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Antimicrobial resistance in methicillin susceptible and methicillin resistant *Staphylococcus pseudintermedius* of canine origin: Literature review from 1980 to 2013

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ABSTRACT

Staphylococcus pseudintermedius is a commensal and a common opportunistic pathogen causing mainly infections of the integumentary system in dogs. The recent emergence of multidrug-resistant *S. pseudintermedius* isolates, in particular methicillin-resistant strains (MRSP) is a threat to small animal health and highlights the need for antimicrobial resistance surveillance to detect trends and potentially perform timeous interventions. We systematically reviewed 202 published articles to investigate temporal changes in antimicrobial resistance in clinical and commensal *S. pseudintermedius* isolated from dogs in 27 countries between 1980 and 2013. Resistance to the most common antimicrobials tested for in published studies and important for the treatment of staphylococcal infections in dogs were assessed separately for methicillin resistant (MRSP) and methicillin susceptible (MSSP) isolates. Stratified by MSSP and MRSP, no significant increases in antimicrobial resistance were observed over time, except for the penicillinase-labile penicillins (penicillin and ampicillin) among MSSP. However, in recent years, a few studies have reported higher-level of resistance to amikacin, gentamicin and enrofloxacin amongst MSSP. The review highlights inconsistencies between studies as a result of several factors, for example the use of different antimicrobial susceptibility testing methods and interpretation criteria. We recommend that data on susceptibility in important companion animal pathogens are collected and presented in a more harmonized way to allow more precise comparison of susceptibility patterns between studies. One way to accomplish this would be through systematic surveillance either at the country-level or at a larger scale across countries e.g. EU level.

1. Introduction

Staphylococcus pseudintermedius is a commensal and the most common bacterial pathogen in dogs. Before the description of *S. pseudintermedius* in 2005 (Devriese et al., 2005), any non-pigmented haemolytic, coagulase-positive staphylococci isolated from dogs were generally referred to as *S. intermedius* without further confirmation. For the purpose of this review, all *S. intermedius* and *S. pseudintermedius* isolated from dogs were referred to as *S. pseudintermedius* irrespective of molecular confirmation of species identification.

The first phenotypic methicillin resistant *S. pseudintermedius* (MRSP) strains were isolated in France in the

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mid-1980s from healthy dogs and dogs with pyoderma (Pellerin et al., 1998). The first *mecA* positive strain was reported in 1999 in a canine pyoderma isolate from the US (Gortel et al., 1999) and in Europe in 2005 (Loeffler et al., 2007). Since these early reports of MRSP, they are now increasingly reported in veterinary clinics around the world, and are recognized as a serious canine health problem due to their multidrug resistance phenotype, limiting treatment options, and challenging infection control measures (Weese and van Duijkeren, 2010; van Duijkeren et al., 2011; Bannoehr and Guardabassi, 2012; Bond and Loeffler, 2012).

Our objective was to investigate temporal changes of antimicrobial resistance in methicillin susceptible- and resistant *S. pseudintermedius* of canine origin by systematically reviewing published studies between 1980 and 2013. The study was limited to the following antimicrobials, which were most often tested for in published studies and represent the major classes for treatment of staphylococcal infections in veterinary medicine: aminoglycosides (amikacin and gentamicin), phenicols (chloramphenicol), fluoroquinolones (ciprofloxacin and enrofloxacin), macrolides (erythromycin), lincosamides (clindamycin), tetracycline, and trimethoprim/sulphonamides. For β-lactams, amongst MSSP only, we analysed resistance to penicillin and ampicillin, since resistance to amoxicillin/clavulanic acid and cephalosporins would indicate the presence of *mecA* (MRSP).

2. Identification and analysis of relevant literature

The free electronic database PubMed was searched for all articles using the following search strings: "staphylococcus and pseudintermedius AND resistance OR resistant AND dog OR canine" and "staphylococcus and intermedius AND resistance OR resistant AND dog OR canine" until 30 June 2013. Papers were screened using six inclusion criteria: (i) full articles in English, (ii) dog specific antimicrobial resistance data could be extracted from the paper, (iii) not a case report, (iv) MRSP were confirmed to harbour *mecA* (see definition below), (v) antimicrobial resistance was reported separately for MSSP and MRSP, and (vi) the Clinical and Laboratory Standards Institute (CLSI, formerly National Committee for Clinical Laboratory Standards (NCCLS)) clinical breakpoints were used, independent of the publication year and whether they were specific for animals or humans. A data extraction form was used to obtain information from the relevant studies, which included general information of the article, study period, country of isolation, type of isolate (clinical or commensal), total number of *S. pseudintermedius* isolates, if strains were tested for oxacillin resistance and phenotypically resistant strains were confirmed by *mecA* PCR, antimicrobial susceptibility testing methods, interpretative breakpoints for resistance, and the number of isolates resistant to the selected antimicrobials. Intermediately resistant isolates were excluded from the analysis.

If oxacillin resistance was tested, resistant isolates confirmed to carry *mecA* were called MRSP and included in the analysis. Oxacillin resistant isolates that were shown to be *mecA* negative were called MSSP and also included in the analysis. Studies reporting oxacillin resistance without confirming the presence of *mecA* were excluded from the analysis.

Antimicrobial resistance was summarised for the following antimicrobials (i) β-lactams (penicillin and ampicillin), (ii) tetracycline, (iii) trimethoprim/sulphonamides, (iv) phenicols (chloramphenicol), (v) macrolides (erythromycin), (vi) lincosamides (clindamycin), (vii) aminoglycosides (gentamicin and amikacin), and (viii) fluoroquinolones (ciprofloxacin and enrofloxacin). The prevalence of resistance reported in each study to the different antimicrobials were depicted in scatter plots for each antimicrobial type over time, and stratified by MRSP and MSSP. For each antimicrobial, a linear relationship of resistance prevalence with time was assessed, while weighing each observation (i.e. each original study) by the number of isolates included. The glm (generalized linear model) -function in R was used to assess if the prevalence of resistance increased or decreased over time (R Core Team, 2013). A linear trend line was added to the resulting plot if a statistical association ($P < 0.05$) was identified.

3. Description of relevant literature

This is the first review systematically analysing temporal trends of phenotypic antimicrobial resistance in *S. pseudintermedius* isolated from geographically dispersed dogs over an extended time period, independent of infection type and methicillin resistance. Initially, 202 unique articles were identified through PubMed, and after the screening process, 57 articles that met all six inclusion criteria were included. References of all 57 included articles are listed in the supplementary material, which also includes the raw data, e.g. the number of isolates and resistance recorded in each study. The 145 articles were excluded for the reasons; (a) articles not in English ($n = 3$); (b) reviews, case reports or articles did not perform antimicrobial susceptibility testing, or did not include the antimicrobials of interest for this review ($n = 71$), (c) did not provide antimicrobial resistance data separately for *S. pseudintermedius* ($n = 9$), (d) dog specific antimicrobial resistance data could not be extracted either because of reporting errors or data was combined for all animal species ($n = 31$), (e) oxacillin resistance was reported but isolates were not confirmed to harbour *mecA* ($n = 5$), (f) provided combined MSSP and MRSP antimicrobial resistance data ($n = 5$), (g) did not use CLSI clinical breakpoints or did not provide information on which antimicrobial breakpoints were used ($n = 21$).

3.1. Penicillinase-labile penicillins

Amongst MSSP, there was a significant increasing trend of resistance to the penicillinase-labile penicillins (Fig. 1). A significant increase in resistance to the penicillinase-labile penicillin and ampicillin was observed amongst MSSP, which is likely the result of dissemination of the narrow spectrum β-lactamase, *blaZ* (Kadlec and Schwarz, 2012). As a result of this widespread resistance, penicillin