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Retrospective multicentre study of methicillin-resistant *Staphylococcus aureus* infections in 115 horses

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Summary

Reasons for performing study: **Methicillin-resistant *Staphylococcus aureus* (MRSA) is an emerging veterinary and zoonotic pathogen, associated with increasing reports of disease in horses.**

Objectives: **To provide an overview of the characteristics of clinical MRSA infections in horses.**

Methods: **A retrospective case study was performed on 115 horses admitted to 6 participating veterinary teaching hospitals in Canada and the United States between 2000 and 2006, and diagnosed with clinical MRSA infection. Descriptive statistics, univariate and multivariable analyses for community- (CA) vs. hospital-associated (HA) MRSA infections, and survival vs. nonsurvival at discharge were performed.**

Results: **The age range of MRSA-infected horses was zero (born in hospital) to 31 years. HA (58/114, 50.9%) and CA infections (56/114, 49.1%) were equally common. Infection of surgical incisions was most frequently reported (44/115, 38.0%). Overall 93/111 (83.8%) cases survived to discharge. Previous hospitalisation and treatment with gentamicin were associated significantly with CA-MRSA, whereas infected incision sites were associated significantly with HA-MRSA. Factors significantly associated with nonsurvival included i.v. catheterisation, CA-MRSA infection and dissemination of infection to other body sites.**

Conclusions: **Equine MRSA infections have a broad range of clinical presentations, appear to be primarily opportunistic and the overall prognosis for survival to discharge is good.**

Potential relevance: **These results should help direct future research with regard to investigation of risk factors for equine MRSA infection in community and hospital populations.**

Introduction

For many years, methicillin-resistant *Staphylococcus aureus* (MRSA) has been one of the most important hospital-associated (HA) pathogens in human medicine. Infection is becoming more common and is associated with increased morbidity, mortality and length of hospitalisation (Cosgrove *et al*. 2003, 2005). Recently, MRSA has become an important cause of disease in community populations and is now also recognised as a veterinary and zoonotic pathogen that can infect several species, including horses (Seguin *et al*. 1999; Baptiste *et al*. 2005; Weese *et al*. 2005a,b, 2006a).

In man, MRSA can cause a wide range of clinical disease, from simple skin and soft tissue infections (SSTIs), to necrotising pneumonia (Cunha 2005; Anon 2007). Reports of severe, even fatal, community-associated (CA) MRSA infections that occur in individuals without traditional healthcare-associated risk factors are increasing (Herold *et al*. 1998; Pannaraj *et al*. 2006; Anon 2007; Castaldo and Yang 2007).

A number of studies have reported clinical MRSA infections in horses (Seguin *et al*. 1999; Baptiste *et al*. 2005; O'Mahony *et al*. 2005; Weese *et al*. 2005a,b; Cuny *et al*. 2006). In general, detailed descriptions of clinical characteristics, evaluation of historical factors, origin of infection, treatments and outcome have not been reported. The purpose of the present study was to provide an overview of the characteristics of clinical MRSA infections in horses, in order to focus more targeted, controlled studies in the future.

Materials and methods

Case selection

All equine cases admitted to 6 participating North American veterinary teaching hospitals (J.T. Vaughan Large Animal Teaching Hospital, Auburn University; James L. Voss Veterinary Teaching Hospital, Colorado State University; College of Veterinary Medicine Veterinary Teaching Hospital, Michigan State University; Boren Veterinary Medical Teaching Hospital, Center for Veterinary Health Sciences, Oklahoma State University; Ontario Veterinary College Veterinary Teaching Hospital, University of Guelph; University of Pennsylvania New Bolton Center) between 2000 and 2006 were considered for the

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study. Cases were included if the horse was diagnosed with a clinical infection (i.e. a site of heat, pain, swelling, discharge) from which MRSA was isolated, and if the medical record was available for review. Horses that were colonised but not infected with MRSA were excluded.

Data collection

Data were collected from medical records on a standardised form and included the following information: date of admission; age; breed; gender; use; presenting complaint; admitting service; most responsible service; within 30 days of admission: antimicrobial treatment, hospitalisation, surgery, endoscopy; previous MRSA-positive horse on home farm; previous MRSA colonisation; time from admission to onset of infection; site of infection; description of infection; antimicrobial susceptibility of MRSA; other bacterial isolates; in-hospital events prior to infection: antimicrobial treatment, surgery, anesthesia, use of an i.v. catheter or other invasive devices, other MRSA-positive horse in hospital, MRSA colonisation detected; events following diagnosis of MRSA infection: systemic antimicrobial treatment, local antimicrobial treatment, dissemination to other body sites, further surgery required; final diagnosis; outcome (survived, died, euthanasia); role of MRSA in nonsurvival; time from infection to resolution; duration of hospitalisation.

Follow-up information for cases that survived to discharge was not obtained.

Classification of infections

Infections present upon admission and those detected <48 h after admission were classified as community associated (CA)-MRSA. Infections that developed at 48 h or more after admission to the hospital were classified as HA-MRSA.

Statistical analysis

Associations between predictor variables and outcomes were estimated using a statistical software program (Stata Intercooled 9.1)[1]. Univariate logistic regression was used to examine associations between predictors and dichotomous outcomes (survival vs. nonsurvival at discharge; CA vs. HA infection). In cases where <10 observations/group were being compared, Fischer's exact tests were employed.

Multivariable logistic regression models were built to control for potential confounding influences of other variables on the significant relationships observed in the unconditional analyses. All predictors identified as being associated with the outcomes of interest with $P \leq 0.20$ in the univariate analyses were considered for inclusion in the final models. In addition, variables with biologically plausible associations with both these predictors and the outcomes were evaluated as potential confounding variables. Associations between predictors were examined to ensure that none were strongly correlated ($r \geq 0.80$). A stepwise approach to model building was employed. Confounding was assessed by determining the effect of each variable's inclusion on the values of coefficients for the other variables. Variables with $P > 0.05$ with no confounding effects were dropped. Confounders were retained, even if their own coefficients were insignificant in the final models. After final models were identified, interaction terms were created for retained variables and added to the analyses. Interaction terms were retained if significant, and their component variables retained even if adding the interaction term caused one of the components to lose significance. A P value ≤0.05 was deemed to indicate a significant association. The fit of each final logistic model to the data was examined using Hosmer-Lemeshow goodness-of-fit tests. Finally, a random effect for hospital of origin was added to each final model to control for clustering by hospital.

Results

The inclusion criteria for the study were met by 115 cases. From the 6 participating veterinary teaching hospitals, 30, 27, 26, 15, 9 and 8 cases were included, respectively. The age range of cases was zero (born in hospital) to 31 years (mean 5.7 years, median 4 years). Animals used for breeding (22/64, 34.4%) were the most common, followed by nonracing performance horses (18/64, 28.1%), and race horses (12/64, 18.8%). Colic was the most common presenting complaint (29/115, 25.2%), followed by wounds (18/115, 15.7%) and incision infections (10/115, 8.7%). Sites of MRSA infection included surgical incisions (44/115, 38.3%), other skin and soft tissue infections: (24/115, 20.9%), joints (11/115, 9.6%), bone/tendon (9/115, 7.8%), i.v. catheter sites (9/115, 7.8%) and lungs (5/115, 4.3%), as well as guttural pouch, sinus, nose, eye, trachea, uterus, udder and bloodstream infections (<2.7% each).

HA and CA infections accounted for 50.9% (58/114) and 49.1% (56/114) of cases, respectively. HA infections were identified between 48 h and 170 days after admission (mean 10.8 days, median 6 days). The most common presenting complaints for horses that developed HA infection were colic

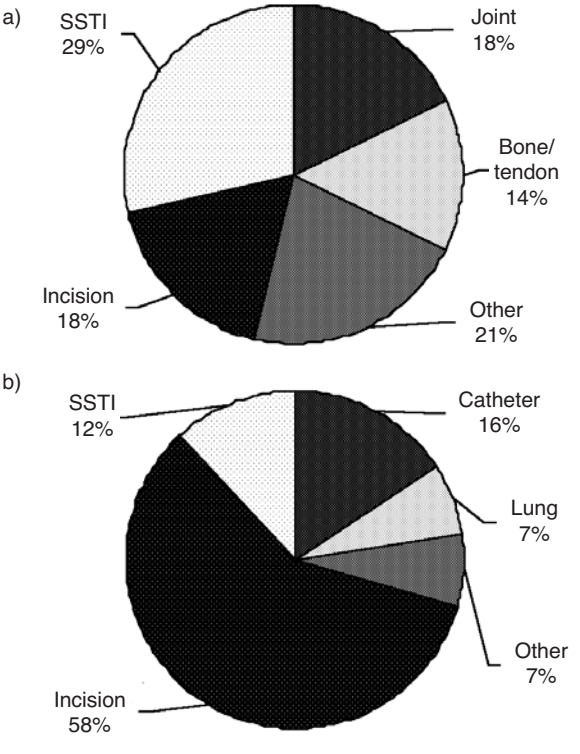

Fig 1: Distribution of site of infection: a) community-associated MRSA infections (diagnosed <48 h after hospital admission; n = 56); and b) hospital-associated MRSA infections (diagnosed >48 h after hospital admission; n = 58) in horses. SSTI = skin and soft tissue infection.

(29/58, 50.0%), wounds (7/58, 12.1%) and lameness or hernia (3/58, 5.2% each), while those for horses that had or developed CA infections were wounds (10/56, 17.9%), incision infections (8/56, 14.3%) and septic joints (5/56, 8.9%). The distributions of site of infection for CA and HA infections, respectively, are shown in Figure 1.

Overall, 93/111 (83.8%) cases survived to discharge. Differences in denominators for descriptive statistics were the result of unavailable data for some cases. There was no significant difference in the ratio of survival vs. nonsurvival of cases at discharge between hospitals (P>0.110), nor between CA and HA infections (P = 0.759), nor was duration of hospitalisation significantly associated with discharge status (P = 0.761).

The prevalences of resistance to the most frequently tested non-β-lactam antimicrobial drugs among the clinical MRSA isolates are shown in Table 1. A total of 59/115 (51.3%) isolates were tested for susceptibility to both tetracycline and enrofloxacin. Of these, 50 (84.7%) isolates were simultaneously resistant to tetracycline and susceptible to enrofloxacin.

Results of univariate analyses of factors significantly associated with CA-MRSA (vs. HA-MRSA) infection and nonsurvival at discharge are shown in Tables 2 and 3, respectively.

TABLE 1: Reported frequency of antimicrobial resistance in MRSA isolates from clinical infections in horses

Antimicrobial drug	n/N	% Resistant
Tetracycline	69/75	92.0
Gentamicin	65/77	84.4
Trimethoprim sulphate	55/77	71.4
Erythromycin	35/56	62.5
Enrofloxacin	5/62	8.1
Amikacin	3/48	6.2
Chloramphenicol	1/42	2.4

n = number of resistant isolates reported. N = total number of isolates tested against the specific antimicrobial drug.

TABLE 2: Factors significantly (P≤0.05) associated with community-associated[a] MRSA infection relative to hospital-associated[b] MRSA infection in horses diagnosed in hospital with clinical MRSA infection, as identified through univariate logistic regression analyses and Fisher's exact tests

Variable		N	n	OR	95% CI	P
Hospital	1	27	9	Ref		
	2	29	17	2.62	0.89–7.68	0.080
	3	26	16	3.20	1.04–9.85	0.043
	4	15	7	1.75	0.48–6.37	0.396
	5	9	1	0.25	0.03–2.32	0.223
	6	8	6	6.00	1.00–35.91	0.050
Joint infection[c]		11	10	12.61	1.66–556.30	0.009
Bone/tendon infection[c]		9	8	9.67	1.17–80.03	0.035
Skin or soft tissue infection[c]		24	16	2.55	0.91–7.56	0.048[e]
Incision infection[c]		44	10	0.16	0.07–0.38	<0.001
Hospitalised in last 30 days[d]		18	14	4.72	1.33–20.93	0.006
Any antimicrobial used in last 30 days[d]		46	32	5.51	2.37–12.83	<0.001
Gentamicin used in last 30 days[d]		18	14	5.91	1.62–26.54	0.002
Penicillin used in last 30 days[d]		18	12	2.94	0.90–10.46	0.044[e]

N = total number of cases in specific category. n = number of cases of community-associated MRSA infection in specific category. CI = confidence interval; OR = odds ratio; [a]Diagnosed less than 48 h after hospital admission. [b]Diagnosed more than 48 h after hospital admission. [c]Versus infection at all other sites combined. [d]Versus not used in the last 30 days. [e]Although the CI for the OR includes 1, a Fisher's exact test showed there was a significant difference between the groups.

In the multivariable model for CA-MRSA (vs. HA-MRSA) infection, when controlling for hospital, the only factors significantly associated with CA infection were previous hospitalisation within 30 days prior to hospital admission (odds ratio (OR) 7.07, 95% confidence interval (CI) 1.60–31.23, P = 0.010), treatment with gentamicin within 30 days prior to hospital admission (OR 5.46, 95% CI 1.15–26.00, P = 0.033), and having an incision infection (OR 0.08, 95% CI 0.02–0.32, P<0.001).

Factors associated significantly with nonsurvival at discharge following multivariable analyses were i.v. catheterisation in hospital prior to infection (OR 15.71, 95% CI 2.12–116.70, P = 0.007), CA-MRSA (vs. HA-MRSA) infection (OR 5.40, 95% CI 1.06–30.75, P = 0.047) and dissemination of MRSA to other body sites (OR 5.12, 95% CI 1.10–26.86, P = 0.043).

Limited typing information for the MRSA isolates was available. Pulsed field gel electrophoresis (PFGE) was performed on only 15 isolates from one hospital (data not shown), and all of these were consistent with the epidemic clone CMRSA-5 (also referred to as USA500).

Discussion

From the results of this study, it is clear that infection by MRSA can affect a broad age range of horses and cause widely variable clinical presentations in both the community and the hospital setting.

The high survival rate (93/111, 83.8%) identified in this study indicates that MRSA infection is a survivable condition in horses. Due to the significant negative media attention surrounding MRSA, veterinarians and horse owners may believe that an equine MRSA infection is an untreatable disease or that such a condition always carries a grave prognosis. This does not appear to be the case. It is unclear how the sample population may have biased the survival data. All of the participating veterinary teaching hospitals were tertiary care referral facilities and, therefore, capable of providing a high level of medical and surgical care, which could improve survival. However, they were also likely to see the more severe or complicated cases that were not conducive to being managed in the field, which could decrease survival.

The lack of a control group of non-MRSA-infected horses precluded evaluation of risk factors for MRSA infection. However, the exposures and demographics of horses identified with CA- vs. HA-MRSA infections were compared, and associations between various factors and nonsurvival at discharge among MRSA-infected horses examined.

Overall, surgical incisions represented the most common site of MRSA infection. Incision infections were significantly associated with HA-MRSA, which was not surprising given that hospitalised animals are presumably more likely to have undergone

TABLE 3: Factors significantly (P≤0.05) associated with nonsurvival in horses diagnosed in hospital with clinical MRSA infection, as identified through univariate logistic regression analyses and Fisher's exact tests

Variable	OR	95% CI	P
Age (years)	0.87	0.77–0.99	0.043
Other bacteria isolated from infection	0.28	0.09–0.86	0.026
Dissemination of MRSA to other body sites	6.58	1.66–26.18	0.007
Catheterised intravenously prior to infection	4.04	1.08–15.20	0.039
Local antimicrobial treatment in hospital	3.03	1.04–8.80	0.041

OR = odds ratio; CI = confidence interval.

surgery than horses in the community; and could also be at higher risk for developing infection due to co-morbidities. The frequency of incision infections in CA-MRSA cases is also noteworthy, as it indicates that MRSA infection should also be considered in community-onset infections following routine surgical procedures, whether they are performed in the field or in hospital.

Among horses with CA-MRSA infection, joint infections were as common as incision infections at 17.9%, and over two-thirds (8/11, 73%) of all MRSA joint infections occurred in mature horses (data not shown). Septic arthritis is of particular concern because of the potential for serious or life-threatening outcomes even with aggressive therapy (Schneider *et al*. 1992; Smith *et al*. 2004). It is tempting to speculate that many of these infections may have been the result of iatrogenic contamination during arthrocentesis or joint injection, but no objective conclusions can be drawn in this regard based on the data available.

Antimicrobial drug administration is a well-recognised risk factor for MRSA infection in man (Monnet 1998; Graffunder and Venezia 2002). Previous equine studies have also identified an association between antimicrobial administration and MRSA colonisation in horses, in both the community and a veterinary hospital (Weese *et al*. 2006b; Weese and Lefebvre 2007). Although the use of gentamicin or penicillin within 30 days of hospital admission was associated significantly with CA infection in the univariate analyses, this may have been confounded by the fact that a horse with a clinical infection would be more likely to be treated in the field prior to referral than a horse referred for an acute and/or noninfectious problem (such as colic). Furthermore, it was not always clear from the medical record whether antimicrobial administration preceded development of the infection or if it occurred after infection was detected, but prior to hospital referral. Based on this study, it is not possible to draw any conclusion regarding the risk of MRSA infection associated with antimicrobial drug administration in either the community or the hospital setting, but further investigation is warranted.

While i.v. catheterisation was associated significantly with nonsurvival, and one-third (3/9) of horses with i.v. catheter site infections were subjected to euthanasia, only one documented case of an MRSA bloodstream infection was reported. It is therefore probable that an i.v. catheter was simply more likely to be used in animals with more severe conditions and therefore the association with nonsurvival. Dissemination of infection to other body sites clearly represents a lack of the body's ability to contain the infection, with or without therapy, and therefore logically would carry a poorer prognosis.

The association of CA-MRSA infection and nonsurvival was a concern. It is tempting to speculate that many of the CA infections were present prior to referral and therefore a delay in obtaining appropriate therapy may have existed compared to horses that developed infection while under close monitoring in hospital. The association may be related to the relatively large number of CA orthopaedic infections (joint, bone, tendon), which can be difficult to treat and lead to loss of use and subsequent need for euthanasia, particularly in performance horses. It is also possible that there were differences in the virulence characteristics of some CA- and HA-MRSA strains, although equine MRSA, at least in North America, appears to be relatively clonal, with the majority of CA and HA infections attributed to one epidemic clone (Weese *et al*. 2005a,b).

All MRSA isolates for which molecular typing information was available were subtypes of CMRSA-5, which is the most common MRSA clone isolated from horses and equine personnel in other reports from North America (Weese *et al*. 2005a,b). Unfortunately, typing data were available only from isolates from one hospital and it is therefore not possible to determine if CMRSA-5 was the dominant MRSA clone overall. However, it is interesting to note that a large percentage of the isolates in this study had a somewhat unusual antimicrobial susceptibility pattern characterised by susceptibility to fluoroquinolones and resistance to tetracycline, which is characteristic of CMRSA-5 and uncommon in other epidemic MRSA clones (J.S. Weese, unpublished data).

The classification of equine MRSA infections into CA and HA infections according to when infection is detected following hospital admission is strictly empirical. No system can eliminate completely the risk of misclassification of some cases. Cut points of 24, 48 or 72 h have been used in numerous human MRSA studies with the same cautions (Herold *et al*. 1998; Goetz *et al*. 1999; Gorak *et al*. 1999; Campbell *et al*. 2003; Jernigan *et al*. 2003a,b; Salgado *et al*. 2003). Descriptors such as community-onset, community-acquired hospital-onset and other combinations thereof have also been used. In this study, due to the lack of any information regarding more appropriate criteria that should be applied to horses, a 48 h cut-off point was selected. This is the point currently used as one of the criteria for identification of human CA-MRSA infections (Anon 2005). The most likely misclassification in this study was horses that acquired MRSA in hospital but did not develop infection until after discharge. These cases would be identified as CA, which could explain, at least in part, the association between CA-MRSA and recent hospitalisation. However, animals that were previously hospitalised may also be more likely to acquire MRSA in the community because they are recovering from a medical condition, suffer from chronic disease, are receiving antimicrobial therapy, or simply because they have undergone the recent stress of transportation and hospitalisation. Appropriate differentiation of CA- and HA-MRSA in such cases would require far more detailed history, surveillance and isolate data than were available for the current study. For these reasons, the term 'community-associated' was used in this study, as it represents the situation encountered by veterinarians when evaluating clinical cases when the source of the MRSA infection is unclear.

Due to the predominance of CMRSA-5 in horses, molecular typing techniques are not useful for inferring the origin of equine MRSA isolates. In contrast, when CA-MRSA first emerged in the human population among individuals with few or no HA risk factors, the clones responsible had distinct molecular and clinical characteristics. However, this distinction between human CA and HA clones has since become considerably blurred due to movement of hospital strains into the community and *vice versa*, such that the molecular characteristics of a human MRSA isolate are now considerably less reliable for determining its origin (Gonzalez *et al*. 2006; Maree *et al*. 2007).

It is unknown whether missing data, particularly with regard to historical factors, may have affected the study results. This is an unfortunate limitation to performing a retrospective study that will have to be addressed in a prospective study. Follow-up information was not obtained for discharged patients, therefore it is unknown if some of the horses may have succumbed to their MRSA infections, or the sequelae thereof, after discharge. The lack of a control group of horses infected by methicillin-susceptible *S. aureus* (MSSA) precluded determination of whether MRSA infections were more severe than MSSA infection. This comparison has been the subject of many studies in human medicine, with conflicting results (Hershow *et al*. 1992; Graffunder and Venezia 2002; Cosgrove *et al*. 2003; Engemann *et al*. 2003; Melzer *et al*. 2003), and warrants further investigation in equine medicine.

Methicillin-resistant *S. aureus* is an important emerging pathogen in horses. A better understanding of the epidemiology of this pathogen and clinical aspects of equine MRSA infections is critical for prevention and management of these cases. The results of this study indicate that equine MRSA infections are predominantly opportunistic in nature and largely are survivable conditions. Factors identified as associated with nonsurvival at discharge and CA- vs. HA-MRSA infections in this study warrant further investigation in more rigorous, prospective studies. This study highlights several differences between human and equine MRSA, indicating that extrapolation of data from human to animal populations must be done with caution; and that species-specific research is required. In particular, further investigation of specific risk factors for equine MRSA infections in both community and hospital populations, as well as comparison of the severity of MRSA and MSSA infections in horses, should be pursued.

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