The Methicillin-Resistant *S pseudintermedius* Crisis

Are We Out of Options to Treat the Most Common Canine Pathogen?

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KEYWORDS

• *Staphylococcus pseudintermedius* • MRSP • Antimicrobial resistance
• Antimicrobial stewardship • Multidrug resistance • Biofilm • Emerging therapeutics

KEY POINTS

- *Staphylococcus pseudintermedius* is the dominant bacterial cause of canine pyoderma and a major driver of antimicrobial use in small animal practice.
- MRSP has emerged globally as a clinically important multidrug-resistant pathogen, with prevalence varying by region, practice setting, and patient population.
- The clinical impact of MRSP is driven by loss of β-lactam efficacy, frequent resistance to additional antimicrobial classes, biofilm-associated persistence, and recurrent disease.
- MRSP is concentrated in patients with chronic dermatologic disease, prior antimicrobial exposure, repeated veterinary care, and recurrent infection, increasing clinical burden and treatment complexity.
- Emerging therapies may help reduce reliance on conventional systemic antimicrobials but require clinical validation.

INTRODUCTION

Staphylococcus pseudintermedius is the dominant bacterial pathogen of canine pyoderma and one of the most frequently encountered bacterial pathogens in small animal practice. *S pseudintermedius* is a coagulase-positive, Gram-positive cocci belonging to the *Staphylococcus intermedius* group (SIG), a commensal and opportunistic pathogen adapted primarily to dogs and, to a lesser extent, cats, with carriage rates ranging from approximately 37% to over 90%.[1]

In dogs, *S pseudintermedius* is the most common bacterium in canine microbiological cultures[1] and is also a frequent cause of otitis externa, wound infections, surgical site infections, and urinary tract infections in dogs.[1] Canine pyoderma is among the

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Abbreviations	
AMR	antimicrobial resistance
MDR	multidrug resistance
MRSP	methicillin-resistant *S pseudintermedius*
XDR	extensively drug-resistant

most common reasons dogs present for veterinary care and the most common indication for antibiotic prescriptions.[2]

Importantly, many *S pseudintermedius* infections occur in patients with chronic or relapsing dermatologic disease, resulting in repeated antimicrobial exposure and making staphylococcal pyoderma one of the major drivers of antimicrobial use in small animal practice.[3,4] This heavy reliance on antimicrobials has created substantial selective pressure for resistance, and over the past 2 decades the emergence and international spread of methicillin-resistant *S pseudintermedius* (MRSP) has fundamentally altered the therapeutic landscape.[5,6] MRSP strains frequently exhibit multidrug resistance and biofilm-associated persistence, making infections harder to treat and more likely to recur.[5,7]

The emergence of MRSP has transformed *S pseudintermedius* from a routine clinical pathogen into a major antimicrobial resistance challenge. This review summarizes the epidemiology, treatment limitations, and emerging therapeutic strategies shaping contemporary MRSP management.

EMERGENCE AND EXPANSION OF METHICILLIN-RESISTANT *S PSEUDINTERMEDIUS*

Over the past 2 decades, MRSP has emerged as a major antimicrobial resistance (AMR) challenge in companion animal medicine.[8] Now reported worldwide, MRSP is endemic in many veterinary hospitals and referral practices.[5,8] Geographic variation is substantial, with MRSP accounting for approximately 30% to 50% of clinical *S pseudintermedius* isolates in some North American populations,[6] to 5% to 10% in European populations,[9] with higher rates in referral and dermatology populations.[9,10]

Methicillin resistance is mediated by acquisition of the *mecA* gene, which encodes the altered penicillin-binding protein PBP2a and confers resistance to β-lactam antimicrobials.[11] MRSP lineages frequently carry additional resistance determinants, resulting in multidrug resistance (MDR).[5,12–14] In several reports, more than 90% of MRSP isolates meet MDR criteria,[15–17] and extensively drug-resistant (XDR) isolates[14] have now emerged in multiple regions, although pan-drug resistant isolates remain rare.[15] Even where MRSP prevalence is low, clinical impact is amplified by frequent co-resistance across drug classes.

In addition to AMR, many *S pseudintermedius* isolates can form biofilms[15,18] that protect bacteria from host immune defenses and reduce antimicrobial susceptibility.[7,19,20] Most isolates from canine skin infections form biofilms *in vitro*, suggesting a role for biofilm-associated tolerance in chronic or recurrent infections.[18,21]

EPIDEMIOLOGY AND BURDEN OF DISEASE

S pseudintermedius is the leading bacterial cause of canine skin and soft tissue infections and is commonly implicated in pyoderma, otitis externa, wound infections, and postoperative infections.[22,23] Large prescribing studies show skin disease accounts for approximately 20% to 30% of antimicrobial prescriptions in dogs,[4] with pyoderma among the most frequent diagnoses prompting treatment.[24–26] As the dominant bacterial pathogen in canine pyoderma, *S pseudintermedius* sits at the intersection of high

disease prevalence and frequent antimicrobial exposure. Consequently, the emergence of MRSP has had a disproportionate impact in patients with chronic or relapsing dermatologic disease, where repeated treatment cycles amplify both clinical burden and antimicrobial selection pressure.[4,27,28]

MRSP prevalence varies by practice setting, with lower rates typically reported in primary care (10%–25%) than in referral hospitals (15%–40%)[29] and dermatology populations (40%–60%).[30] These differences reflect case complexity and the concentration of chronic infections in referral settings.[28,31] Importantly, regardless of prevalence, MRSP isolates are frequently MDR, reinforcing their clinical relevance across all levels of practice.[4]

MRSP risk is associated with prior antimicrobial exposure, chronic dermatologic disease, and frequent health care contact.[27,32,33] Atopic dermatitis, hospitalization,[21,27] surgery, and repeated veterinary visits further increase risk by disrupting skin defenses and creating repeated treatment opportunities.[4,34] MRSP infections are thus more likely to recur, fail empiric therapy, and require culture-guided treatment.[4,31] Colonized animals can also serve as reservoirs, contributing to environmental contamination and health care-associated transmission.[8,35,36] In veterinary settings, MRSP has been recovered from environmental surfaces, equipment, and personnel. Although zoonotic transmission is less common than with MRSA, human colonization and infection have been documented in individuals with close animal contact.[37]

CURRENT TREATMENT LIMITATIONS

Management has shifted toward stewardship-focused care emphasizing cytology, topical therapy, susceptibility-guided treatment, and control of underlying disease.[4] International Society for Companion Animal Infectious Diseases (ISCAID) guidelines recommend topical therapy alone for surface and superficial pyoderma where feasible, reserving systemic antimicrobials for deep pyoderma or cases where topical treatment is ineffective or impractical.[4,38,39] When systemic therapy is required, culture and susceptibility testing are increasingly essential, particularly in recurrent infections, prior treatment failures, deep pyoderma, suspected MRSP, or patients with substantial prior antimicrobial exposure.[40]

The most immediate therapeutic consequence of MRSP is the loss of β-lactams as reliable first-line options. Because *mecA* encodes the altered penicillin-binding protein PBP2a, MRSP is resistant to essentially all β-lactam antimicrobials[8] eliminating key drugs used for canine pyoderma, including cephalexin and amoxicillin-clavulanate.[4,23] Alternative oral options—clindamycin, potentiated sulfonamides, tetracyclines, and fluoroquinolones—may be useful when susceptibility is confirmed but cannot be assumed active against MRSP.[3,9] Tetracycline-class susceptibility is variable; fluoroquinolones remain useful for selected infections but resistance and stewardship concerns limit empiric use.[3]

Salvage antimicrobials do not fully address this treatment gap.[3,4] Chloramphenicol, rifampin combinations, linezolid, vancomycin, and teicoplanin may retain activity against some MRSP isolates, but safety concerns, monitoring requirements, lack of veterinary breakpoints, and stewardship considerations restrict their routine use.[4,31] Critically important human medicines should be avoided except under exceptional circumstances with specialist oversight.[4,41] Their use does not close the treatment gap created by MDR and XDR *S pseudintermedius*.

Topical therapy remains one of the most important tools for managing *S pseudintermedius* infections, particularly for pyoderma and otitis externa.[4,38] Chlorhexidine-based shampoos, mousses, wipes, sprays, and flushes deliver high local antiseptic

concentrations while minimizing systemic exposure and selection pressure.[4,42] However, success depends on lesion accessibility, product selection, contact time, frequency of application, patient[38] tolerance, and owner adherence.[39] Topical antibiotics such as mupirocin or fusidic acid may be useful for focal lesions, but use should be limited given resistance risk and human medicine stewardship concerns.[39]

Antimicrobial therapy alone is rarely sufficient in recurrent disease. Successful management requires identifying and controlling underlying drivers such as atopic dermatitis, ectoparasitism, endocrinopathy, keratinization disorders, anatomic skin folds, wounds, foreign material, or other causes of impaired barrier function.[4,43] Without addressing these factors, treatment may reduce bacterial burden without preventing recurrence.[44] Owner adherence and realistic treatment planning are equally important, particularly when topical protocols are time-consuming or systemic drugs require prolonged administration.[45] In cats, MRSP is less common and less well studied, with treatment similarly constrained by susceptibility patterns, drug tolerance, and limited species-specific data.

These limitations underscore a widening treatment gap. Although several antimicrobial classes may appear available, few are predictably active, safe, practical, and supported by clinical evidence for routine use. Topical therapy and correction of underlying disease remain essential but insufficient for all patients, particularly those with deep, invasive, or extensively drug-resistant infections. As MDR and XDR *S pseudintermedius* erode conventional therapy, antimicrobial-sparing and adjunctive strategies are urgently needed.

EMERGING THERAPEUTIC OPTIONS

The growing prevalence of MRSP and MDR *S pseudintermedius* has intensified interest in strategies beyond conventional antibiotics. Emerging approaches include novel small molecules, bacteriophages and endolysins, microbiome-based therapies, immune modulation, nanomaterials, photodynamic therapy, vaccines, and antimicrobial peptides (AMPs).[5] All share a common goal: improving management of resistant, recurrent, and biofilm-associated infections while reducing reliance on conventional antimicrobials. Most remain preclinical or early translational, with limited efficacy data in naturally occurring canine disease.[5,46,47]

Novel small molecules and repurposed drugs—including compounds from antimicrobial, antiparasitic, and agricultural pipelines—have shown activity against MRSP in vitro.[48] However, most candidates remain limited by uncertain safety, pharmacokinetics, and formulation, and substantial translational work is needed before clinical use.[49]

Bacteriophage therapy is attractive because phages can selectively target bacterial pathogens while sparing the surrounding microbiota.[50,51] Several phages and phage-derived enzymes show activity against MRSP and biofilms, suggesting utility for difficult-to-treat infections.[51,52] However, narrow host range, formulation challenges, regulatory uncertainty, phage resistance emergence, and isolate-specific testing requirements remain important barriers.[50,53]

Oclacitinib and lokivetmab provide a clinically relevant example of host-directed management that may indirectly reduce recurrent pyoderma by improving barrier function and reducing self-trauma.[54–56] However, whether these therapies directly reduce *S pseudintermedius* colonization, MRSP carriage, or pyoderma recurrence remains untested.[57] Future host-directed approaches may target cutaneous immunity, AMP production, and barrier function while dampening inflammatory pathways that promote bacterial persistence.[58–61]

Vaccination would be an attractive strategy for recurrent MRSP infections, but no licensed vaccine exists and development remains largely conceptual.[1,44] Although adhesins, toxins, and biofilm antigens have been proposed as targets, repeated failures of *Staphylococcus aureus* vaccine programs highlight the difficulty of identifying protective immune responses for staphylococcal disease.[62] These challenges may be especially relevant for *S pseudintermedius*, where immune evasion, antigenic diversity, and recurrent exposure could complicate vaccine design.[1,63]

Nanomaterial-based platforms and photodynamic therapy have shown anti-staphylococcal and antibiofilm activity experimentally and are particularly attractive for localized skin, wound, and otic infections.[47] Nanoparticles can deliver antimicrobial payloads, disrupt biofilms, generate oxidative or photothermal effects, or enhance existing drugs.[64] Photodynamic approaches use light-activated compounds to generate reactive oxygen species locally, targeting accessible skin, wound, or otic infections.[65] These platforms may act through multitarget mechanisms less vulnerable to classical resistance. However, for *S pseudintermedius*, these approaches remain largely preclinical, with open questions regarding tissue safety, dosing, delivery, and efficacy in naturally occurring disease.[47]

Microbiome-based approaches are particularly attractive for recurrent *S pseudintermedius* infections because they address the disrupted skin ecosystem underlying pyoderma.[5,66,67] In healthy skin, resident microbes and innate defenses create colonization resistance that limits opportunistic pathogens. In canine pyoderma, allergic inflammation, barrier dysfunction, antimicrobial exposure, and dysbiosis weaken this resistance and favor *S pseudintermedius* expansion.[66,67] Human *S aureus*-associated atopic dermatitis shows this ecosystem can be therapeutically manipulated, with topical commensal delivery reducing pathogen colonization or disease severity in some studies.[68] In companion animals, microbiome-based approaches remain at the discovery stage—identifying commensal bacteria that inhibit MRSP *in vitro* rather than demonstrating efficacy of live biotherapeutics in naturally occurring disease.[69]

AMPs bridge microbiome restoration and targeted anti-staphylococcal therapy.[70,71] Produced by epithelial cells, immune cells, and microbes, AMPs kill bacteria through mechanisms distinct from conventional antibiotics while influencing inflammation, barrier repair, and biofilm formation.[71] Bacteriocins—peptide antimicrobials produced by bacteria to compete with closely related organisms—are especially relevant in this context.[70,71] Live biotherapeutics, commensal-derived bacteriocins, and synthetic AMPs are thus complementary strategies for restoring selective antimicrobial pressure at the skin surface.[68,70,72] Studies in the *S aureus* system show that commensal-derived AMPs can reduce pathogen colonization and reshape microbial communities, supporting translational rationale for similar approaches in *S pseudintermedius* infections.[70,72] AMP-based therapies remain early in development. Clinical translation requires demonstrated activity against MRSP isolates and biofilms, compatibility with topical or otic formulations, and durability in complex skin and otic environments.[1,71,73]

CHALLENGES AND FUTURE DIRECTIONS

The central challenge in MRSP management is not merely treating resistant infections, but preventing recurrence and reducing antimicrobial selection pressure. Effective management requires earlier risk recognition, culture-guided therapy, topical management, infection control, and correction of underlying disease.

Future progress requires improved surveillance, faster diagnostics, and stronger stewardship integration. Equally important are strategies addressing the biologic

drivers of recurrence: biofilm persistence, barrier dysfunction, dysbiosis, and loss of colonization resistance.

Emerging therapies offer an important path forward, but require rigorous evaluation in naturally occurring disease. The most promising approaches will complement rather than replace conventional therapy by reducing recurrence, preserving antimicrobial efficacy, and supporting barrier and microbiome health. Clinical studies should prioritize outcomes relevant to practice: recurrence rates, safety, owner feasibility, and stewardship impact.

CLINICS CARE POINTS

- Culture high-risk cases, including deep pyoderma, recurrent infection, prior treatment failure, suspected MRSP, or cases requiring systemic antimicrobial therapy.
- Prioritize topical therapy for surface and superficial pyoderma when feasible, and choose protocols owners can realistically perform.
- Use systemic antimicrobials selectively and base drug choice on susceptibility results, infection depth, patient safety, drug penetration, and stewardship principles; avoid β-lactams when MRSP is suspected or confirmed.
- Prevent recurrence by controlling underlying disease, including allergic dermatitis, ectoparasites, endocrinopathies, keratinization disorders, skin folds, wounds, foreign material, or other barrier-disrupting conditions.
- Support treatment success through stewardship, owner education, adherence planning, environmental hygiene, and infection control to reduce recurrence and MRSP transmission.
- Monitor emerging therapies, but adopt them cautiously. New approaches should meet appropriate regulatory standards and be supported by robust clinical evidence for safety, efficacy, feasibility, and stewardship impact before routine use.

DECLARATION OF AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work, the authors used Generative AI to assist with finding relevant references and edit content for brevity. All references were reviewed for accuracy and the authors take full responsibility for the content of the publication.

DISCLOSURE

Dr Jessica M. Gilbertie is Chief Scientific Officer, co-founder, and an equity holder in Qentoros, Inc., a biotechnology company developing host-defense peptide therapeutics for veterinary applications. Portions of this review discuss antimicrobial peptides and related emerging therapeutic strategies that overlap with the company's research interests. The authors have sought to present a balanced review of the available evidence, including the current limitations and translational challenges of these approaches.

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