein-Friesian dairy cows that were able to move freely and had no history of hoof diseases were included in the study. The cows were walked on rubber mats with a high friction coefficient (HFM) and a low friction coefficient (LFM) due to the spraying of sodium polyacrylate. Each cow had 15 reflective markers applied to its right side. A high-speed camera was set to 200 frames per second (fps) on the image analysis software, and the images of the cows were captured while cows walked on the test mat. The tests were conducted 1 wk before and 1 wk after hoof trimming, and the cows were trimmed by the functional hoof trimming method. With image analysis software, video clips of walking cows were confirmed visually and tracked during 1 gait cycle by each reflective marker attached to the hoof of the forelimb and hindlimb, after which the stance phase and swing phase were identified. The durations of the stance phase and swing phase of the forelimb and hindlimb, respectively, and the maximum, minimum, and range of motion (ROM) values of the 8 joint angles (shoulder joint, elbow joint, carpus joint, forelimb fetlock joint, hip joint, stifle joint, hock joint, and hindlimb fetlock joint) during 1 gait cycle were included in the analysis. The maximum and minimum angles of the hip and stifle joints were narrower after hoof trimming than before, although the ROM did not change and was clearer for HFM than for LFM. It was thought that the flexion of the proximal hindlimb would progress smoothly during walking after trimming.

Key words: dairy cow, hoof trimming, joint angle, photogrammetry

INTRODUCTION

Lameness in dairy cows is associated with economic losses and animal welfare concerns in the dairy industry (Huxley, 2013; Liang et al., 2017). Lameness causes changes in behavior because of a pain response. Changes in cow behavior are among the most important standards for assessing animal welfare and health (Cook et al., 2005; Chapinal et al., 2011; Viazzi et al., 2013). The functional hoof trimming method is thought to prevent lameness (Toussaint Raven, 1985). Hoof trimming is associated with behavioral and physiological changes. Common behavioral indicators used to evaluate the effect of hoof trimming include locomotion score, lying time, activity, and walking speed (Manske et al., 2002; Chapinal et al., 2010; Van Hertem et al., 2014). In addition, some reports have used a force plate to evaluate the balance of weight bearing between 2 claws (van der Tol et al., 2004; Carvalho et al., 2006), and others have reported the use of a 3-dimensional acceleration sensor or a video camera to determine changes in cows' gait behaviors (Aoki et al., 2006; Tanida et al., 2011).

In horses, photogrammetry of kinematic traits is an objective method that has been used to evaluate gait quality under experimental and field conditions (Back et al., 1994; Clayton, 1994; Morales et al., 1998). These studies have focused on analyzing the gait symmetry of horses to identify potential injuries (Rhodin et al., 2016) and are also useful in the definition of gait quality indicators (Barrey et al., 2002).

In cows, kinematic studies using vision-based technologies have been reported for the detection of lameness or for the analysis of gait biomechanics (Flower et al., 2005; Viazzi et al., 2013; Weiss et al., 2019). To our knowledge, there have been no reports of kinematic traits following changes in limb joint angles, including proximal joints, during 1 gait cycle according to photogrammetry. The aim of this study was to evaluate the effect of hoof trimming on overall limb movements by comparing the changes in limb joint angles 1 wk before and 1 wk after hoof trimming. Specifically, the angular changes in 8 distal-to-proximal limb joints, including

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*Corresponding author: ayanok@rakuno.ac.jp

The list of standard abbreviations for JDS is available at adsa.org/jds-abbreviations-24. Nonstandard abbreviations are available in the Notes.

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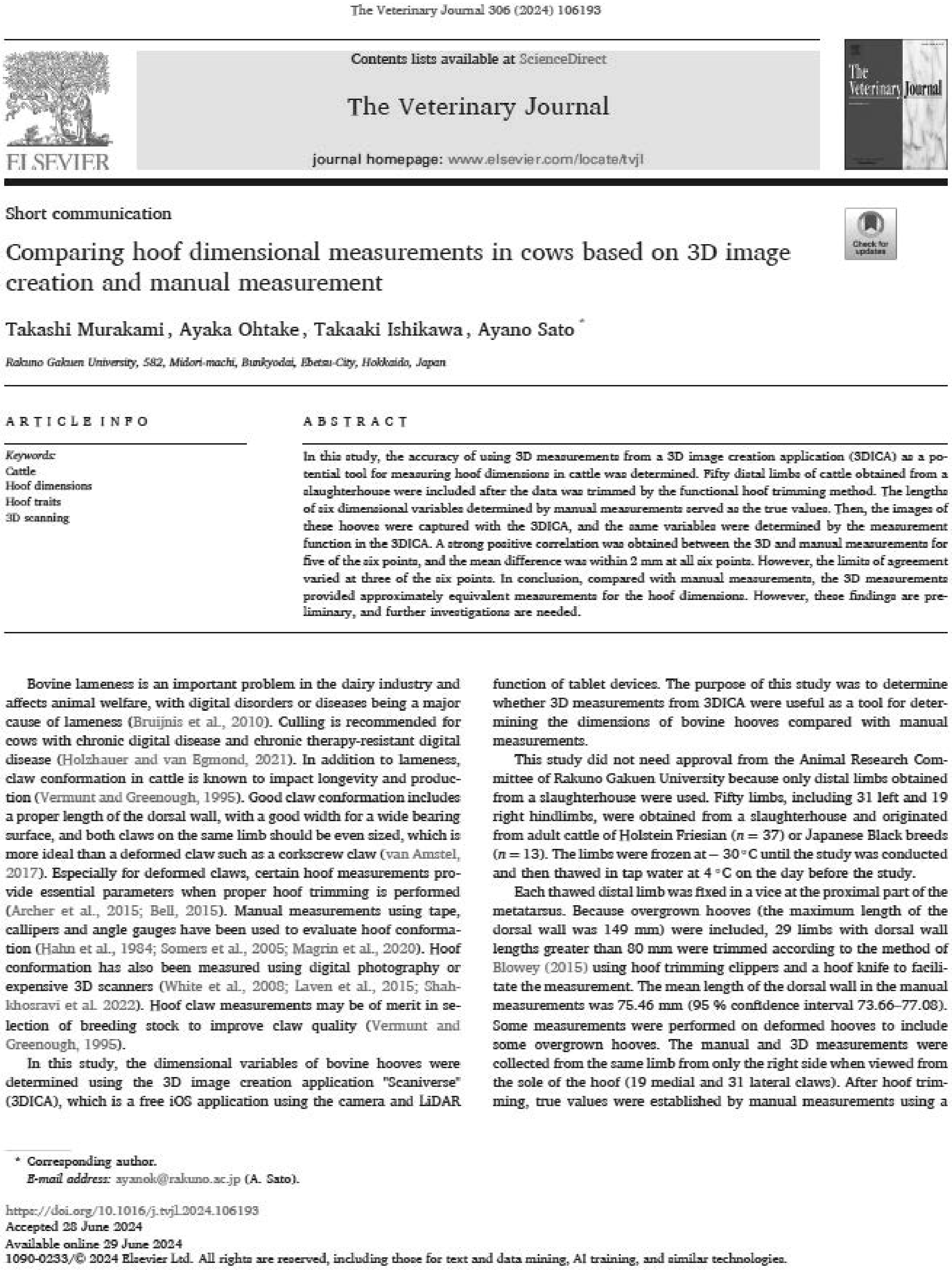

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Short communication

Comparing hoof dimensional measurements in cows based on 3D image creation and manual measurement

Takashi Murakami, Ayaka Ohtake, Takaaki Ishikawa, Ayano Sato *

Rakuno Gakuen University, 582, Midori-machi, Bunkyodai, Ebetsu-City, Hokkaido, Japan

ARTICLE INFO

Keywords:
Cattle
Hoof dimensions
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3D scanning

ABSTRACT

In this study, the accuracy of using 3D measurements from a 3D image creation application (3DICA) as a potential tool for measuring hoof dimensions in cattle was determined. Fifty distal limbs of cattle obtained from a slaughterhouse were included after the data was trimmed by the functional hoof trimming method. The lengths of six dimensional variables determined by manual measurements served as the true values. Then, the images of these hooves were captured with the 3DICA, and the same variables were determined by the measurement function in the 3DICA. A strong positive correlation was obtained between the 3D and manual measurements for five of the six points, and the mean difference was within 2 mm at all six points. However, the limits of agreement varied at three of the six points. In conclusion, compared with manual measurements, the 3D measurements provided approximately equivalent measurements for the hoof dimensions. However, these findings are preliminary, and further investigations are needed.

Bovine lameness is an important problem in the dairy industry and affects animal welfare, with digital disorders or diseases being a major cause of lameness (Bruijnis et al., 2010). Culling is recommended for cows with chronic digital disease and chronic therapy-resistant digital disease (Holzhauer and van Egmond, 2021). In addition to lameness, claw conformation in cattle is known to impact longevity and production (Vermunt and Greenough, 1995). Good claw conformation includes a proper length of the dorsal wall, with a good width for a wide bearing surface, and both claws on the same limb should be even sized, which is more ideal than a deformed claw such as a corkscrew claw (van Amstel, 2017). Especially for deformed claws, certain hoof measurements provide essential parameters when proper hoof trimming is performed (Archer et al., 2015; Bell, 2015). Manual measurements using tape, callipers and angle gauges have been used to evaluate hoof conformation (Hahn et al., 1984; Somers et al., 2005; Magrin et al., 2020). Hoof conformation has also been measured using digital photography or expensive 3D scanners (White et al., 2008; Laven et al., 2015; Shahkhosravi et al. 2022). Hoof claw measurements may be of merit in selection of breeding stock to improve claw quality (Vermunt and Greenough, 1995).

In this study, the dimensional variables of bovine hooves were determined using the 3D image creation application "Scaniverse" (3DICA), which is a free iOS application using the camera and LiDAR function of tablet devices. The purpose of this study was to determine whether 3D measurements from 3DICA were useful as a tool for determining the dimensions of bovine hooves compared with manual measurements.

This study did not need approval from the Animal Research Committee of Rakuno Gakuen University because only distal limbs obtained from a slaughterhouse were used. Fifty limbs, including 31 left and 19 right hindlimbs, were obtained from a slaughterhouse and originated from adult cattle of Holstein Friesian ($n = 37$) or Japanese Black breeds ($n = 13$). The limbs were frozen at − 30 °C until the study was conducted and then thawed in tap water at 4 °C on the day before the study.

Each thawed distal limb was fixed in a vice at the proximal part of the metatarsus. Because overgrown hooves (the maximum length of the dorsal wall was 149 mm) were included, 29 limbs with dorsal wall lengths greater than 80 mm were trimmed according to the method of Blowey (2015) using hoof trimming clippers and a hoof knife to facilitate the measurement. The mean length of the dorsal wall in the manual measurements was 75.46 mm (95 % confidence interval 73.66–77.08). Some measurements were performed on deformed hooves to include some overgrown hooves. The manual and 3D measurements were collected from the same limb from only the right side when viewed from the sole of the hoof (19 medial and 31 lateral claws). After hoof trimming, true values were established by manual measurements using a

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* Corresponding author.
E-mail address: ayanok@rakuno.ac.jp (A. Sato).

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NOTE

Epidemiology

Evaluating the impact of application of anaerobic bacterial fermentation enhancer on digital dermatitis

Ryota MATSUYAMA[1), Noritsugu ABE[2), Ayano SATO[1), Yui ISHIKURA[1), Takaaki ISHIKAWA[1), Ayaka OTAKE[1), Ryunosuke WATANABE[3), Mitsutoshi SUNADOME[3), Kohei MAKITA[1), Takashi MURAKAMI[1)]*

[1)]School of Veterinary Medicine, Rakuno Gakuen University, Hokkaido, Japan
[2)]Total Herd Management Service, Inc., Hokkaido, Japan
[3)]Agricultural Research Institute, HOKUREN Federation of Agricultural Cooperatives, Hokkaido, Japan

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ABSTRACT. The control of digital dermatitis (DD) among cattle is crucial; however, effective and environmentally-sound control measures have yet to be identified. From the monitoring data of DD which were recorded during regular hoof trimmings in a farm in Hokkaido, Japan, we detected a decrease in the DD prevalence in a herd where an anaerobic bacterial fermentation enhancer (ABFE) was distributed. The possible effect of ABFE was analyzed using a retrospective repeated cross-sectional design. The prevalence of DD decreased over time in the ABFE-distributed group. Furthermore, a selected regression model indicated the time-dependent enhancement of the decreasing trend. While potential coincidental factors may influence, this study provides a basis for further research on the preventive effect of ABFE against DD.

KEYWORDS: anaerobic bacterial fermentation accelerator, dairy cattle, digital dermatitis, hoof trimming, retrospective cross-sectional study

Digital dermatitis (DD) is a common infectious disease that causes hoof lesions and is one of a major risk factors of lameness in cattle [3]. DD is caused by multiple bacterial species, particularly anaerobic bacteria belonging to the genus *Treponema* [8]. The control of DD is essential because the painful condition due to DD results in losses in animal productivity and welfare [4, 5]. Numerous potential control measures against DD have been considered, including regular hoof trimming [14, 16], improvements in diet [14], the introduction of grazing [14], and supplementing with fermented products as a feed additive [1]. However, due to variations in the susceptibility of individual cows and the difference of key risk factors between farms, effective control measures have yet to be determined [11]. The administration of antibiotics and copper sulfate are considered an effective treatment; however, these are associated with an elevated risk of antimicrobial resistance, as well as environmental damage [9].

Since February 2019, our research team has regularly monitored the incidence of DD by recording the hoof status of individual cows during routine hoof trimming on a dairy farm in Tokoro District, Hokkaido, Japan. During our monitoring, we observed a significant decrease in the prevalence of DD over time in a heifer group that lived in a barn where a commercially available fermentation enhancer, which included anaerobic bacteria (RecycleMate: FarmTech Japan Co., Ltd., Sapporo, Japan [6]), was distributed on the alley in a barn. According to FarmTech Japan Co., the company confirmed that the anaerobic bacteria included in this fermentation enhancer suppressed the growth of Treponema species collected from DD lesion under experimental condition (FarmTech Japan Co., personal communication). In the present study, we aimed to report the descriptive epidemiology responsible for the decrease in the prevalence of DD associated with the distribution of the anaerobic bacterial fermentation enhancer (ABFE). In addition, we also estimated the effect of ABFE distribution on the prevalence of DD by comparing the change in the DD prevalence in an ABFE-distributed cow group with that in a non-distributed group.

The distribution of ABFE was conducted at a farm located in Kunneppu-cho, Tokoro District, Hokkaido, Japan. The herds in the farm consisted of: (i) calves under 12 months old (usually 40–50 cows); (ii) heifers of 12–18 months old (usually 40–50 cows); (iii) heifers of 18–24 months old with matured cows in their dry period (usually 25 heifers and 15 matured cows in dry period); and (iv) matured cows in the lactation period (usually approximately 120 cows). Each herd is kept separately in a different free-stall barn with a concrete floor. The cows were shifted between herds in accordance with their growth/lactation stage. Among them, a heifer

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*Correspondence to: Murakami T: t-murakami@rakuno.ac.jp, Department of Large Animal Surgery, School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyodai Midori-cho, Ebetsu, Hokkaido 069-8501, Japan

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最終責任者　Takashi Murakami (Corresponding Author)

獣医伴侶内科学（Companion Animal Internal Medicine）

Masahiro Tamura

Lecturer

講師　田村　昌大

I. 筆頭または責任著者　＜First or Corresponding Author＞

II.　その他　＜Others＞

1) Comparison of chemotherapy outcomes between normal and high serum cortisol concentration in dogs with lymphoma.
Yamazaki H, Bunbai K, Deguchi T, **Tamura M**, Ohota H.
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STANDARD ARTICLE

Comparison of chemotherapy outcomes between normal and high serum cortisol concentration in dogs with lymphoma

Hiroki Yamazaki | Kaito Bunbai | Tatsuya Deguchi | Masahiro Tamura | Hiroshi Ohota

Laboratory of Companion Animal Internal Medicine, Department of Companion Animal, Clinical Sciences, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan

Correspondence
Hiroki Yamazaki, Laboratory of Companion Animal Internal Medicine, Department of Companion Animal, Clinical Sciences, School of Veterinary Medicine, Rakuno Gakuen University, 582-1 Bunkyodai, Midorimachi, Ebetsu, Hokkaido, 069-8501, Japan.
Email: hyamazaki@rakuno.ac.jp

Abstract

Background: Increased serum cortisol (COR) concentrations may induce glucocorticoid resistance by down-regulation of glucocorticoid receptor (GCR), resulting in decreased chemotherapy efficacy in dogs with lymphoma.

Hypothesis: Investigate the relationship between serum COR concentrations and chemotherapy outcomes in dogs with lymphoma.

Animals: Thirty client-owned dogs with lymphoma, with serum COR concentration measured using serum samples collected at diagnosis.

Methods: Retrospective study. Dogs were divided into 2 groups based on serum COR concentrations: a normal group (n = 16) with COR concentrations <6 μg/dL and a high group (14) with COR concentrations ≥6 μg/dL. We compared signalment, clinical signs, stage, type of lymphoma, adrenal gland size, alkaline phosphatase (ALP) activity, response to chemotherapy, progression-free survival (PFS), overall survival (OS), and rate of P-glycoprotein (P-gp)- and GCR-positive cells between the 2 groups.

Results: No significant differences were found in the demographic characteristics between the 2 groups. However, the high COR group exhibited a significantly lower response to chemotherapy, PFS, and OS compared with the normal COR group. Serum ALP activity was significantly higher in the high COR group than in the normal COR group. Adrenal gland size was also significantly larger in the high COR group. Although no significant differences were found in the rate of P-gp-positive cells between the 2 groups, the rate of GCR-positive cells was significantly lower in the high COR group.

Conclusions and Clinical Importance: Our data suggests that measurement of serum COR concentrations may serve as a potential prognostic factor and evaluation index.

KEYWORDS
endogenous corticosteroid, glucocorticoid receptor, glucocorticoid resistance, P-glycoprotein

Abbreviations: ACNU, 1-(4-amino-2-methyl-5-pyrimidinyl)methyl-3-(2-chloroethyl)-3-nitrosourea; ALP, alkaline phosphatase; CCNU, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea; CI, confidence intervals; COR, cortisol; CR, complete response; GCR, glucocorticoid receptors; L-CHOP, L-asparaginase, cyclophosphamide, doxorubicin, vincristine, prednisone; MTL, maximum dorsoventral thicknesses of the left; MTR, maximum dorsoventral thicknesses of the right; ORR, overall response rate; OS, overall survival; PBS, phosphate-buffered saline; PD, progressive disease; PFS, progression-free survival; P-gp, P-glycoprotein; PR, partial response; RECIST, response evaluation criteria in solid tumors; SD, stable disease; VCOG-CTCAE, Veterinary Cooperative Oncology Group-Common Terminology Criteria for Adverse Events; WHO, World Health Organization.

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最終責任者　Hiroki Yamazaki (Corresponding Author)

疾患モデル学（Disease models）

Masaki Fujimoto

Assistant Professor

助教　藤本　政毅

I. 筆頭または責任著者　＜First or Corresponding Author＞

II.　その他　＜Others＞

1） Mechanism of the Radioresistant Colorectal Cancer Cell Line SW480RR Established after Fractionated X Irradiation.
Yamashita K, Yasui H, Bo T, **Fujimoto M**. Inanami O.
Radiat Res 202:38–50. 2024. doi :10.1667/RADE-23-00021.1

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Kitamura H, **Fujimoto M**, Hashimoto M, Yasui H, Inanami O.
Int J Mol Sci 25:11936. 2024. doi: 10.3390/ijms252211936.

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Mechanism of the Radioresistant Colorectal Cancer Cell Line SW480RR Established after Fractionated X Irradiation

Koya Yamashita, Hironobu Yasui,[1] Tomoki Bo, Masaki Fujimoto, Osamu Inanami

Laboratory of Radiation Biology, Department of Applied Veterinary Sciences, Faculty of Veterinary Medicine, Hokkaido University, Sapporo, Japan

Yamashita K, Yasui H, Bo T, Fujimoto M, Inanami O, Mechanism of the Radioresistant Colorectal Cancer Cell Line SW480RR Established after Fractionated X Irradiation. Radiat Res. 202, 000–000 (2024).

Radioresistant cancer cells are risk factors for recurrence and are occasionally detected in recurrent tumors after radiotherapy. Intratumor heterogeneity is believed to be a potential cause of treatment resistance. Heterogeneity in DNA content has also been reported in human colorectal cancer; however, little is known about how such heterogeneity changes with radiotherapy or how it affects cancer radioresistance. In the present study, we established radioresistant clone SW480RR cells after fractionated X-ray irradiation of human colorectal cancer-derived SW480.hu cells, which are composed of two cell populations with different chromosome numbers, and examined how cellular radioresistance changed with fractionated radiotherapy. Compared with the parental cell population, which mostly comprised cells with higher ploidy, the radioresistant clones showed lower ploidy and less initial DNA damage. The lower ploidy cells in the parental cell population were identified as having radioresistance prior to irradiation; thus, SW480RR cells were considered intrinsically radioresistant cells selected from the parental population through fractionated irradiation. This study presents a practical example of the emergence of radioresistant cells from a cell population with ploidy heterogeneity after irradiation. The most likely mechanism is the selection of an intrinsically radioresistant population after fractionated X-ray irradiation, with a background in which lower ploidy cells exhibit lower initial DNA damage.

INTRODUCTION

Intratumor heterogeneity, which refers to the non-uniformity of cancer cells or tumor microenvironment, is associated with therapeutic resistance, and this is also the case in radiotherapy *(1–3)*. Various factors contribute to the heterogeneity of the tumor microenvironment, such as the distribution of blood vessels in tumor tissues and involvement of stromal cells *(2–4)*. Additionally, the genomic, epigenetic, and transcriptomic heterogeneity of cancer cells increases over time *(5–7)*. DNA ploidy heterogeneity, a type of intratumor heterogeneity that indicates the presence of two or more cancer cells with different ploidy or DNA content in the same tumor, has been observed within a single tumor *(8, 9)* and its emergence within a single-origin tumor has been demonstrated *(10)*. Regarding the heterogeneity of cancer cells, both the presence of preexisting therapy-resistant clones (intrinsic resistance) and the emergence of resistance via treatment-induced modifications (acquired resistance) could play a significant role in therapy resistance *(3)*.

The presence of radioresistant cancer cells is an important factor for recurrence after cancer radiotherapy *(11)*. In colorectal cancer, neoadjuvant radiotherapy reduces the local recurrence rate by half compared to surgical resection alone, however, a 5–10% local recurrence rate remains even with radiotherapy *(12, 13)*. Head and neck carcinoma cells obtained from clinically recurrent patients after radiotherapy exhibited enhanced radioresistance compared with those obtained from patients before radiotherapy *(14)*. Radioresistant cells after fractionated irradiation have been detected not only in the cancer tissues of postirradiation patients but also in cloned tumor cell lines derived from many types of cancers, including colorectal carcinoma *(15)*, esophageal adenocarcinoma *(16–18)*, and non-small cell lung cancer *(19–21)*. Although the appearance of radioresistant cells after fractionated irradiation has been reported as described above, limited information is available on how the cell populations that constitute tumors with ploidy heterogeneity change after fractionated irradiation and what kind of radioresistance mechanisms contribute to this process.

Fractionated irradiation of cancer cells can result in changes in the ploidy distribution of the cell population compared to that before irradiation. However, the direction of ploidy alteration is inconsistent *(22–26)*. These changes can be caused either by the selection of clones with a certain ploidy owing to differences in sensitivity *(23)*, or by the chromosomal mutagenicity of ionizing radiation *(24, 26)*.

Although ploidy and DNA content have been extensively discussed as potential factors affecting radiosensitivity, there is no clear relationship between ploidy and radiosensitivity. The presence of intrinsically radioresistant cells with low

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[1] Corresponding author: Hironobu Yasui, Laboratory of Radiation Biology, Department of Applied Veterinary Sciences, Faculty of Veterinary Medicine, Hokkaido University, Kita 18, Nishi 9, Kita-ku, Sapporo 060-0818, Japan; email: yassan@vetmed.hokudai.ac.jp.

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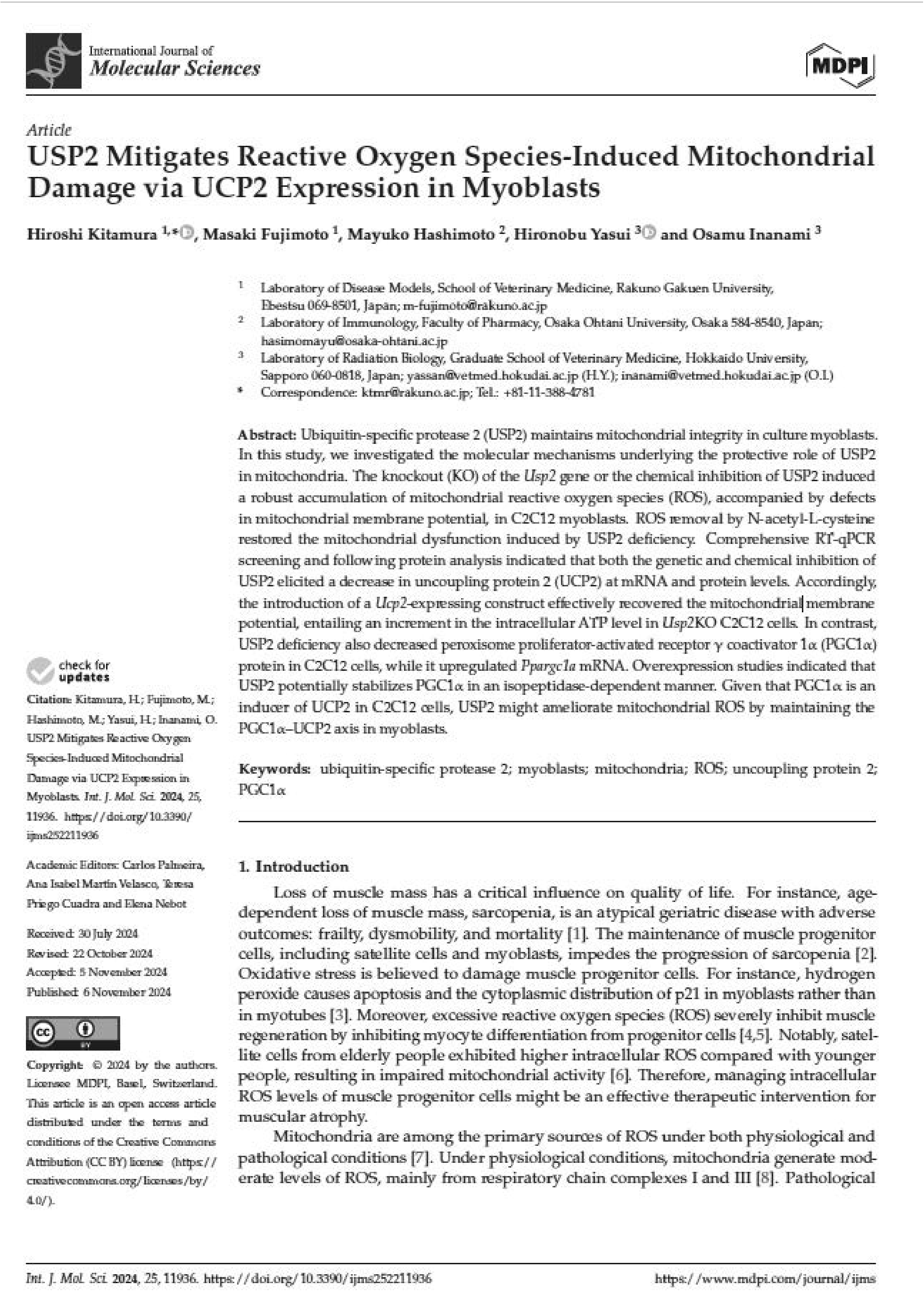
最終責任者　Osamu Inanami (Corresponding Author)



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Article

USP2 Mitigates Reactive Oxygen Species-Induced Mitochondrial Damage via UCP2 Expression in Myoblasts

Hiroshi Kitamura [1,*], Masaki Fujimoto [1], Mayuko Hashimoto [2], Hironobu Yasui [3] and Osamu Inanami [3]

[1] Laboratory of Disease Models, School of Veterinary Medicine, Rakuno Gakuen University, Ebestsu 069-8501, Japan; m-fujimoto@rakuno.ac.jp
[2] Laboratory of Immunology, Faculty of Pharmacy, Osaka Ohtani University, Osaka 584-8540, Japan; hasimomayu@osaka-ohtani.ac.jp
[3] Laboratory of Radiation Biology, Graduate School of Veterinary Medicine, Hokkaido University, Sapporo 060-0818, Japan; yassan@vetmed.hokudai.ac.jp (H.Y.); inanami@vetmed.hokudai.ac.jp (O.I.)
[*] Correspondence: ktmr@rakuno.ac.jp; Tel.: +81-11-388-4781

Abstract: Ubiquitin-specific protease 2 (USP2) maintains mitochondrial integrity in culture myoblasts. In this study, we investigated the molecular mechanisms underlying the protective role of USP2 in mitochondria. The knockout (KO) of the *Usp2* gene or the chemical inhibition of USP2 induced a robust accumulation of mitochondrial reactive oxygen species (ROS), accompanied by defects in mitochondrial membrane potential, in C2C12 myoblasts. ROS removal by N-acetyl-L-cysteine restored the mitochondrial dysfunction induced by USP2 deficiency. Comprehensive RT-qPCR screening and following protein analysis indicated that both the genetic and chemical inhibition of USP2 elicited a decrease in uncoupling protein 2 (UCP2) at mRNA and protein levels. Accordingly, the introduction of a *Ucp2*-expressing construct effectively recovered the mitochondrial membrane potential, entailing an increment in the intracellular ATP level in *Usp2*KO C2C12 cells. In contrast, USP2 deficiency also decreased peroxisome proliferator-activated receptor γ coactivator 1α (PGC1α) protein in C2C12 cells, while it upregulated *Ppargc1a* mRNA. Overexpression studies indicated that USP2 potentially stabilizes PGC1α in an isopeptidase-dependent manner. Given that PGC1α is an inducer of UCP2 in C2C12 cells, USP2 might ameliorate mitochondrial ROS by maintaining the PGC1α–UCP2 axis in myoblasts.

Keywords: ubiquitin-specific protease 2; myoblasts; mitochondria; ROS; uncoupling protein 2; PGC1α

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1. Introduction

Loss of muscle mass has a critical influence on quality of life. For instance, age-dependent loss of muscle mass, sarcopenia, is an atypical geriatric disease with adverse outcomes: frailty, dysmobility, and mortality [1]. The maintenance of muscle progenitor cells, including satellite cells and myoblasts, impedes the progression of sarcopenia [2]. Oxidative stress is believed to damage muscle progenitor cells. For instance, hydrogen peroxide causes apoptosis and the cytoplasmic distribution of p21 in myoblasts rather than in myotubes [3]. Moreover, excessive reactive oxygen species (ROS) severely inhibit muscle regeneration by inhibiting myocyte differentiation from progenitor cells [4,5]. Notably, satellite cells from elderly people exhibited higher intracellular ROS compared with younger people, resulting in impaired mitochondrial activity [6]. Therefore, managing intracellular ROS levels of muscle progenitor cells might be an effective therapeutic intervention for muscular atrophy.

Mitochondria are among the primary sources of ROS under both physiological and pathological conditions [7]. Under physiological conditions, mitochondria generate moderate levels of ROS, mainly from respiratory chain complexes I and III [8]. Pathological

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最終責任者　Hiroshi Kitamura (Corresponding Author)

画像診断学（Veterinary Diagnostic Imaging）

Yoshimichi Goda

Assistant Professor

助教　五田　嘉倫

I. 筆頭または責任著者　＜First or Corresponding Author＞

1）Preliminary experience of initial and re-administration of nimustine as a new primary treatment for feline nasal lymphoma.
Goda Y, Hidaka Y, Goto M, Inoue Y, KurodaK, Nakatake Y, Sato R, Satoh H.
Jap J Vet Res 72:56–64. 2024. doi: 10.57494/jjvr.72.2_56

2）A case of primary pulmonary paraganglioma in a dog.
Goda Y, Mizutani S, Akashi N, Kanda T, Kutara K, Okamura Y, Asanuma T.
Open Vet J 14:2714–2720. 2024. doi: 10.5455/OVJ.2024.v14.i10.22

II.　その他　＜Others＞

1）A chronic intermittent haemodialysis pig model for functional evaluation of dialysis membranes.
Yamamoto S, Umeno H, Sano Y, Koremoto M, **Goda Y**, Kaneko Y, Torisu S, Tsuruda T, Fujimoto S.
Int J Artif Organs 47:321–328. 2024. doi:10.1177/03913988241253152.

Japanese Journal of Veterinary Research 72(2): 56–64, 2024

JJVR

SHORT COMMUNICATION **Clinical Case Report**

Preliminary experience of initial and re-administration of nimustine as a new primary treatment for feline nasal lymphoma: a case report

Yoshimichi Goda[1], Yuichi Hidaka[1,2], Mifumi Goto[3], Yoshiyuki Inoue[2], Kohei Kuroda[2], Yuki Nakatake[4], Reiichiro Sato[1,2] and Hiroyuki Satoh[1,2,*]

[1] Graduate School of Medicine and Veterinary Medicine, University of Miyazaki, 1-1 Gakuen Kibanadai-nishi, Miyazaki-shi, Miyazaki 889-2192, Japan
[2] Faculty of Agriculture, University of Miyazaki, 1-1 Gakuen Kibanadai-nishi, Miyazaki-shi, Miyazaki 889-2192, Japan
[3] Myuu Animal Clinic, 2-1-15 Otsubo-nishi, Miyazaki-shi, Miyazaki 880-0932, Japan
[4] The Miyazaki University Veterinary Teaching Hospital, 1-1 Gakuen Kibanadai-nishi, Miyazaki-shi 889-2192, Miyazaki, Japan

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Abstract

A 5-year-old spayed female domestic short haired cat presented with chronic nasal obstruction. The cat was diagnosed with B-cell nasal lymphoma based on histological examination of biopsy specimens and intracranial invasion was suspected. We initiated treatment with nimustine (ACNU), known to pass the blood–brain barrier, as the primary protocol with prednisolone, with the owner's consent. The ACNU dose was 20–25 mg/m^2 (4–5-week intervals, four or six administrations, two courses). The cat remained oligosymptomatic until day 962 after the first dose and no serious adverse events were reported. The cat lived until day 1089. To our knowledge, this is the first report of long-term survival achieved using ACNU as the primary treatment in a cat with nasal lymphoma.

Key Words: cat, nasal lymphoma, nimustine

Lymphoma is a common cancer (neoplasm) in cats, accounting for 50–90% of all feline hematopoietic tumors[21]. Lymphomas in cats are classified into the following categories based on several anatomical sites: alimentary, mediastinal, nodal, and extranodal (nasal, renal, central nervous system (CNS), cutaneous, and hepatic)[22]. Among these, nasal lymphoma (NL) accounts for 6.3%[7]. NL is the most common intranasal tumor in cats[5,12]. B-cell lymphoma accounts for 61–85% of all NL cases in cats[6,12,15]. Radiotherapy is effective for NL, with median survival time (MST) reported to be 365–922 days[4,8,13]. In addition, a combination of chemotherapy and radiotherapy reportedly results in an MST of 174–955 days[4,16]. However, radiotherapy is available only in a limited number of hospitals, and chemotherapy alone is widely used. Long-term survival with chemotherapy, such as cyclophosphamide, hydroxydaunorubicin (doxorubicin), vincristine, and prednisolone (CHOP), is possible, with an MST of 116–358 days[4,20,21]. In previous reports, no significant difference was observed in the outcomes of NL among the three treatment methods[4]. However,

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* Corresponding author: Hiroyuki Satoh
Faculty of Agriculture, University of Miyazaki, 1-1 Gakuen Kibanadai-nishi, Miyazaki-shi, Miyazaki 889-2192, Japan
E-mail: hsatoh@cc.miyazaki-u.ac.jp
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Case Report
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A case of primary pulmonary paraganglioma in a dog

Yoshimichi Goda[1], Shinya Mizutani[1,2]*, Natsuki Akashi[1,2], Teppei Kanda[1,2], Kenji Kutara[1,2], Yasuhiko Okamura[1,2] and Taketoshi Asanuma[1,2]

[1]*Okayama University of Science, Veterinary Medical Teaching Hospital, Imabari, Japan*
[2]*Faculty of Veterinary Medicine, Okayama University of Science, Imabari, Japan*

Abstract

Background: Lung tumors in dogs, significantly primary paragangliomas, are rare and have not been reported. This report describes a dog with a lung tumor diagnosed as a primary paraganglioma.

Case Description: A 12-year-old spayed French bulldog presented with a left-sided pulmonary mass. The dog was in good general condition and had no clinical symptoms. Computed tomography (CT) revealed a pulmonary mass near the bifurcation of the posterior lobe bronchus of the left lung. The mass showed a strong contrast enhancement effect that was subsequently attenuated. The dog underwent Surgery to remove the mass from the left lung. Abnormal hypertension was observed during surgery, and hypertensive crisis was suspected. Based on the histopathology and preoperative and postoperative urinary metanephrine and normetanephrine levels, the dog was diagnosed with primary paraganglioma of the lung. Although the CT scan showed findings suggestive of the development of a neuroendocrine tumor, it was difficult to suspect the development of a paraganglioma.

Conclusion: The possibility of catecholamine-producing tumors should be considered when we encounter a lung tumor with no clinical symptoms and a neuroendocrine tumor-like contrast enhancement pattern on a CT scan.

Keywords: Canine, Dog, Paraganglioma, Pulmonary.

Introduction

The incidence of pulmonary tumors in dogs is rare, less than 1% (Brodey and Craig, 1965; Moulton *et al.*, 1981). Carcinoma is the most common occurrence (87.1%) (McPhetridge *et al.*, 2021), and rare neuroendocrine tumors have also been reported (Saegusa *et al.*, 1994: McPhetridge *et al.*, 2021). The neuroendocrine tumors of the lung in dogs are few, and clinical information is limited.

Canine neuroendocrine tumors generally include catecholamine-producing tumors, the most common of which are pheochromocytomas of the adrenal glands (Barthez *et al.*, 1997). Extra-adrenal catecholamine-producing tumors are known as paragangliomas (Lunn and Boston, 2020), and there have been few reports on paragangliomas in dogs (Ilha and Styer, 2013; Rodrigues *et al.*, 2020; Park and Minamoto, 2021; Hu *et al.*, 2022). Although there have been reports of pulmonary metastases from pheochromocytomas, there have been no reports on the diagnosis of primary paragangliomas of the lungs (Barthez *et al.*, 1997). In dogs, paragangliomas originating from the tongue, heart, retroperitoneum, and urinary bladder have been reported (Ilha and Styer, 2013; Rodrigues *et al.*, 2020; Park and Minamoto, 2021; Hu *et al.*, 2022). Previous paragangliomas in dogs have been reported to cause clinical symptoms such as anorexia and lethargy (Hu *et al.*, 2022), but the clinical symptoms vary depending on the location of the disease (Ilha and Styer, 2013; Rodrigues *et al.*, 2020; Wilson and Soto-Blanco, 2020; Park and Minamoto, 2021; Hu *et al.*, 2022). Surgical excision is the preferred treatment (Yanagawa *et al.*, 2014; Park and Minamoto, 2021; Hu *et al.*, 2022; Tamura *et al.*, 2023). To the best of the authors' knowledge, the maximum survival time for paragangliomas was reported to be 670 days (Robat *et al.*, 2016; Rodrigues *et al.*, 2020), while lung neuroendocrine tumors were reported to be 11 months (Choi *et al.*, 2008). This report describes a dog with an incidentally found lung tumor that was diagnosed as a primary paraganglioma.

Case Details

A 12-year-old spayed female French bulldog weighing 12.2 kg was visited by a veterinarian for a medical checkup. The dog had no clinical symptoms and was in good general condition; however, chest radiography revealed a mass in the left thoracic region. The dog was referred to the Okayama University of

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***Corresponding Author:** Shinya Mizutani. Okayama University of Science, Veterinary Medical Teaching Hospital, Imabari, Japan. Email: *s-mizutani@ous.ac.jp*

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最終責任者　Shinya Mizutani (Corresponding Author)

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A chronic intermittent haemodialysis pig model for functional evaluation of dialysis membranes

Shushi Yamamoto[1,4], Hiroshi Umeno[2], Yusuke Sano[2], Masahide Koremoto[3], Yoshimichi Goda[4], Yasuyuki Kaneko[5], Shidow Torisu[1], Toshihiro Tsuruda[4] and Shouichi Fujimoto[6]

Abstract

Performance evaluation of new dialysis membranes is primarily performed in vitro, which can lead to differences in clinical results. Currently, data on dialysis membrane performance and safety are available only for haemodialysis patients. Herein, we aimed to establish an in vivo animal model of dialysis that could be extrapolated to humans. We created a bilateral nephrectomy pig model of renal failure, which placed a double-lumen catheter with the hub exposed dorsally. Haemodialysis was performed in the same manner as in humans, during which clinically relevant physiologic data were evaluated. Next, to evaluate the utility of this model, the biocompatibility of two kinds of membranes coated with or without vitamin E used in haemodiafiltration therapy were compared. Haemodialysis treatment was successfully performed in nephrectomized pigs under the same dialysis conditions (4h per session, every other day, for 2weeks). In accordance with human clinical data, regular dialysis alleviated renal failure in pigs. The vitamin E-coated membrane showed a significant reduction rate of advanced oxidation protein products during dialysis than non-coated membrane. In conclusion, this model mimics the pathophysiology and dialysis condition of patients undergoing haemodialysis. This dialysis treatment model of renal failure will be useful for evaluating the performance and safety of dialysis membranes.

Keywords

Haemodialysis, animal models, pig, acute renal failure, vitamin E-coated membrane, dialysis membrane

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Introduction

Since the introduction of blood purification by haemodialysis for treating human renal failure in the 1940s,[1] dialysis membranes have been improved to increase the efficiency of water and uraemic substance removal.[2–4] Recently, dialysis membranes with high cut-off points and sharp solute fractionation, which block albumin permeation while removing low molecular weight proteins such as β_2-microglobulin, and dialysis membranes with improvements in biocompatibility and hemocompatibility, which reduce oxidative stress and complement activation, are being developed to prevent various dialysis complications.[5,6] During the development of new dialysis membranes, membrane performance is generally evaluated in vitro,[7,8] while in vivo data during haemodialysis to evaluate the function of dialysis membranes, for example, are only available from patients undergoing haemodialysis.

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[1] Division of Companion Animal Surgery, Department of Small Animal Clinical Sciences, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido Prefecture, Japan
[2] Medical Technology and Material Laboratory, Asahi Kasei Medical Co. Ltd., Fuji, Shizuoka, Japan
[3] Product Development Strategy Department, Asahi Kasei Medical Co. Ltd., Chiyoda-ku, Tokyo, Japan
[4] Department of Hemo-Vascular Advanced Medicine, Cardiorenal Reseach Laboratory, Faculty of Medicine, University of Miyazaki, Miyazaki, Japan
[5] Veterinary Teaching Hospital, Faculty of Agriculture, University of Miyazaki, Miyazaki, Japan
[6] M&M Collaboration Research Laboratory, Department of Medical Environment Innovation, Faculty of Medicine, University of Miyazaki, Miyazaki, Japan

Corresponding author:
Shouichi Fujimoto, University of Miyazaki, 5200, Kihara, Kiyotake, Miyazaki 889-1601, Japan.
Email: fujimos@med.miyazaki-u.ac.jp

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最終責任者　Shouichi Fujimoto (Corresponding Author)

獣医麻酔学（Veterinary Anesthesiology）

Keiko Kato

Assistant Professor

助教　加藤　桂子

Ⅰ．筆頭または責任著者　＜First or Corresponding Author＞

1）Cardiorespiratory effects of intramuscular alfaxalone combined with low-dose medetomidine and butorphanol in dogs anesthetized with sevoflurane.
Kato K, Itami T, Oyama N, Yamashita K.
Open Vet J 14:1251–1258. 2024. doi: 10.5455/OVJ.2024.v14.i5.20.

Ⅱ．その他　＜Others＞

1）The anti-inflammatory effects of Fuzapladib in an endotoxemic porcine model.
Sugita C, Itami T, Miyasho T, Chen IY, Hirokawa T, Tsukui H, Kato M, Shibuya M, Sano Y, **Kato K**, Yamashita K.
J Vet Med Sci 86:1145–1155. 2024. doi: 10.1292/jvms.24-0190.

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Research Article
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Cardiorespiratory effects of intramuscular alfaxalone combined with low-dose medetomidine and butorphanol in dogs anesthetized with sevoflurane

Keiko Kato, Takaharu Itami*, Norihiko Oyama and Kazuto Yamashita

Department of Companion Animal Clinical Sciences, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan

Abstract

Background: The intramuscular (IM) administration of 7.5–10 mg/kg of alfaxalone produces anesthetic effects that enable endotracheal intubation with mild cardiorespiratory depression in dogs. However, the effects of IM co-administration of medetomidine, butorphanol, and alfaxalone on cardiorespiratory function under inhalation anesthesia have not been studied.

Aim: To assess the cardiorespiratory function following the IM co-administration of 5 µg/kg of medetomidine, 0.3 mg/kg of butorphanol, and 2.5 mg/kg of alfaxalone (MBA) in dogs anesthetized with sevoflurane.

Methods: Seven intact healthy Beagles (three males and four females, aged 3–6 years old and weighing 10.0–18.1 kg) anesthetized with a predetermined minimum alveolar concentration (MAC) of sevoflurane were included in this study. The baseline cardiorespiratory variable values were recorded using the thermodilution method with a pulmonary artery catheter after stabilization for 15 minutes at 1.3 times their individual sevoflurane MAC. The cardiorespiratory variables were measured again following the IM administration of MBA. Data are expressed as median [interquartile range] and compared with the corresponding baseline values using the Friedman test and Sheff's method. A $p < 0.05$ was considered statistically significant.

Results: The intramuscular administration of MBA transiently decreased the cardiac index [baseline: 3.46 (3.18–3.69), 5 minutes: 1.67 (1.57–1.75) l/minute/m^2 : $p < 0.001$], respiratory frequency, and arterial pH. In contrast, it increased the systemic vascular resistance index [baseline: 5,367 (3,589–6,617), 5 minutes:10,197 (9,955–15,005) dynes second/cm^5/m^2 : $p = 0.0092$], mean pulmonary arterial pressure, and arterial partial pressure of carbon dioxide.

Conclusion: The intramuscular administration of MBA in dogs anesthetized with sevoflurane transiently decreased cardiac output due to vasoconstriction. Although spontaneous breathing was maintained, MBA administration resulted in respiratory acidosis due to hypoventilation. Thus, it is important to administer MBA with caution to dogs with insufficient cardiovascular function. In addition, ventilatory support is recommended.

Keywords: Alfaxalone, Medetomidine, Butorphanol, Dog, Cardiorespiratory effects.

***Corresponding Author:** Takaharu Itami. Department of Companion Animal Clinical Sciences, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan. Email: *t-itami@rakuno.ac.jp*

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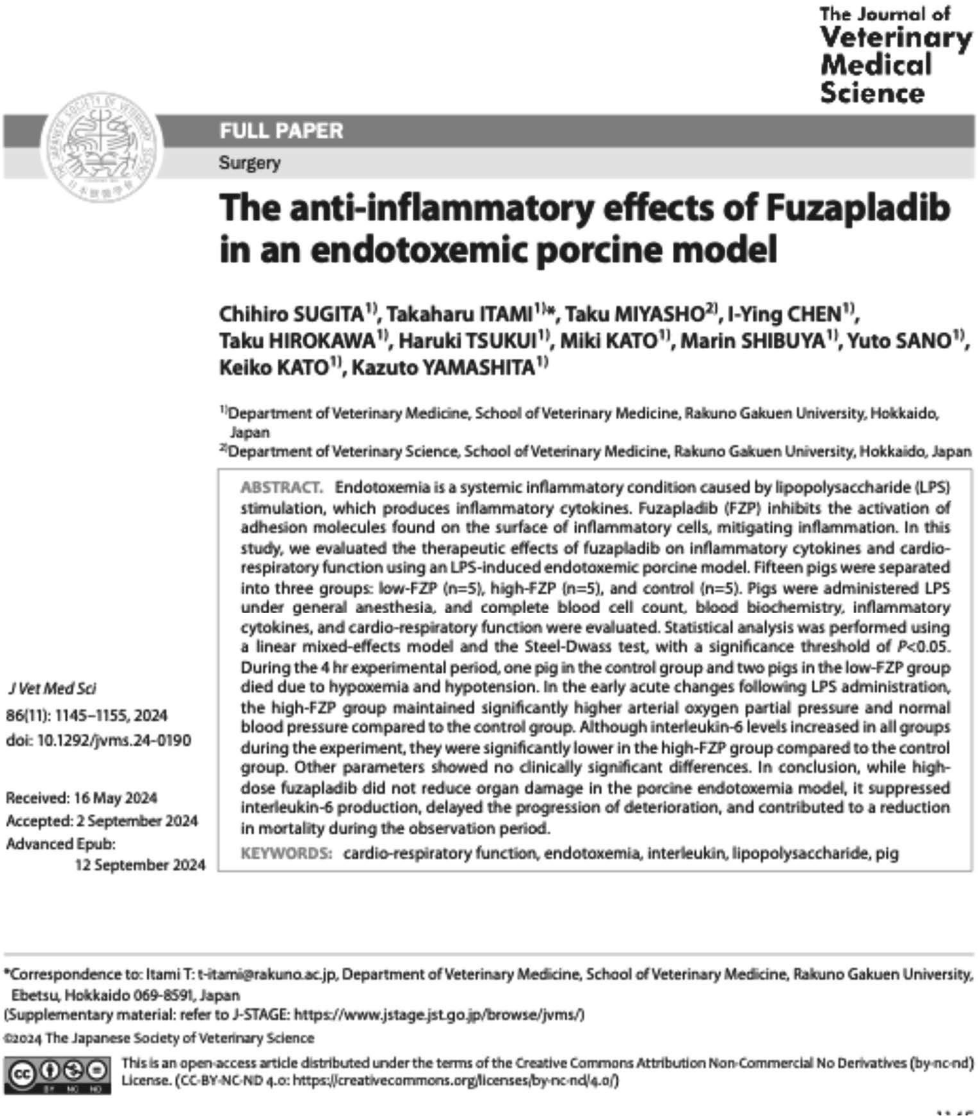
最終責任者　Takaharu Itami (Corresponding Author)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FULL PAPER
Surgery

The anti-inflammatory effects of Fuzapladib in an endotoxemic porcine model

Chihiro SUGITA[1)], Takaharu ITAMI[1)*], Taku MIYASHO[2)], I-Ying CHEN[1)], Taku HIROKAWA[1)], Haruki TSUKUI[1)], Miki KATO[1)], Marin SHIBUYA[1)], Yuto SANO[1)], Keiko KATO[1)], Kazuto YAMASHITA[1)]

[1)]Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Hokkaido, Japan
[2)]Department of Veterinary Science, School of Veterinary Medicine, Rakuno Gakuen University, Hokkaido, Japan

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ABSTRACT. Endotoxemia is a systemic inflammatory condition caused by lipopolysaccharide (LPS) stimulation, which produces inflammatory cytokines. Fuzapladib (FZP) inhibits the activation of adhesion molecules found on the surface of inflammatory cells, mitigating inflammation. In this study, we evaluated the therapeutic effects of fuzapladib on inflammatory cytokines and cardio-respiratory function using an LPS-induced endotoxemic porcine model. Fifteen pigs were separated into three groups: low-FZP (n=5), high-FZP (n=5), and control (n=5). Pigs were administered LPS under general anesthesia, and complete blood cell count, blood biochemistry, inflammatory cytokines, and cardio-respiratory function were evaluated. Statistical analysis was performed using a linear mixed-effects model and the Steel-Dwass test, with a significance threshold of $P<0.05$. During the 4 hr experimental period, one pig in the control group and two pigs in the low-FZP group died due to hypoxemia and hypotension. In the early acute changes following LPS administration, the high-FZP group maintained significantly higher arterial oxygen partial pressure and normal blood pressure compared to the control group. Although interleukin-6 levels increased in all groups during the experiment, they were significantly lower in the high-FZP group compared to the control group. Other parameters showed no clinically significant differences. In conclusion, while high-dose fuzapladib did not reduce organ damage in the porcine endotoxemia model, it suppressed interleukin-6 production, delayed the progression of deterioration, and contributed to a reduction in mortality during the observation period.

KEYWORDS: cardio-respiratory function, endotoxemia, interleukin, lipopolysaccharide, pig

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*Correspondence to: Itami T: t-itami@rakuno.ac.jp, Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8591, Japan

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最終責任者　Takaharu Itami (Corresponding Author)

Ryosuke Kobayashi

Assistant professor

助教　小林　良祐

I. 筆頭または責任著者　＜First or Corresponding Author＞

1）The histone methyltransferase KMT2D is essential for embryo implantation via regulating precise differentiation of endometrial cells
Kobayashi R, Tajika Y, Kohmaru J, Morita S, Horii T, Mizukami Y, Aikawa S, Hirota Y, Hatada I.
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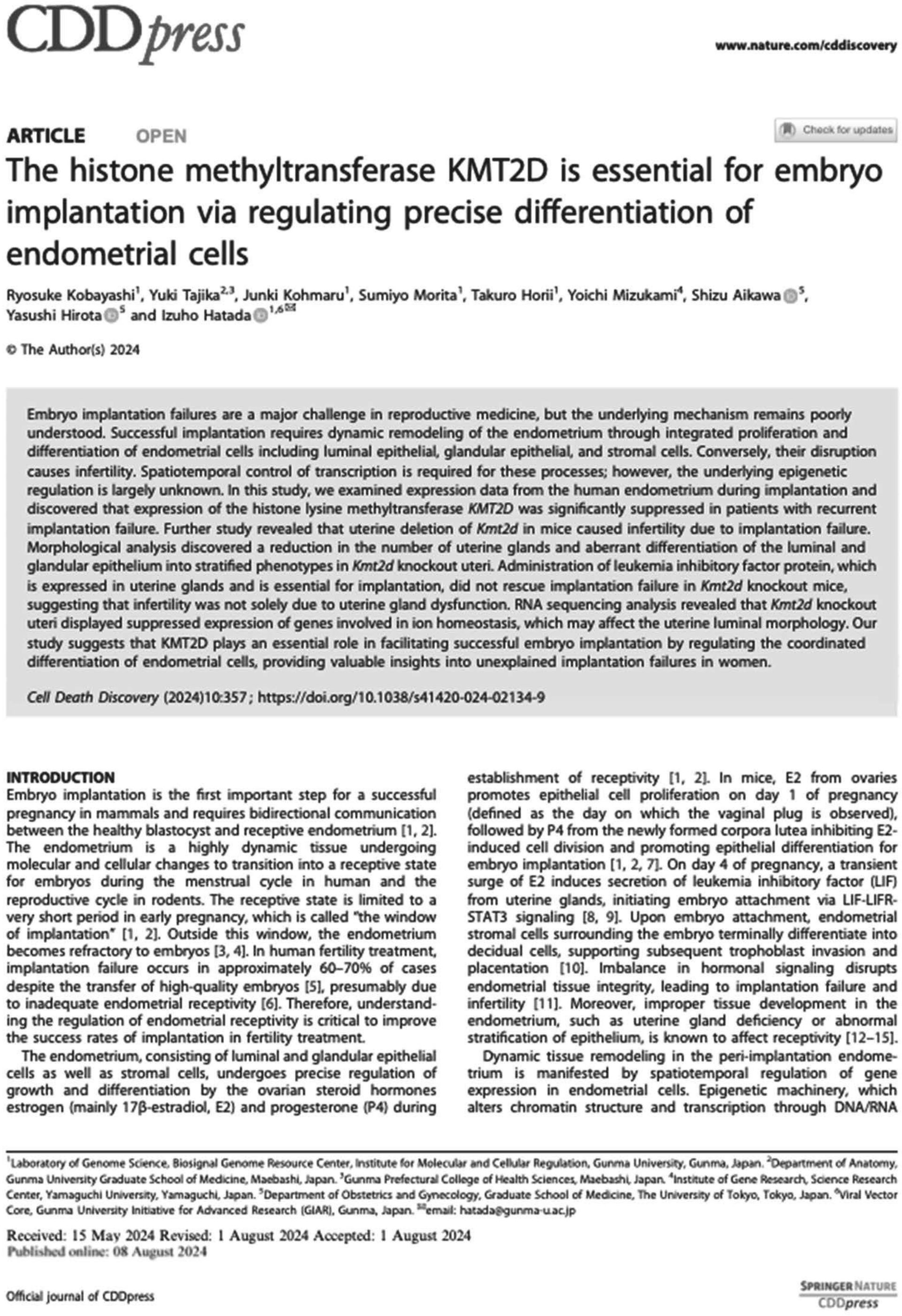

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ARTICLE OPEN

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The histone methyltransferase KMT2D is essential for embryo implantation via regulating precise differentiation of endometrial cells

Ryosuke Kobayashi[1], Yuki Tajika[2,3], Junki Kohmaru[1], Sumiyo Morita[1], Takuro Horii[1], Yoichi Mizukami[4], Shizu Aikawa[5], Yasushi Hirota[5] and Izuho Hatada[1,6]✉

Embryo implantation failures are a major challenge in reproductive medicine, but the underlying mechanism remains poorly understood. Successful implantation requires dynamic remodeling of the endometrium through integrated proliferation and differentiation of endometrial cells including luminal epithelial, glandular epithelial, and stromal cells. Conversely, their disruption causes infertility. Spatiotemporal control of transcription is required for these processes; however, the underlying epigenetic regulation is largely unknown. In this study, we examined expression data from the human endometrium during implantation and discovered that expression of the histone lysine methyltransferase *KMT2D* was significantly suppressed in patients with recurrent implantation failure. Further study revealed that uterine deletion of *Kmt2d* in mice caused infertility due to implantation failure. Morphological analysis discovered a reduction in the number of uterine glands and aberrant differentiation of the luminal and glandular epithelium into stratified phenotypes in *Kmt2d* knockout uteri. Administration of leukemia inhibitory factor protein, which is expressed in uterine glands and is essential for implantation, did not rescue implantation failure in *Kmt2d* knockout mice, suggesting that infertility was not solely due to uterine gland dysfunction. RNA sequencing analysis revealed that *Kmt2d* knockout uteri displayed suppressed expression of genes involved in ion homeostasis, which may affect the uterine luminal morphology. Our study suggests that KMT2D plays an essential role in facilitating successful embryo implantation by regulating the coordinated differentiation of endometrial cells, providing valuable insights into unexplained implantation failures in women.

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INTRODUCTION

Embryo implantation is the first important step for a successful pregnancy in mammals and requires bidirectional communication between the healthy blastocyst and receptive endometrium [1, 2]. The endometrium is a highly dynamic tissue undergoing molecular and cellular changes to transition into a receptive state for embryos during the menstrual cycle in human and the reproductive cycle in rodents. The receptive state is limited to a very short period in early pregnancy, which is called "the window of implantation" [1, 2]. Outside this window, the endometrium becomes refractory to embryos [3, 4]. In human fertility treatment, implantation failure occurs in approximately 60–70% of cases despite the transfer of high-quality embryos [5], presumably due to inadequate endometrial receptivity [6]. Therefore, understanding the regulation of endometrial receptivity is critical to improve the success rates of implantation in fertility treatment.

The endometrium, consisting of luminal and glandular epithelial cells as well as stromal cells, undergoes precise regulation of growth and differentiation by the ovarian steroid hormones estrogen (mainly 17β-estradiol, E2) and progesterone (P4) during establishment of receptivity [1, 2]. In mice, E2 from ovaries promotes epithelial cell proliferation on day 1 of pregnancy (defined as the day on which the vaginal plug is observed), followed by P4 from the newly formed corpora lutea inhibiting E2-induced cell division and promoting epithelial differentiation for embryo implantation [1, 2, 7]. On day 4 of pregnancy, a transient surge of E2 induces secretion of leukemia inhibitory factor (LIF) from uterine glands, initiating embryo attachment via LIF-LIFR-STAT3 signaling [8, 9]. Upon embryo attachment, endometrial stromal cells surrounding the embryo terminally differentiate into decidual cells, supporting subsequent trophoblast invasion and placentation [10]. Imbalance in hormonal signaling disrupts endometrial tissue integrity, leading to implantation failure and infertility [11]. Moreover, improper tissue development in the endometrium, such as uterine gland deficiency or abnormal stratification of epithelium, is known to affect receptivity [12–15].

Dynamic tissue remodeling in the peri-implantation endometrium is manifested by spatiotemporal regulation of gene expression in endometrial cells. Epigenetic machinery, which alters chromatin structure and transcription through DNA/RNA

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[1]Laboratory of Genome Science, Biosignal Genome Resource Center, Institute for Molecular and Cellular Regulation, Gunma University, Gunma, Japan. [2]Department of Anatomy, Gunma University Graduate School of Medicine, Maebashi, Japan. [3]Gunma Prefectural College of Health Sciences, Maebashi, Japan. [4]Institute of Gene Research, Science Research Center, Yamaguchi University, Yamaguchi, Japan. [5]Department of Obstetrics and Gynecology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan. [6]Viral Vector Core, Gunma University Initiative for Advanced Research (GIAR), Gunma, Japan. ✉email: hatada@gunma-u.ac.jp

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RESEARCH ARTICLE

Medium-chain triglyceride-specific appetite is regulated by the β-oxidation of medium-chain fatty acids in the liver

Tsugunori Maruyama,[1] Sho Matsui,[1] Ryosuke Kobayashi,[2] Takuro Horii,[2] Yasuo Oguri,[1] Satoshi Tsuzuki,[1] Takahiro Horie,[4] Koh Ono,[4] Izuho Hatada,[2,3] and Tsutomu Sasaki[1]

[1]Laboratory of Nutrition Chemistry, Division of Food Science and Biotechnology, Graduate School of Agriculture, Kyoto University, Kyoto, Japan; [2]Laboratory of Genome Science, Biosignal Genome Resource Center, Institute for Molecular and Cellular Regulation, Gunma University, Maebashi, Japan; [3]Viral Vector Core, Gunma University Initiative for Advanced Research, Maebashi, Japan; and [4]Department of Cardiovascular Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Abstract

Most studies on fat appetite have focused on long-chain triglycerides (LCTs) due to their obesogenic properties. Medium-chain triglycerides (MCTs), conversely, exhibit antiobesogenic effects; however, the regulation of MCT intake remains elusive. Here, we demonstrate that mice can distinguish between MCTs and LCTs, and the specific appetite for MCTs is governed by hepatic β-oxidation. We generated liver-specific medium-chain acyl-CoA dehydrogenase (MCAD)-deficient ($\text{MCAD}^{L-/-}$) mice and analyzed their preference for MCT and LCT solutions using glyceryl trioctanoate (C8-TG), glyceryl tridecanoate (C10-TG), corn oil, and lard oil in two-bottle choice tests conducted over 8 days. In addition, we used lick microstructure analyses to evaluate the palatability and appetite for MCT and LCT solutions. Finally, we measured the expression levels of genes associated with fat ingestion (*Galanin*, *Qrfp*, and *Nmu*) in the hypothalamus 2 h after oral gavage of fat. Compared with control mice, $\text{MCAD}^{L-/-}$ mice exhibited a significantly reduced preference for MCT solutions, with no alteration in the preference for LCTs. Lick analysis revealed that $\text{MCAD}^{L-/-}$ mice displayed a significantly decreased appetite for MCT solutions only while the palatability of both MCT and LCT solutions remained unaffected. Hypothalamic *Galanin* expression in control mice was elevated by oral gavage of C8-TG but not by LCTs, and this response was abrogated in $\text{MCAD}^{L-/-}$ mice. In summary, our data suggest that hepatic β-oxidation is required for MCT-specific appetite but not for LCT-specific appetite. The induction of hypothalamic galanin upon MCT ingestion, dependent on hepatic β-oxidation, could be involved in the regulation of MCT-specific appetite.

NEW & NOTEWORTHY Whether and how medium-chain triglyceride (MCT) intake is regulated remains unknown. Here, we showed that mice can discriminate between MCTs and LCTs. Hepatic β-oxidation participates in MCT-specific appetite, and hypothalamic galanin may be one of the factors that regulate MCT intake. Because of the antiobesity effects of MCTs, studying MCT-specific appetite may help combat obesity by promoting the intake of MCTs instead of LCTs.

Acadm; fat preference; galanin; hepatic β-oxidation; MCT

INTRODUCTION

Obesity has a major impact on public health and economy. Obesity is a direct or indirect cause of various pathologies and was ranked 5th in the global disease burden in 2019 (1). The number of adults with obesity worldwide exceeded 650 million in 2016 and continues to rise (2). Organisation for Economic Co-operation and Development (OECD) countries allocate ~8.4% of their healthcare budget to obesity-related diseases (3). Thus, obesity prevention is not only an individual health concern but also a societal issue.

The genesis of obesity lies in a chronic energy surplus, partly attributed to long-chain triglycerides (LCTs) from a high-fat diet (4, 5). Medium-chain triglycerides (MCTs) have exhibited antiobesity effects, such as reducing weight gain and lipid accumulation (6). Continued consumption of a high-MCT diet improves obesity and insulin resistance in diet-induced obese mice (7, 8). A meta-analysis suggests that high-MCT diets can satisfy appetite with less amount than high-LCT diets (9). However, the existence of MCT-specific appetite and the body's mechanism for distinguishing between LCTs and MCTs remain elusive.

Long-chain fatty acids (LCFAs) constitute LCTs, whereas medium-chain fatty acids (MCFAs) make up MCTs. LCTs and MCTs undergo distinct processes in digestion, absorption, distribution, and metabolism. MCTs are fully hydrolyzed by lingual and gastric lipases (10–12). Following absorption, LCFAs are resynthesized into triacylglycerol (TAG) and enter systemic circulation via the intestinal lymph. Conversely, few MCFAs are reincorporated into TAG,

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Correspondence: T. Sasaki (sasaki.tsutomu.5m@kyoto-u.ac.jp).
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biomedicines

Article

Morphometric Analysis of the Eye by Magnetic Resonance Imaging in *MGST*2-Gene-Deficient Mice

Chaomulige [1,*], Toshihiko Matsuo [1,2,*], Kohei Sugimoto [1], Mary Miyaji [3], Osamu Hosoya [3], Masashi Ueda [4], Ryosuke Kobayashi [5], Takuro Horii [5] and Izuho Hatada [5,6]

[1] Graduate School of Interdisciplinary Science and Engineering in Health Systems, Okayama University, Okayama 700-8558, Japan; sugimotokohei@s.okayama-u.ac.jp
[2] Department of Ophthalmology, Okayama University Hospital, Okayama 700-8558, Japan
[3] Department of Medical Neurobiology, Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama University, Okayama 700-8558, Japan; mmiyaji@okayama-u.ac.jp (M.M.); hosoya@okayama-u.ac.jp (O.H.)
[4] Department of Biofunctional Imaging Analysis, Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama University, Okayama 700-8530, Japan; mueda@cc.okayama-u.ac.jp
[5] Biosignal Genome Resource Center, Institute for Molecular and Cellular Regulation, Gunma University, Maebashi 371-8512, Japan; rkobayashi@gunma-u.ac.jp (R.K.); horii@gunma-u.ac.jp (T.H.); hatada@gunma-u.ac.jp (I.H.)
[6] Viral Vector Core, Gunma University Initiative for Advanced Research (GIAR), Maebashi 371-8511, Japan
[*] Correspondence: baochaomulige@s.okayama-u.ac.jp (C.); matsuot@cc.okayama-u.ac.jp (T.M.)

Abstract: Strabismus, a neuro-ophthalmological condition characterized by misalignment of the eyes, is a common ophthalmic disorder affecting both children and adults. In our previous study, we identified the microsomal glutathione *S*-transferase 2 (*MGST2*) gene as one of the potential candidates for comitant strabismus susceptibility in a Japanese population. The *MGST2* gene belongs to the membrane-associated protein involved in the generation of pro-inflammatory mediators, and it is also found in the protection against oxidative stress by decreasing the reactivity of oxidized lipids. To look for the roles of the *MGST2* gene in the development, eye alignment, and overall morphology of the eye as the possible background of strabismus, *MGST2* gene knockout (KO) mice were generated by CRISPR/Cas9-mediated gene editing with guide RNAs targeting the *MGST2* exon 2. The ocular morphology of the KO mice was analyzed through high-resolution images obtained by a magnetic resonance imaging (MRI) machine for small animals. The morphometric analyses showed that the height, width, and volume of the eyeballs in *MGST2* KO homozygous mice were significantly greater than those of wild-type mice, indicating that the eyes of *MGST2* KO homozygous mice were significantly enlarged. There were no significant differences in the axis length and axis angle. These morphological changes may potentially contribute to the development of a subgroup of strabismus.

Keywords: comitant strabismus; *MGST2* gene; mouse models; genetics; CRISPR/Cas9; PCR; MRI; eye morphology; neuro-ophthalmology

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1. Introduction

Strabismus refers to the inability of both eyes to focus on the target at the same time, which is frequently associated with reduction or loss of binocularity [1–5]. The causes of strabismus are varied but are usually due to a lack of coordination among extraocular muscle movements [2]. In addition, several studies indicate that different regions of the brain, including the brainstem, pons, cerebellum, cortex, visual pathways, and neurons, are associated with abnormal eye alignment and eye movement [6,7]. These findings suggest complicated processes of eye coordination. Strabismus can be divided into two main types as comitant strabismus and incomitant strabismus [1–5]. In comitant strabismus, the misalignment remains relatively constant regardless of the direction of gaze, and the common forms include esotropia and exotropia. Incomitant strabismus presents

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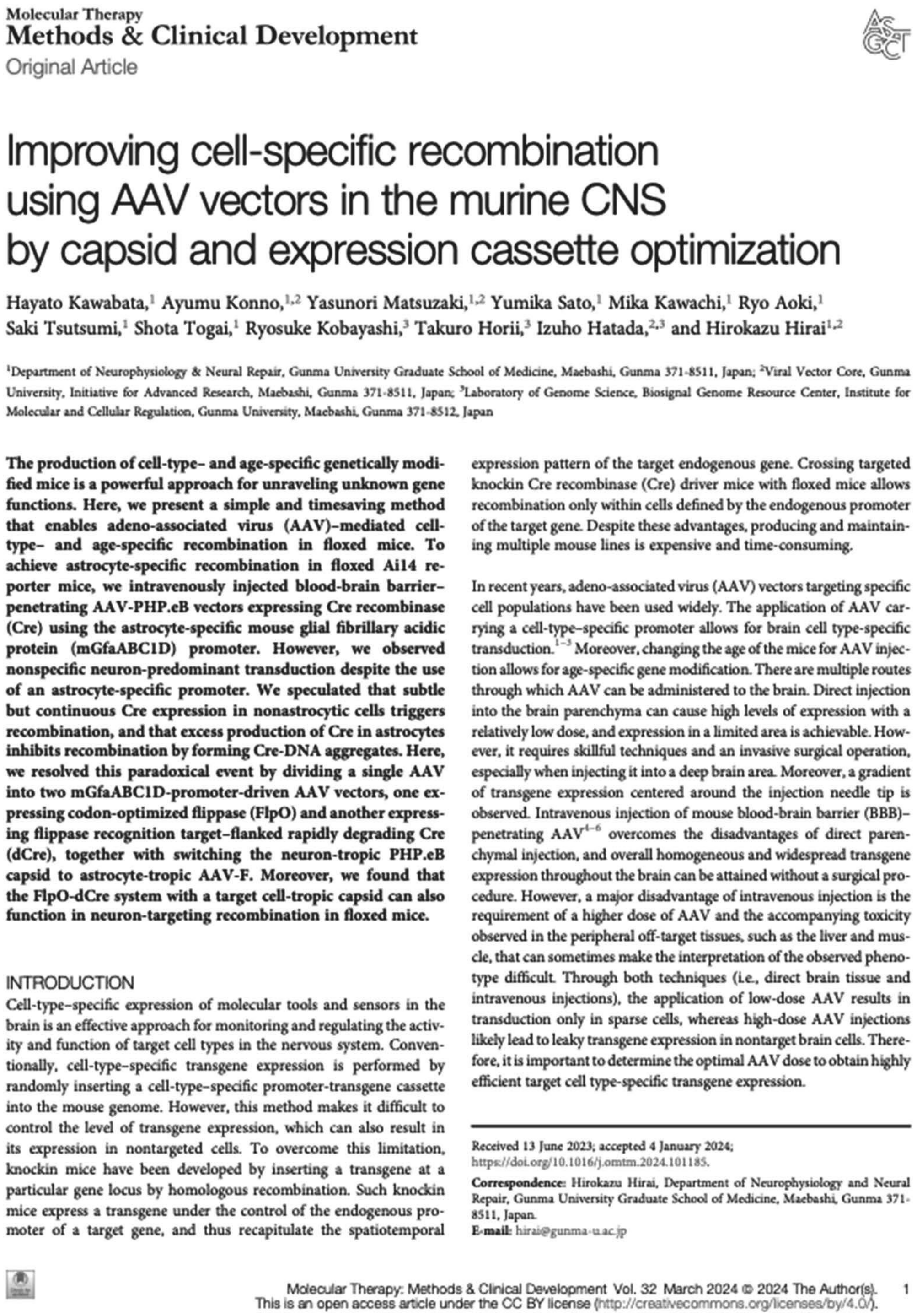
最終責任者　Toshihiko Matsuo (Corresponding Author)



Molecular Therapy
Methods & Clinical Development
Original Article

Improving cell-specific recombination using AAV vectors in the murine CNS by capsid and expression cassette optimization

Hayato Kawabata,[1] Ayumu Konno,[1,2] Yasunori Matsuzaki,[1,2] Yumika Sato,[1] Mika Kawachi,[1] Ryo Aoki,[1]
Saki Tsutsumi,[1] Shota Togai,[1] Ryosuke Kobayashi,[3] Takuro Horii,[3] Izuho Hatada,[2,3] and Hirokazu Hirai[1,2]

[1]Department of Neurophysiology & Neural Repair, Gunma University Graduate School of Medicine, Maebashi, Gunma 371-8511, Japan; [2]Viral Vector Core, Gunma University, Initiative for Advanced Research, Maebashi, Gunma 371-8511, Japan; [3]Laboratory of Genome Science, Biosignal Genome Resource Center, Institute for Molecular and Cellular Regulation, Gunma University, Maebashi, Gunma 371-8512, Japan

The production of cell-type– and age-specific genetically modified mice is a powerful approach for unraveling unknown gene functions. Here, we present a simple and timesaving method that enables adeno-associated virus (AAV)–mediated cell-type– and age-specific recombination in floxed mice. To achieve astrocyte-specific recombination in floxed Ai14 reporter mice, we intravenously injected blood-brain barrier–penetrating AAV-PHP.eB vectors expressing Cre recombinase (Cre) using the astrocyte-specific mouse glial fibrillary acidic protein (mGfaABC1D) promoter. However, we observed nonspecific neuron-predominant transduction despite the use of an astrocyte-specific promoter. We speculated that subtle but continuous Cre expression in nonastrocytic cells triggers recombination, and that excess production of Cre in astrocytes inhibits recombination by forming Cre-DNA aggregates. Here, we resolved this paradoxical event by dividing a single AAV into two mGfaABC1D-promoter-driven AAV vectors, one expressing codon-optimized flippase (FlpO) and another expressing flippase recognition target–flanked rapidly degrading Cre (dCre), together with switching the neuron-tropic PHP.eB capsid to astrocyte-tropic AAV-F. Moreover, we found that the FlpO-dCre system with a target cell-tropic capsid can also function in neuron-targeting recombination in floxed mice.

INTRODUCTION

Cell-type–specific expression of molecular tools and sensors in the brain is an effective approach for monitoring and regulating the activity and function of target cell types in the nervous system. Conventionally, cell-type–specific transgene expression is performed by randomly inserting a cell-type–specific promoter-transgene cassette into the mouse genome. However, this method makes it difficult to control the level of transgene expression, which can also result in its expression in nontargeted cells. To overcome this limitation, knockin mice have been developed by inserting a transgene at a particular gene locus by homologous recombination. Such knockin mice express a transgene under the control of the endogenous promoter of a target gene, and thus recapitulate the spatiotemporal expression pattern of the target endogenous gene. Crossing targeted knockin Cre recombinase (Cre) driver mice with floxed mice allows recombination only within cells defined by the endogenous promoter of the target gene. Despite these advantages, producing and maintaining multiple mouse lines is expensive and time-consuming.

In recent years, adeno-associated virus (AAV) vectors targeting specific cell populations have been used widely. The application of AAV carrying a cell-type–specific promoter allows for brain cell type-specific transduction.[1–3] Moreover, changing the age of the mice for AAV injection allows for age-specific gene modification. There are multiple routes through which AAV can be administered to the brain. Direct injection into the brain parenchyma can cause high levels of expression with a relatively low dose, and expression in a limited area is achievable. However, it requires skillful techniques and an invasive surgical operation, especially when injecting it into a deep brain area. Moreover, a gradient of transgene expression centered around the injection needle tip is observed. Intravenous injection of mouse blood-brain barrier (BBB)–penetrating AAV[4–6] overcomes the disadvantages of direct parenchymal injection, and overall homogeneous and widespread transgene expression throughout the brain can be attained without a surgical procedure. However, a major disadvantage of intravenous injection is the requirement of a higher dose of AAV and the accompanying toxicity observed in the peripheral off-target tissues, such as the liver and muscle, that can sometimes make the interpretation of the observed phenotype difficult. Through both techniques (i.e., direct brain tissue and intravenous injections), the application of low-dose AAV results in transduction only in sparse cells, whereas high-dose AAV injections likely lead to leaky transgene expression in nontarget brain cells. Therefore, it is important to determine the optimal AAV dose to obtain highly efficient target cell type-specific transgene expression.

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Correspondence: Hirokazu Hirai, Department of Neurophysiology and Neural Repair, Gunma University Graduate School of Medicine, Maebashi, Gunma 371-8511, Japan.
E-mail: hirai@gunma-u.ac.jp

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最終責任者　Hirokazu Hirai (Corresponding Author)

生産動物病態学（Farm Animal Pathophysiology）

Keigo Kosenda

Assistant Professor

助教　小千田　圭吾

I. 筆頭または責任著者　＜First or Corresponding Author＞

II.　その他＜Others＞

1）Photogrammetric analysis of limb joint angles in cows with normal gait before and after hoof trimming.
Sato A, **Kosenda K**, Sugiura T, Murakami T.
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Photogrammetric analysis of limb joint angles in cows with normal gait before and after hoof trimming

A. Sato,* K. Kosenda, T. Sugiura, and T. Murakami
Department of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, 069-8501 Japan

ABSTRACT

The aim of this study was to evaluate the effect of hoof trimming on overall limb movements by comparing the changes in 8 limb joint angles 1 wk before and 1 wk after hoof trimming. Seventeen Holstein-Friesian dairy cows that were able to move freely and had no history of hoof diseases were included in the study. The cows were walked on rubber mats with a high friction coefficient (HFM) and a low friction coefficient (LFM) due to the spraying of sodium polyacrylate. Each cow had 15 reflective markers applied to its right side. A high-speed camera was set to 200 frames per second (fps) on the image analysis software, and the images of the cows were captured while cows walked on the test mat. The tests were conducted 1 wk before and 1 wk after hoof trimming, and the cows were trimmed by the functional hoof trimming method. With image analysis software, video clips of walking cows were confirmed visually and tracked during 1 gait cycle by each reflective marker attached to the hoof of the forelimb and hindlimb, after which the stance phase and swing phase were identified. The durations of the stance phase and swing phase of the forelimb and hindlimb, respectively, and the maximum, minimum, and range of motion (ROM) values of the 8 joint angles (shoulder joint, elbow joint, carpus joint, forelimb fetlock joint, hip joint, stifle joint, hock joint, and hindlimb fetlock joint) during 1 gait cycle were included in the analysis. The maximum and minimum angles of the hip and stifle joints were narrower after hoof trimming than before, although the ROM did not change and was clearer for HFM than for LFM. It was thought that the flexion of the proximal hindlimb would progress smoothly during walking after trimming.

Key words: dairy cow, hoof trimming, joint angle, photogrammetry

INTRODUCTION

Lameness in dairy cows is associated with economic losses and animal welfare concerns in the dairy industry (Huxley, 2013; Liang et al., 2017). Lameness causes changes in behavior because of a pain response. Changes in cow behavior are among the most important standards for assessing animal welfare and health (Cook et al., 2005; Chapinal et al., 2011; Viazzi et al., 2013). The functional hoof trimming method is thought to prevent lameness (Toussaint Raven, 1985). Hoof trimming is associated with behavioral and physiological changes. Common behavioral indicators used to evaluate the effect of hoof trimming include locomotion score, lying time, activity, and walking speed (Manske et al., 2002; Chapinal et al., 2010; Van Hertem et al., 2014). In addition, some reports have used a force plate to evaluate the balance of weight bearing between 2 claws (van der Tol et al., 2004; Carvalho et al., 2006), and others have reported the use of a 3-dimensional acceleration sensor or a video camera to determine changes in cows' gait behaviors (Aoki et al., 2006; Tanida et al., 2011).

In horses, photogrammetry of kinematic traits is an objective method that has been used to evaluate gait quality under experimental and field conditions (Back et al., 1994; Clayton, 1994; Morales et al., 1998). These studies have focused on analyzing the gait symmetry of horses to identify potential injuries (Rhodin et al., 2016) and are also useful in the definition of gait quality indicators (Barrey et al., 2002).

In cows, kinematic studies using vision-based technologies have been reported for the detection of lameness or for the analysis of gait biomechanics (Flower et al., 2005; Viazzi et al., 2013; Weiss et al., 2019). To our knowledge, there have been no reports of kinematic traits following changes in limb joint angles, including proximal joints, during 1 gait cycle according to photogrammetry. The aim of this study was to evaluate the effect of hoof trimming on overall limb movements by comparing the changes in limb joint angles 1 wk before and 1 wk after hoof trimming. Specifically, the angular changes in 8 distal-to-proximal limb joints, including

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*Corresponding author: ayanok@rakuno.ac.jp

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最終責任者　Ayano Sato (Corresponding Author)

生産動物外科学（Farm Animal Surgery）

Takashi Murakami

Assistant Professor

助教　村上　高志

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1) Evaluating the impact of application of anaerobic bacterial fermentation enhancer on digital dermatitis
Matsuyama R, Abe N, Sato A, Ishikura Y, Ishikawa T, Otake A, Watanabe R, Sunadome M, Makita K, **Murakami T.**
J Vet Med Sci 86:796–800. 2024. doi: 10.1292/jvms.23-0442

2) Comparing hoof dimensional measurements in cows based on 3D image creation and manual measurement
Murakami T, Ohtake A, Ishikawa T, Sato A.
Vet J 306:106193. 2024. doi: 10.1016/j.tvjl.2024.106193

II. その他　＜Others＞

1) Photogrammetric analysis of limb joint angles in cows with normal gait before and after hoof trimming
Sato A, Kosenda K, Sugiura T, **Murakami T**
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Science

NOTE

Epidemiology

Evaluating the impact of application of anaerobic bacterial fermentation enhancer on digital dermatitis

Ryota MATSUYAMA[1)], Noritsugu ABE[2)], Ayano SATO[1)], Yui ISHIKURA[1)],
Takaaki ISHIKAWA[1)], Ayaka OTAKE[1)], Ryunosuke WATANABE[3)],
Mitsutoshi SUNADOME[3)], Kohei MAKITA[1)], Takashi MURAKAMI[1)]*

1)School of Veterinary Medicine, Rakuno Gakuen University, Hokkaido, Japan
2)Total Herd Management Service, Inc., Hokkaido, Japan
3)Agricultural Research Institute, HOKUREN Federation of Agricultural Cooperatives, Hokkaido, Japan

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ABSTRACT. The control of digital dermatitis (DD) among cattle is crucial; however, effective and environmentally-sound control measures have yet to be identified. From the monitoring data of DD which were recorded during regular hoof trimmings in a farm in Hokkaido, Japan, we detected a decrease in the DD prevalence in a herd where an anaerobic bacterial fermentation enhancer (ABFE) was distributed. The possible effect of ABFE was analyzed using a retrospective repeated cross-sectional design. The prevalence of DD decreased over time in the ABFE-distributed group. Furthermore, a selected regression model indicated the time-dependent enhancement of the decreasing trend. While potential coincidental factors may influence, this study provides a basis for further research on the preventive effect of ABFE against DD.

KEYWORDS: anaerobic bacterial fermentation accelerator, dairy cattle, digital dermatitis, hoof trimming, retrospective cross-sectional study

Digital dermatitis (DD) is a common infectious disease that causes hoof lesions and is one of a major risk factors of lameness in cattle [3]. DD is caused by multiple bacterial species, particularly anaerobic bacteria belonging to the genus *Treponema* [8]. The control of DD is essential because the painful condition due to DD results in losses in animal productivity and welfare [4, 5]. Numerous potential control measures against DD have been considered, including regular hoof trimming [14, 16], improvements in diet [14], the introduction of grazing [14], and supplementing with fermented products as a feed additive [1]. However, due to variations in the susceptibility of individual cows and the difference of key risk factors between farms, effective control measures have yet to be determined [11]. The administration of antibiotics and copper sulfate are considered an effective treatment; however, these are associated with an elevated risk of antimicrobial resistance, as well as environmental damage [9].

Since February 2019, our research team has regularly monitored the incidence of DD by recording the hoof status of individual cows during routine hoof trimming on a dairy farm in Tokoro District, Hokkaido, Japan. During our monitoring, we observed a significant decrease in the prevalence of DD over time in a heifer group that lived in a barn where a commercially available fermentation enhancer, which included anaerobic bacteria (RecycleMate: FarmTech Japan Co., Ltd., Sapporo, Japan [6]), was distributed on the alley in a barn. According to FarmTech Japan Co., the company confirmed that the anaerobic bacteria included in this fermentation enhancer suppressed the growth of Treponema species collected from DD lesion under experimental condition (FarmTech Japan Co., personal communication). In the present study, we aimed to report the descriptive epidemiology responsible for the decrease in the prevalence of DD associated with the distribution of the anaerobic bacterial fermentation enhancer (ABFE). In addition, we also estimated the effect of ABFE distribution on the prevalence of DD by comparing the change in the DD prevalence in an ABFE-distributed cow group with that in a non-distributed group.

The distribution of ABFE was conducted at a farm located in Kunneppu-cho, Tokoro District, Hokkaido, Japan. The herds in the farm consisted of: (i) calves under 12 months old (usually 40–50 cows); (ii) heifers of 12–18 months old (usually 40–50 cows); (iii) heifers of 18–24 months old with matured cows in their dry period (usually 25 heifers and 15 matured cows in dry period); and (iv) matured cows in the lactation period (usually approximately 120 cows). Each herd is kept separately in a different free-stall barn with a concrete floor. The cows were shifted between herds in accordance with their growth/lactation stage. Among them, a heifer

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*Correspondence to: Murakami T: t-murakami@rakuno.ac.jp, Department of Large Animal Surgery, School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyodai Midori-cho, Ebetsu, Hokkaido 069-8501, Japan

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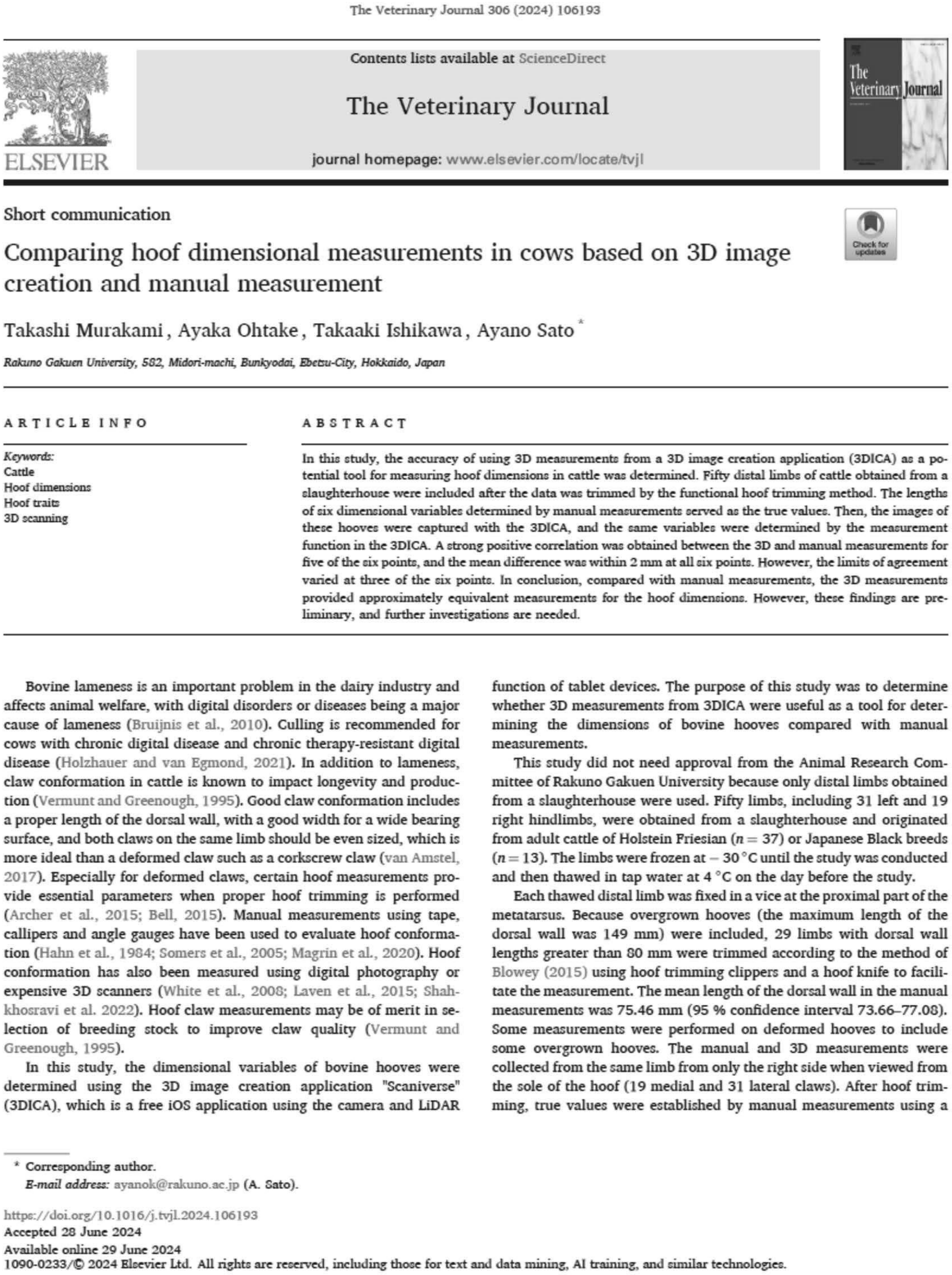
最終責任者　Takashi Murakami (Corresponding Author)



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Short communication

Comparing hoof dimensional measurements in cows based on 3D image creation and manual measurement

Takashi Murakami, Ayaka Ohtake, Takaaki Ishikawa, Ayano Sato *

Rakuno Gakuen University, 582, Midori-machi, Bunkyodai, Ebetsu-City, Hokkaido, Japan

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ABSTRACT

In this study, the accuracy of using 3D measurements from a 3D image creation application (3DICA) as a potential tool for measuring hoof dimensions in cattle was determined. Fifty distal limbs of cattle obtained from a slaughterhouse were included after the data was trimmed by the functional hoof trimming method. The lengths of six dimensional variables determined by manual measurements served as the true values. Then, the images of these hooves were captured with the 3DICA, and the same variables were determined by the measurement function in the 3DICA. A strong positive correlation was obtained between the 3D and manual measurements for five of the six points, and the mean difference was within 2 mm at all six points. However, the limits of agreement varied at three of the six points. In conclusion, compared with manual measurements, the 3D measurements provided approximately equivalent measurements for the hoof dimensions. However, these findings are preliminary, and further investigations are needed.

Bovine lameness is an important problem in the dairy industry and affects animal welfare, with digital disorders or diseases being a major cause of lameness (Bruijnis et al., 2010). Culling is recommended for cows with chronic digital disease and chronic therapy-resistant digital disease (Holzhauer and van Egmond, 2021). In addition to lameness, claw conformation in cattle is known to impact longevity and production (Vermunt and Greenough, 1995). Good claw conformation includes a proper length of the dorsal wall, with a good width for a wide bearing surface, and both claws on the same limb should be even sized, which is more ideal than a deformed claw such as a corkscrew claw (van Amstel, 2017). Especially for deformed claws, certain hoof measurements provide essential parameters when proper hoof trimming is performed (Archer et al., 2015; Bell, 2015). Manual measurements using tape, callipers and angle gauges have been used to evaluate hoof conformation (Hahn et al., 1984; Somers et al., 2005; Magrin et al., 2020). Hoof conformation has also been measured using digital photography or expensive 3D scanners (White et al., 2008; Laven et al., 2015; Shahkhosravi et al. 2022). Hoof claw measurements may be of merit in selection of breeding stock to improve claw quality (Vermunt and Greenough, 1995).

In this study, the dimensional variables of bovine hooves were determined using the 3D image creation application "Scaniverse" (3DICA), which is a free iOS application using the camera and LiDAR function of tablet devices. The purpose of this study was to determine whether 3D measurements from 3DICA were useful as a tool for determining the dimensions of bovine hooves compared with manual measurements.

This study did not need approval from the Animal Research Committee of Rakuno Gakuen University because only distal limbs obtained from a slaughterhouse were used. Fifty limbs, including 31 left and 19 right hindlimbs, were obtained from a slaughterhouse and originated from adult cattle of Holstein Friesian ($n = 37$) or Japanese Black breeds ($n = 13$). The limbs were frozen at − 30 °C until the study was conducted and then thawed in tap water at 4 °C on the day before the study.

Each thawed distal limb was fixed in a vice at the proximal part of the metatarsus. Because overgrown hooves (the maximum length of the dorsal wall was 149 mm) were included, 29 limbs with dorsal wall lengths greater than 80 mm were trimmed according to the method of Blowey (2015) using hoof trimming clippers and a hoof knife to facilitate the measurement. The mean length of the dorsal wall in the manual measurements was 75.46 mm (95 % confidence interval 73.66–77.08). Some measurements were performed on deformed hooves to include some overgrown hooves. The manual and 3D measurements were collected from the same limb from only the right side when viewed from the sole of the hoof (19 medial and 31 lateral claws). After hoof trimming, true values were established by manual measurements using a

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* Corresponding author.
E-mail address: ayanok@rakuno.ac.jp (A. Sato).

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最終責任者　Ayano Sato (Corresponding Author)

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Photogrammetric analysis of limb joint angles in cows with normal gait before and after hoof trimming

A. Sato,* K. Kosenda, T. Sugiura, and T. Murakami
Department of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, 069-8501 Japan

ABSTRACT

The aim of this study was to evaluate the effect of hoof trimming on overall limb movements by comparing the changes in 8 limb joint angles 1 wk before and 1 wk after hoof trimming. Seventeen Holstein-Friesian dairy cows that were able to move freely and had no history of hoof diseases were included in the study. The cows were walked on rubber mats with a high friction coefficient (HFM) and a low friction coefficient (LFM) due to the spraying of sodium polyacrylate. Each cow had 15 reflective markers applied to its right side. A high-speed camera was set to 200 frames per second (fps) on the image analysis software, and the images of the cows were captured while cows walked on the test mat. The tests were conducted 1 wk before and 1 wk after hoof trimming, and the cows were trimmed by the functional hoof trimming method. With image analysis software, video clips of walking cows were confirmed visually and tracked during 1 gait cycle by each reflective marker attached to the hoof of the forelimb and hindlimb, after which the stance phase and swing phase were identified. The durations of the stance phase and swing phase of the forelimb and hindlimb, respectively, and the maximum, minimum, and range of motion (ROM) values of the 8 joint angles (shoulder joint, elbow joint, carpus joint, forelimb fetlock joint, hip joint, stifle joint, hock joint, and hindlimb fetlock joint) during 1 gait cycle were included in the analysis. The maximum and minimum angles of the hip and stifle joints were narrower after hoof trimming than before, although the ROM did not change and was clearer for HFM than for LFM. It was thought that the flexion of the proximal hindlimb would progress smoothly during walking after trimming.

Key words: dairy cow, hoof trimming, joint angle, photogrammetry

INTRODUCTION

Lameness in dairy cows is associated with economic losses and animal welfare concerns in the dairy industry (Huxley, 2013; Liang et al., 2017). Lameness causes changes in behavior because of a pain response. Changes in cow behavior are among the most important standards for assessing animal welfare and health (Cook et al., 2005; Chapinal et al., 2011; Viazzi et al., 2013). The functional hoof trimming method is thought to prevent lameness (Toussaint Raven, 1985). Hoof trimming is associated with behavioral and physiological changes. Common behavioral indicators used to evaluate the effect of hoof trimming include locomotion score, lying time, activity, and walking speed (Manske et al., 2002; Chapinal et al., 2010; Van Hertem et al., 2014). In addition, some reports have used a force plate to evaluate the balance of weight bearing between 2 claws (van der Tol et al., 2004; Carvalho et al., 2006), and others have reported the use of a 3-dimensional acceleration sensor or a video camera to determine changes in cows' gait behaviors (Aoki et al., 2006; Tanida et al., 2011).

In horses, photogrammetry of kinematic traits is an objective method that has been used to evaluate gait quality under experimental and field conditions (Back et al., 1994; Clayton, 1994; Morales et al., 1998). These studies have focused on analyzing the gait symmetry of horses to identify potential injuries (Rhodin et al., 2016) and are also useful in the definition of gait quality indicators (Barrey et al., 2002).

In cows, kinematic studies using vision-based technologies have been reported for the detection of lameness or for the analysis of gait biomechanics (Flower et al., 2005; Viazzi et al., 2013; Weiss et al., 2019). To our knowledge, there have been no reports of kinematic traits following changes in limb joint angles, including proximal joints, during 1 gait cycle according to photogrammetry. The aim of this study was to evaluate the effect of hoof trimming on overall limb movements by comparing the changes in limb joint angles 1 wk before and 1 wk after hoof trimming. Specifically, the angular changes in 8 distal-to-proximal limb joints, including

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*Corresponding author: ayanok@rakuno.ac.jp

The list of standard abbreviations for JDS is available at adsa.org/jds-abbreviations-24. Nonstandard abbreviations are available in the Notes.

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最終責任者　Ayano Sato (Corresponding Author)

伴侶動物外科学（Companion Animal Surgery）

Toshikazu Sakai

Assistant Professor

助教 酒井 俊和

I. 筆頭または責任著者 ＜First or Corresponding Author＞

II. **その他**＜Others＞

1) Surgical treatment offeline inductive odontogenic tumor by marginal resection in a cat.
   Niwa A, **Sakai T**, Hirayama K, Okamoto M, Kadosawa T.
   J Vet Med Sci 86:507–511. 2024. doi: 10.1292/jvms.23-0425.
2) Changes in cytokine concentrations during passage through a granulocyte and monocyte adsorption column in a porcine lipopolysaccharide-induced inflammation model
   Nakamura T, Moriyama K, **Sakai T**, Kato K, Nishida O.
   Ren Replace Ther 10:51. 2024. doi: https://doi.org/10.1186/s41100-024-00565-9

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NOTE

Surgery

Surgical treatment of feline inductive odontogenic tumor by marginal resection in a cat

Akihiro NIWA[1,2], Toshikazu SAKAI[1], Kazuko HIRAYAMA[3], Minoru OKAMOTO[3], Tsuyoshi KADOSAWA[1,4]*

[1]Rakuno Gakuen University Animal Medical Center, Hokkaido, Japan
[2]Aichi Animal Surgical Hospital, Aichi, Japan
[3]Department of Veterinary Pathology, School of Veterinary Medicine, Rakuno Gakuen University, Hokkaido, Japan
[4]Japan Small Animal Medical Center, Saitama, Japan

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ABSTRACT. A 1-year-old mixed-breed cat was referred for an approximately 2-cm mass centered on the upper right canine tooth. Computed tomography (CT) revealed the lesion extended to the nasal cavity and orbit, causing thinning and expansion of the adjacent cortical bone. Excisional biopsy confirmed the diagnosis of a feline inductive odontogenic tumor. Based on the findings of CT imaging, the primary alveolar bone lesion was removed with the tumor, while the adjacent bones, which had been expanded and thinned, wereere preserved by marginal resection including the surrounding periosteum-like membrane. No local recurrence was observed for seven years. To validate the therapeutic outcome of this case, further research in diagnostic imaging and pathology will be crucial.

KEYWORDS: computed tomography, feline inductive odontogenic tumor, marginal resection

Odontogenic tumors are categorized based on their differentiated cell types and inductive properties; specifically, the capacity of the neoplastic epithelial elements to induce differentiation in mesenchymal elements to form odontogenic components [1, 11, 16]. The incidence of odontogenic tumors in cats is rare. A feline inductive odontogenic tumor (FIOT) arises from the odontogenic epithelium and induces mesenchymal cellular elements to form aggregated dental papillae [1, 3, 12]. Feline inductive odontogenic tumors typically manifest between 8 and 18 months of age, with no significant difference in incidence between males and females. While FIOTs generally occur on the rostral aspect of the maxilla, the tumors rarely occur in the mandible [1, 6, 13]. Despite being benign tumors, FIOTs are thought to be locally invasive and are usually treated with surgical excision, including maxillary or mandibular resection [2, 4, 6, 12]. These tumors have a favorable prognosis when surgical excision achieves clean margins [1, 8, 12]. Previous reports have shown positive prognoses following extensive excision of FIOTs including adjacent bone resection [1, 8]. The present report describes the details and surgical management of a specific case that was successfully performed without resorting to radical maxillectomy.

A 1-year-old neutered male mixed-breed cat weighing 5.4 kg presented to a referral veterinarian with swelling on the right side of the face. The upper right canine tooth (104) had fallen out, and six months later, this lesion began to swell. Following the excision, histopathological assessment of the lesion indicated the possibility of an odontogenic cyst. The lesion recurred after two months and was re-excised, revealing a histopathological diagnosis of an ameloblastoma. Thereafter, the cat was referred to Rakuno Gakuen University Animal Hospital. Upon a general physical examination involving palpation, it was revealed that the swelling extended from the bridge of the nose to the caudal maxillary bone. Additionally, the patient also had a red, smooth, oral lesion, measuring approximately 2 cm. This lesion extended from the inside to the outside the dentition, and was centered on the missing right maxillary canine tooth (104).

Radiographic examination revealed that the right maxillary bone was compressed medially and laterally from the third incisor (103) to the second premolar (106) of the right maxilla (Fig. 1).

To assess the extent of the lesion and changes in surrounding tissues, a head computed tomography (CT) was performed with 2.5 mm slice thickness using pre- and postcontrast imaging sequences in the prone position. The lesion had a soft tissue density characterized with a mixed contrast pattern. It extended towards the right nasal cavity, centered at the scar on the upper maxillary canine tooth (104), causing the displacement of the nasal septum (Fig. 2A and 2D). Additionally, a non-enhancing cystic lesion

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*Correspondence to: Kadosawa T: kado3564@gmail.com, Japan Small Animal Medical Center, 1-10-4 Higashi-tokorozawa, Tokorozawa, Saitama 359-0025, Japan

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最終責任者　Tsuyoshi Kadosawa(Corresponding Author)

Nakamura *et al. Renal Replacement Therapy* (2024) 10:51
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Renal Replacement Therapy

RESEARCH **Open Access**

Changes in cytokine concentrations during passage through a granulocyte and monocyte adsorption column in a porcine lipopolysaccharide-induced inflammation model

Tomoyuki Nakamura[1], Kazuhiro Moriyama[2*], Toshikazu Sakai[3], Yu Kato[4] and Osamu Nishida[1]

Abstract

Background Sepsis 3 definitions have shifted the focus from nonspecific inflammation to sepsis as an organ dysfunction caused by a dysregulated host response to infection. Neutrophils have become therapeutic targets because of their intimate but complex involvement in sepsis. We conducted ex vivo and animal experiments to apply a granulocyte and monocyte adsorption column, which is clinically used for inflammatory bowel disease, in sepsis. In this study, the biocompatibility was evaluated in sepsis-like hypercytokinemia.

Methods Six female outbred pigs were anesthetized. Extracorporeal direct hemoperfusion (DHP) with an Adacolumn or a sham column was initiated after lipopolysaccharide (LPS) administration. The DHP was performed for 2 h at a blood flow rate (QB) of 30 or 60 mL/min. Blood samples were collected before and during the DHP (30, 60, 90, and 120 min). The percentage change in white blood cell count, platelet count, and cytokine concentration was compared between the Adacolumn and sham columns.

Results The percentage change in white blood cells were 96 (95–98)% and 106 (101–108)% in the Adacolumn and sham groups, respectively, at QB = 60 mL/min ($p < 0.01$). The percentage change in platelets were 95 (90–96)% and 97 (93–99)% in the in the Adacolumn and sham groups, respectively, at QB = 60 mL/min (not significant; n.s.). At QB = 60 mL/min, the percentage change in tumor necrosis factor-α, interleukin (IL)-6, and IL-10 were 92 (81–106)%, 95 (93–102)%, and 98 (95–100)%, respectively, for the Adacolumn and 100 (95–102)%, 98 (87–104)%, and 97 (93–99)%, respectively, for the sham column. The percentage change in white blood cell counts, platelet counts, and all cytokines at QB = 30 and 60 mL/min showed similar trends.

Conclusion The biocompatibility of the Adacolumn was evaluated using a porcine LPS-induced inflammation model. No decrease in platelet counts or significant cytokine production was observed, suggesting that the Adacolumn could be safely used in patients with sepsis with QB = 30–60 mL/min for 2 h. However, production of mediators other than cytokines remains unknown and requires further investigation.

Keywords Adacolumn, Sepsis, Biocompatibility, Cytokines, Porcine model

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*Correspondence:
Kazuhiro Moriyama
anbix55@gmail.com
Full list of author information is available at the end of the article

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最終責任者　Kazuhiro Moriyama(Corresponding Author)

動物生殖学（Theriogenology）

Tomochika Sugiura

Assistant Professor

助教　杉浦　智親

Ⅰ. 筆頭または責任著者　＜First or Corresponding Author＞

Ⅱ. その他　＜Others＞

1） Changes in mammary infection status in dairy cows during the dry period using dry cow therapy approaches on three farms.
Nagahata H, Komori N, Fukutome M, **Sugiura T**, Hisaeda K, Gondaira S, Higuchi H, Ando T, Nakada K.
Anim Sci J 95:e13993. 2024. https://doi.org/10.1111/asj.13993

RESEARCH ARTICLE

Animal Science Journal WILEY

Changes in mammary infection status in dairy cows during the dry period using dry cow therapy approaches on three farms

Hajime Nagahata[1] | Nodoka Komori[2] | Mayu Fukutome[2] | Tomochika Sugiura[3] | Keiichi Hisaeda[1] | Satoshi Gondaira[4] | Hidetoshi Higuchi[4] | Tatsuya Ando[2] | Ken Nakada[3]

[1]Former Department of Veterinary Associated Studies, Okayama University of Sciences, Imabari, Ehime, Japan

[2]Farm Animal Internal Medicine Unit, Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

[3]Theriogenology Unit, Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

[4]Animal Health Unit, Department of Preventive Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

Correspondence
Satoshi Gondaira, Animal Health Unit, Department of Preventive Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan.
Email: s-gondaira@rakuno.ac.jp

Hajime Nagahata, Bunkyo-dai Minami 61-15, Ebetsu, Hokkaido 069-0835, Japan.
Email: nagahatahajime11@gmail.com

Abstract

This case study evaluated the mammary infection status of dairy cows during the dry periods and explored the associated problems in their quarters with dry cow therapy (DCT). This study assessed intramammary infections, antibiotic efficacy, and antimicrobial resistance of pathogens in 464-quarter milk samples from 59 dairy cows during the dry periods after applying blanket DCT, non-DCT, and selective DCT approaches on three farms. The recovery rates of intramammary infections were 95% (19/20 quarters) with blanket DCT on farm A, 70% (14/20) with non-DCT on farm B, and 19% (4/21) with selective DCT on farm C. Analysis of mammary infections in cows with DCT revealed that mammary infections were controlled by blanket DCT, well controlled by non-DCT, and substantial problems remained in selective DCT. Lower intramammary infection prevalence in the quarters at postpartum appeared to be associated with higher recovery of mammary infections, fewer new infections, and lower uncured mammary infections within the herds. Antibacterial resistance in 14 coagulase-negative staphylococci isolated to six antimicrobial drugs was suggested to be linked to antibiotic use on the farm. Follow-up studies on the quarter-based infection status with DCT will assist in improving mastitis control in cows during the dry period.

KEYWORDS
antibiotic resistance, blanket therapy, dry cow therapy, non-treated, selective therapy

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最終責任者　Satoshi Gondaira and Hajime Nagahata (Corresponding Authors)

伴侶動物外科学（Companion Animal Surgery）

Shushi Yamamoto

Assistant Professor

助教　山本　集士

Ⅰ. 筆頭または責任著者　＜First or Corresponding Author＞

1）A chronic intermittent haemodialysis pig model for functional evaluation of dialysis membranes.
Yamamoto S, Umeno H, Sano Y, Koremoto M, Goda Y, Kaneko Y, Torisu S, Tsuruda T, Fujimoto S.
Int J Artif Organs 47:321–328. 2024. doi:10.1177/03913988241253152.

Ⅱ. その他　＜Others＞

> Int J Artif Organs. 2024 May;47(5):321-328. doi: 10.1177/03913988241253152. Epub 2024 May 13.

A chronic intermittent haemodialysis pig model for functional evaluation of dialysis membranes

Shushi Yamamoto [1 2], Hiroshi Umeno [3], Yusuke Sano [3], Masahide Koremoto [4], Yoshimichi Goda [2], Yasuyuki Kaneko [5], Shidow Torisu [1], Toshihiro Tsuruda [2], Shouichi Fujimoto [6]

Affiliations — collapse

Affiliations

1 Division of Companion Animal Surgery, Department of Small Animal Clinical Sciences, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido Prefecture, Japan.
2 Department of Hemo-Vascular Advanced Medicine, Cardiorenal Reseach Laboratory, Faculty of Medicine, University of Miyazaki, Miyazaki, Japan.
3 Medical Technology and Material Laboratory, Asahi Kasei Medical Co. Ltd., Fuji, Shizuoka, Japan.
4 Product Development Strategy Department, Asahi Kasei Medical Co. Ltd., Chiyoda-ku, Tokyo, Japan.
5 Veterinary Teaching Hospital, Faculty of Agriculture, University of Miyazaki, Miyazaki, Japan.
6 M&M Collaboration Research Laboratory, Department of Medical Environment Innovation, Faculty of Medicine, University of Miyazaki, Miyazaki, Japan.

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Abstract

Performance evaluation of new dialysis membranes is primarily performed in vitro, which can lead to differences in clinical results. Currently, data on dialysis membrane performance and safety are available only for haemodialysis patients. Herein, we aimed to establish an in vivo animal model of dialysis that could be extrapolated to humans. We created a bilateral nephrectomy pig model of renal failure, which placed a double-lumen catheter with the hub exposed dorsally. Haemodialysis was performed in the same manner as in humans, during which clinically relevant physiologic data were evaluated. Next, to evaluate the utility of this model, the biocompatibility of two kinds of membranes coated with or without vitamin E used in haemodiafiltration therapy were compared. Haemodialysis treatment was successfully performed in nephrectomized pigs under the same dialysis conditions (4 h per session, every other day, for 2 weeks). In accordance with human clinical data, regular dialysis alleviated renal failure in pigs. The vitamin E-coated membrane showed a significant reduction rate of advanced oxidation protein products during dialysis than non-coated membrane. In conclusion, this model mimics the pathophysiology and dialysis condition of patients undergoing haemodialysis. This dialysis treatment model of renal failure will be useful for evaluating the performance and safety of dialysis membranes.

Keywords: Haemodialysis; acute renal failure; animal models; dialysis membrane; pig; vitamin E-coated membrane.

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最終責任者　Syushi Yamamoto (First and Corresponding Author)

動物と人の関係学（Animal Human Relations）

Takanori Kooriyama

Professor

教授　郡山　尚紀

I. 筆頭または責任著者　＜First or Corresponding Author＞

1） Human Impact on the Twenty-Four-Hour Patterns of Steller Sea Lions' Use of a Haulout in Hokkaido, Japan.
Chayahara Y, Nakanowataru Y, Abe S, Kurosawa R, Suma S, Murasato N, **Kooriyama T.**
Animals 14:1312. doi: 10.3390/ani14091312.

II. その他　＜Others＞

1） Epidemiological Survey of Canine Distemper Virus Infection: Exploring the Link Between Virus Spread and Invasive Raccoon (Procyon lotor) Population Growth in Hokkaido, Japan.
Minamikawa M, Ito M, Kovba A, Kobayashi Y, Abe G, **Kooriyama T**, Sashika M.
Integr Zool 2024 Dec 1. doi: 10.1111/1749-4877.12922. Online ahead of print.

animals

MDPI

Article

Human Impact on the Twenty-Four-Hour Patterns of Steller Sea Lions' Use of a Haulout in Hokkaido, Japan

Yuko Chayahara [1,†], Yumiko Nakanowataru [1,†], Sara Abe [1], Runa Kurosawa [1], Sayuki Suma [1], Nana Murasato [1], Rin Oyamada [1], Natsuki Ebashi [1], Masatoshi Tsunokawa [2], Mayu Sakurama [1] and Takanori Kooriyama [1,*]

[1] Department of Veterinary Science, Rakuno Gakuen University, 582 Bunkyodai-Midori, Ebetsu 069-8501, Hokkaido, Japan
[2] Otaru Aquarium, 3-303 Shukutsu, Otaru City 047-0047, Hokkaido, Japan
[*] Correspondence: kooriyam@rakuno.ac.jp; Tel.: +81-11-388-4755
[†] These authors contributed equally to this work.

Simple Summary: The Steller sea lion (SSL) is the largest Otariidae family species widely distributed in the cold North Pacific Ocean. SSLs also migrate to Hokkaido, Japan, in the winter. SSLs travel south along the Sea of Japan coast for winter to catch the herring that spawn near the coast. SSLs utilize haulouts as rest sites during herring season, but this can be affected by weather- and human-related pressures. In this study, we investigated the haulout use patterns of SSLs and the effect of human disturbance over a period of three years. The behavior of the SSLs on the haulouts differed from when they were on rookeries. Furthermore, the number of SSLs on the haulout and the duration of time they spent there reduced from the first year (lower human pressure) to the third year (human presence increased). Based on these findings, the SSLs may adjust the timing of when they enter the water to around sunrise, following the ecology of the herring and to avoid human disturbance. Therefore, it is necessary to continue investigating the relationship between the ecology of the SSLs and environmental changes in order to determine the damage that the SSLs cause to fishery interests.

Abstract: Steller sea lions (SSLs) migrate to the Hokkaido coast to spend the winter there, leading to conflicts arising with fishermen over herring. This study analyzed the trends in the SSLs' use of a haulout as a rest site under human pressure. From January to March in 2017, 2018, and 2019, we recorded the SSL behavior at the haulout site off Otaru City, Hokkaido, for 24 h a day using a fixed-point video recorder. We investigated three years of data to analyze the relationships between the SSL behaviors (attendance/landing–entry timings/remaining on land) and herring caught. We also monitored the SSL behaviors during changes in weather conditions and under human pressure. Throughout the three years, the SSLs used the haulout site during harsher weather or under human pressure. In 2017 and 2018, there was a correlation between the herring caught and the maximum number of SSLs on the haulout, but not in 2019. The number of SSLs on the haulout increased from evening to night; most individuals entered the water in the morning. The SSLs probably return to the water around sunrise not only for foraging but also to avoid anthropogenic pressure. The damage caused to the herring fishery by the SSLs was severe, but it is also clear that human pressure changed their behavior in response.

Keywords: conflict; human disturbance; haulout; herring; Steller sea lions

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1. Introduction

Marine mammals have long been vital to human life and are used for food, oil, and fur [1]. However, with the establishment of the Convention for the Protection of Mammals and the development of modern fisheries, marine mammals and humans have become competitors for the same fish stocks [2]. In addition, with the decline in fishery resources, the damage caused by marine mammals to fisheries, especially in coastal fishing, has

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最終責任著者　Takanori Kooriyama (Corresponding Author)

Integrative Zoology

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INTEGRATIVE ZOOLOGY

ORIGINAL ARTICLE

Epidemiological Survey of Canine Distemper Virus Infection: Exploring the Link Between Virus Spread and Invasive Raccoon (*Procyon lotor*) Population Growth in Hokkaido, Japan

Miku Minamikawa[1,#] | Mebuki Ito[1] | Anastasiia Kovba[2] | Yumi Kobayashi[3] | Go Abe[4] | Takanori Kooriyama[5] | Ken Maeda[6] | Michito Shimozuru[1,7] | Toshio Tsubota[1] | Mariko Sashika[1]

[1]Laboratory of Wildlife Biology and Medicine, Faculty of Veterinary Medicine, Hokkaido University, Sapporo, Japan | [2]Laboratory of Wildlife Biology and Medicine, Graduate School of Veterinary Medicine, Hokkaido University, Sapporo, Japan | [3]Laboratory of Animal Ecology, Research Faculty of Agriculture, Hokkaido University, Sapporo, Japan | [4]Wildlife Research & Consulting Services, Ltd., Wildlife Research & Consulting Services, Ltd., Tamba, Japan | [5]Department of Veterinary Science, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan | [6]Department of Veterinary Science, National Institute of Infectious Diseases, Tokyo, Japan | [7]One Health Research Center, Hokkaido University, Sapporo, Japan

Correspondence: Mariko Sashika (msashika@vetmed.hokudai.ac.jp)

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ABSTRACT

Invasive raccoons (*Procyon lotor*) naturalized in Hokkaido, Japan, potentially spreading infectious diseases. Canine distemper virus infection is a serious epizootic disease, for which the raccoon is one of the hosts. We investigated the virus's prevalence in Hokkaido's wild raccoons, using 611 serum samples collected from captured raccoons in 2007–2012, 2021, and 2022. Higher seropositivity rates were confirmed in 2007 (32.7%), 2021 (46.4%), and 2022 (46.8%) than in 2008–2012 (0.00%–6.06%), suggesting the occurrence of an epidemic in 2007, 2021, and 2022 and its disappearance in 2008–2012. However, the infection status has recently changed, with high seropositivity rates consecutively confirmed in 2021 and 2022. Logistic regression analysis was performed to investigate the relationships among the catch per unit effort (an index of animal population density), host and environmental factors, and antibody status. The catch per unit effort correlated with seropositivity in 2007. As for environmental factors, the forest area ratio had a weak influence on seroprevalence in 2007; however, the residential area ratio had a clear influence on seroprevalence in 2021 and 2022. The epidemic occurred in forested areas in 2007; nonetheless, recent raccoon population growth and habitat expansion may have caused widespread infections even around residential areas in 2021 and 2022. Continuous monitoring of the infection and reinforcement of raccoon control programs are necessary to avoid serious damage through disease transmission to sympatric native raccoon dog (*Nyctereutes procyonoides*) and fox (*Vulpes vulpes*) populations, as well as health consequences for domestic dogs (*Canis familiaris*).

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最終責任著者　Miku Minamikawa (First Author and Corresponding Author)

Jun Noda

Professor

教授　能田　淳

I. 筆頭または責任著者　＜First or Corresponding Author＞

1）Efficacy of treating bacterial bioaerosols with weakly acidic hypochlorous water: A simulation chamber study.
Norkaewa S, Narikawa S, Nagashima U, Uemura R, **Noda J.**
Heliyon 10:e26574. 2024. doi: 10.1016/j.heliyon.2024.e26574.

II. その他　＜Others＞

1）Comparative Evaluation of Microorganism Disinfection Methodsfor N95 Respirators
Mitarai S, **Noda J**, Gondaira S, Uchida I, Kirisawa R.
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Research article

Efficacy of treating bacterial bioaerosols with weakly acidic hypochlorous water: A simulation chamber study

Saowanee Norkaew [a,b], Sumiyo Narikawa [c], Ukyo Nagashima [c], Ryoko Uemura [d], Jun Noda [c,*]

[a] *Faculty of Public Health, Thammasat University, Khlong Nueng, Klong Luang, Pathum Thani, 12121, Thailand*
[b] *Research Unit in Occupational Ergonomics, Thammasat University, Khlong Nueng, Klong Luang, Pathum Thani, 12121, Thailand*
[c] *School of Veterinary Medicine, Rakuno Gakuen University, Bunkyodai-Midorimachi, Ebetsu, Hokkaido, 069-8501, Japan*
[d] *Department of Veterinary Sciences, Faculty of Agriculture, University of Miyazaki, GakuenKibanadai-Nishi, Miyazaki, 889-2192, Japan*

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ABSTRACT

The COVID-19 pandemic highlighted the dangers of airborne transmission and the risks of pathogen-containing small airborne droplet inhalation as an infection route. As a pathogen control, Weakly Acidic Hypochlorous Water (WAHW) is used for surface disinfection. However, there are limited assessments of air disinfection by WAHW against airborne pathogens like bioaerosols. This was an empirical study evaluating the disinfection efficacy of WAHW in an atmospheric simulation chamber system against four selected model bacteria. The strains tested included *Staphylococcus aureus* (SA), *Escherichia coli* (EC), *Pseudomonas aeruginosa* (PA), and *Pseudomonas aeruginosa* (PAO1). Each bacterial solution was nebulized into the chamber system as the initial step, and bioaerosol was collected into the liquid medium by a bio-sampler for colony forming units (CFU) determination. Secondly, the nebulized bacterial bioaerosol was exposed to nebulized double distilled water (DDW) as the control and nebulized 150 ppm of WAHW as the experimental groups. After the 3 and 30-min reaction periods, the aerosol mixture inside the chamber was sampled in liquid media and then cultured on agar plates with different dilution factors to determine the CFU. Survival rates were calculated by a pre-exposed CFU value as a reference point. The use of WAHW decreased bacterial survival rates to 1.65–30.15% compared to the DDW control. PAO1 showed the highest survival rates and stability at 3 min was higher than 30 min in all experiments. Statistical analysis indicated that bacteria survival rates were significantly reduced compared to the controls. This work verifies the bactericidal effects against Gram-positive/negative bioaerosols of WAHW treatment. As WAHW contains chlorine in the acid solution, residual chlorine air concentration is a concern and the disinfection effect at different concentrations also requires investigation. Future studies should identify optimal times to minimize the treated time range and require measurements in a real environment.

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[*] Corresponding author. School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyodai-Midorimachi, Ebestu, Hokkaido, 069-8501, Japan.

E-mail address: jnoda@rakuno.ac.jp (J. Noda).

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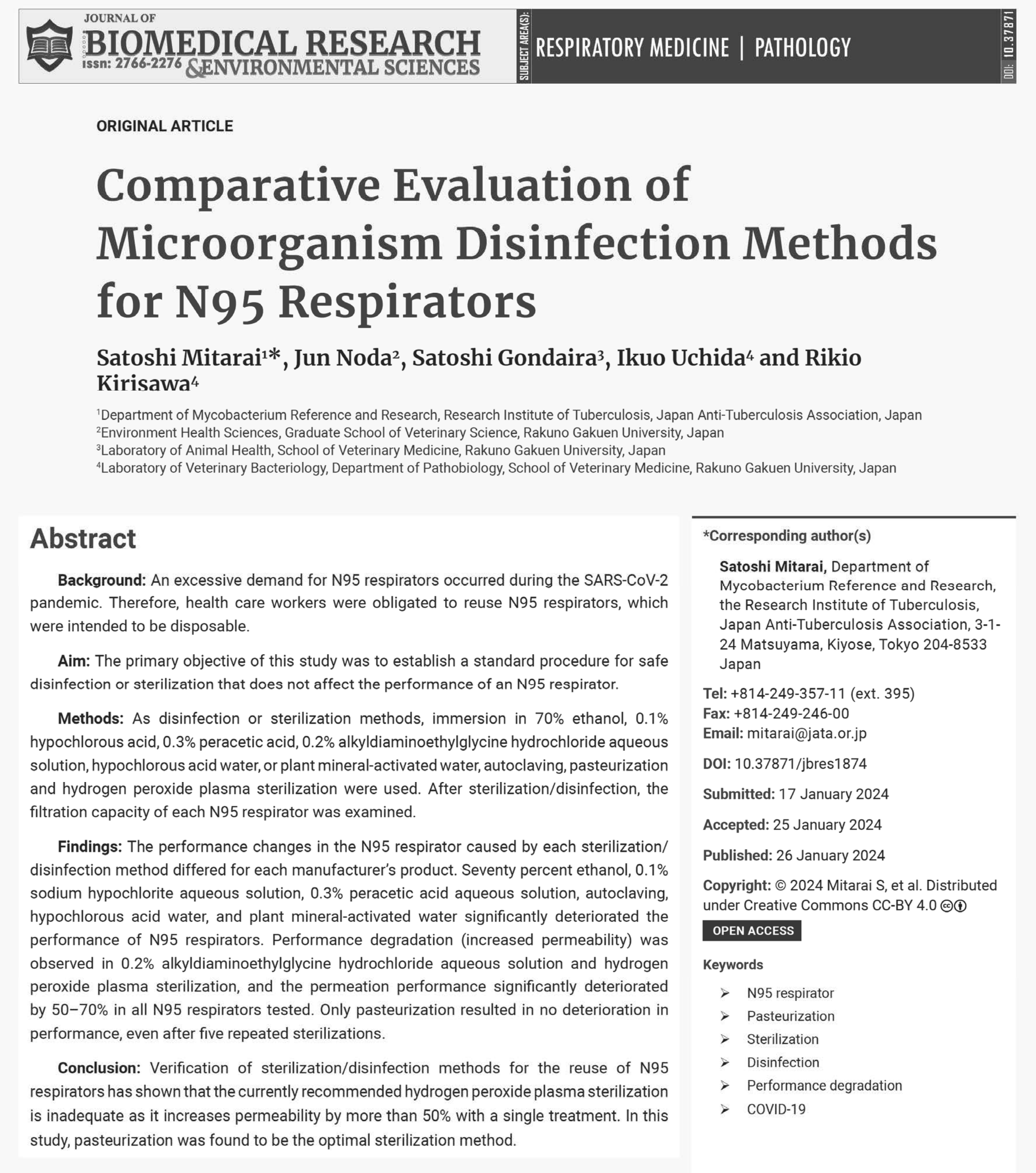
最終責任者　Jun Noda (Corresponding Author)



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ORIGINAL ARTICLE

Comparative Evaluation of Microorganism Disinfection Methods for N95 Respirators

Satoshi Mitarai[1]*, Jun Noda[2], Satoshi Gondaira[3], Ikuo Uchida[4] and Rikio Kirisawa[4]

[1]Department of Mycobacterium Reference and Research, Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association, Japan
[2]Environment Health Sciences, Graduate School of Veterinary Science, Rakuno Gakuen University, Japan
[3]Laboratory of Animal Health, School of Veterinary Medicine, Rakuno Gakuen University, Japan
[4]Laboratory of Veterinary Bacteriology, Department of Pathobiology, School of Veterinary Medicine, Rakuno Gakuen University, Japan

Abstract

Background: An excessive demand for N95 respirators occurred during the SARS-CoV-2 pandemic. Therefore, health care workers were obligated to reuse N95 respirators, which were intended to be disposable.

Aim: The primary objective of this study was to establish a standard procedure for safe disinfection or sterilization that does not affect the performance of an N95 respirator.

Methods: As disinfection or sterilization methods, immersion in 70% ethanol, 0.1% hypochlorous acid, 0.3% peracetic acid, 0.2% alkyldiaminoethylglycine hydrochloride aqueous solution, hypochlorous acid water, or plant mineral-activated water, autoclaving, pasteurization and hydrogen peroxide plasma sterilization were used. After sterilization/disinfection, the filtration capacity of each N95 respirator was examined.

Findings: The performance changes in the N95 respirator caused by each sterilization/disinfection method differed for each manufacturer's product. Seventy percent ethanol, 0.1% sodium hypochlorite aqueous solution, 0.3% peracetic acid aqueous solution, autoclaving, hypochlorous acid water, and plant mineral-activated water significantly deteriorated the performance of N95 respirators. Performance degradation (increased permeability) was observed in 0.2% alkyldiaminoethylglycine hydrochloride aqueous solution and hydrogen peroxide plasma sterilization, and the permeation performance significantly deteriorated by 50–70% in all N95 respirators tested. Only pasteurization resulted in no deterioration in performance, even after five repeated sterilizations.

Conclusion: Verification of sterilization/disinfection methods for the reuse of N95 respirators has shown that the currently recommended hydrogen peroxide plasma sterilization is inadequate as it increases permeability by more than 50% with a single treatment. In this study, pasteurization was found to be the optimal sterilization method.

***Corresponding author(s)**

Satoshi Mitarai, Department of Mycobacterium Reference and Research, the Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association, 3-1-24 Matsuyama, Kiyose, Tokyo 204-8533 Japan

Tel: +814-249-357-11 (ext. 395)
Fax: +814-249-246-00
Email: mitarai@jata.or.jp

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最終責任者　Satoshi Mitarai (Corresponding Author)

動物生命科学（Animal Life Science）

Taku Miyasho

Associate Professor

准教授　宮庄　拓

I. 筆頭または責任著者　＜First or Corresponding Author＞

II. **その他**　＜Others＞

1）Estimating the change in pleural pressure using the change in central venous pressure in various clinical scenarios: a pig model study.
Kyogoku M, Mizuguchi S, **Miyasho T**, Endo Y, Inata Y, Tachibana K, Fujino Y, Yamashita K, Takeuchi M.
Intensive Care Med Exp 12:4. 2024. doi: 10.1186/s40635-023-00590-8.

2）The anti-inflammatory effects of Fuzapladib in an endotoxemic porcine model.
Sugita C, Itami T, **Miyasho T**, Chen IY, Hirokawa T, Tsukui H, Kato M, Shibuya M, Sano Y, Kato K, Yamashita K.
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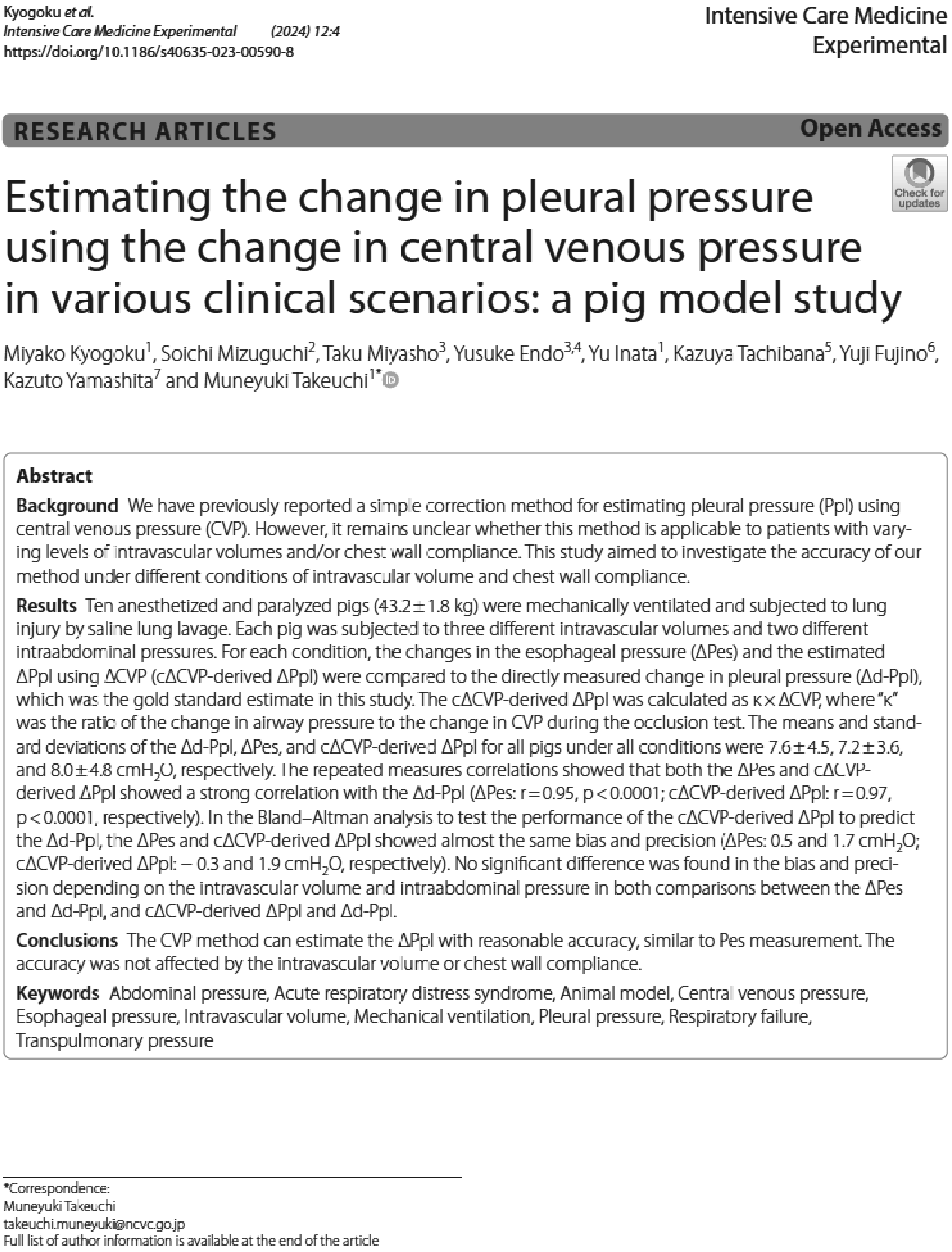

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RESEARCH ARTICLES **Open Access**

Estimating the change in pleural pressure using the change in central venous pressure in various clinical scenarios: a pig model study

Miyako Kyogoku[1], Soichi Mizuguchi[2], Taku Miyasho[3], Yusuke Endo[3,4], Yu Inata[1], Kazuya Tachibana[5], Yuji Fujino[6], Kazuto Yamashita[7] and Muneyuki Takeuchi[1*]

Abstract

Background We have previously reported a simple correction method for estimating pleural pressure (Ppl) using central venous pressure (CVP). However, it remains unclear whether this method is applicable to patients with varying levels of intravascular volumes and/or chest wall compliance. This study aimed to investigate the accuracy of our method under different conditions of intravascular volume and chest wall compliance.

Results Ten anesthetized and paralyzed pigs (43.2 ± 1.8 kg) were mechanically ventilated and subjected to lung injury by saline lung lavage. Each pig was subjected to three different intravascular volumes and two different intraabdominal pressures. For each condition, the changes in the esophageal pressure (ΔPes) and the estimated ΔPpl using ΔCVP (cΔCVP-derived ΔPpl) were compared to the directly measured change in pleural pressure (Δd-Ppl), which was the gold standard estimate in this study. The cΔCVP-derived ΔPpl was calculated as κ × ΔCVP, where "κ" was the ratio of the change in airway pressure to the change in CVP during the occlusion test. The means and standard deviations of the Δd-Ppl, ΔPes, and cΔCVP-derived ΔPpl for all pigs under all conditions were 7.6 ± 4.5, 7.2 ± 3.6, and 8.0 ± 4.8 cmH$_2$O, respectively. The repeated measures correlations showed that both the ΔPes and cΔCVP-derived ΔPpl showed a strong correlation with the Δd-Ppl (ΔPes: $r = 0.95$, $p < 0.0001$; cΔCVP-derived ΔPpl: $r = 0.97$, $p < 0.0001$, respectively). In the Bland–Altman analysis to test the performance of the cΔCVP-derived ΔPpl to predict the Δd-Ppl, the ΔPes and cΔCVP-derived ΔPpl showed almost the same bias and precision (ΔPes: 0.5 and 1.7 cmH$_2$O; cΔCVP-derived ΔPpl: − 0.3 and 1.9 cmH$_2$O, respectively). No significant difference was found in the bias and precision depending on the intravascular volume and intraabdominal pressure in both comparisons between the ΔPes and Δd-Ppl, and cΔCVP-derived ΔPpl and Δd-Ppl.

Conclusions The CVP method can estimate the ΔPpl with reasonable accuracy, similar to Pes measurement. The accuracy was not affected by the intravascular volume or chest wall compliance.

Keywords Abdominal pressure, Acute respiratory distress syndrome, Animal model, Central venous pressure, Esophageal pressure, Intravascular volume, Mechanical ventilation, Pleural pressure, Respiratory failure, Transpulmonary pressure

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*Correspondence:
Muneyuki Takeuchi
takeuchi.muneyuki@ncvc.go.jp
Full list of author information is available at the end of the article

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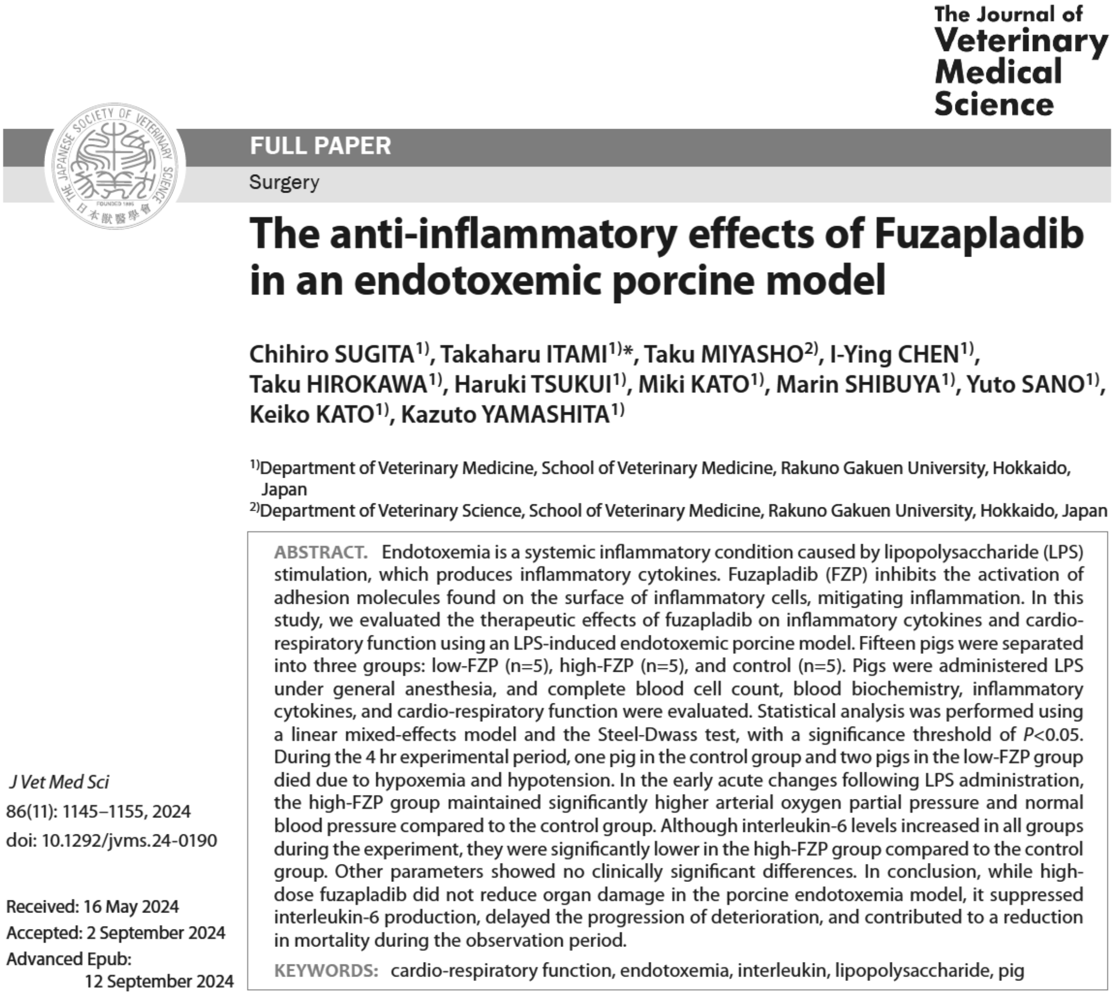

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The anti-inflammatory effects of Fuzapladib in an endotoxemic porcine model

Chihiro SUGITA[1], Takaharu ITAMI[1]*, Taku MIYASHO[2], I-Ying CHEN[1], Taku HIROKAWA[1], Haruki TSUKUI[1], Miki KATO[1], Marin SHIBUYA[1], Yuto SANO[1], Keiko KATO[1], Kazuto YAMASHITA[1]

[1]Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Hokkaido, Japan
[2]Department of Veterinary Science, School of Veterinary Medicine, Rakuno Gakuen University, Hokkaido, Japan

ABSTRACT. Endotoxemia is a systemic inflammatory condition caused by lipopolysaccharide (LPS) stimulation, which produces inflammatory cytokines. Fuzapladib (FZP) inhibits the activation of adhesion molecules found on the surface of inflammatory cells, mitigating inflammation. In this study, we evaluated the therapeutic effects of fuzapladib on inflammatory cytokines and cardio-respiratory function using an LPS-induced endotoxemic porcine model. Fifteen pigs were separated into three groups: low-FZP (n=5), high-FZP (n=5), and control (n=5). Pigs were administered LPS under general anesthesia, and complete blood cell count, blood biochemistry, inflammatory cytokines, and cardio-respiratory function were evaluated. Statistical analysis was performed using a linear mixed-effects model and the Steel-Dwass test, with a significance threshold of $P<0.05$. During the 4 hr experimental period, one pig in the control group and two pigs in the low-FZP group died due to hypoxemia and hypotension. In the early acute changes following LPS administration, the high-FZP group maintained significantly higher arterial oxygen partial pressure and normal blood pressure compared to the control group. Although interleukin-6 levels increased in all groups during the experiment, they were significantly lower in the high-FZP group compared to the control group. Other parameters showed no clinically significant differences. In conclusion, while high-dose fuzapladib did not reduce organ damage in the porcine endotoxemia model, it suppressed interleukin-6 production, delayed the progression of deterioration, and contributed to a reduction in mortality during the observation period.

KEYWORDS: cardio-respiratory function, endotoxemia, interleukin, lipopolysaccharide, pig

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最終責任者　Takaharu Itami (Corresponding Author)