Vancomycin for the treatment of methicillin-resistant staphylococcal and enterococcal infections in 15 horses

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Abstract

We retrospectively reviewed the cases of 15 foals and adult horses in which vancomycin was used, alone or in combination with an aminoglycoside, to treat methicillin-resistant staphylococcal and enterococcal infections. Signalment, presenting complaint, history (including history of treatment for the current complaint), results of bacterial culture and antimicrobial susceptibility testing, treatment, and outcome were reviewed. The average vancomycin dosage was 7.5 mg/kg q8h, administered by intravenous infusion over 30 min. The infection resolved in all 7 horses with soft tissue infections and in 6 of the 8 horses with infections involving a bone or a joint, or both. No adverse effects of vancomycin therapy were noted. Although the number of cases is small, our findings suggest that vancomycin, alone or in combination with an aminoglycoside, is safe and effective for the treatment of resistant staphylococcal and enterococcal infections in horses and foals. However, owing to the importance of staphylococci and enterococci in human medicine and the problems with emerging resistance, we recommend that the use of vancomycin in horses be limited to cases in which culture and susceptibility results clearly indicate that this agent is likely to be effective and in which there is no reasonable alternative.

Résumé

Cette étude rapporte les résultats d'une étude rétrospective de 15 cas de poulains et de chevaux adultes où la vancomycine fut utilisée, seule ou en combinaison avec un aminoglycoside, pour traiter des infections associées à des staphylocoques résistants à la méthicilline et à des entérocoques. Le signalement, la raison de la consultation, l'histoire (incluant l'historique de traitement pour la présente consultation), les résultats de la culture bactérienne et des tests de sensibilité antimicrobienne, le traitement, et la résolution du cas ont été revus. La dose moyenne de vancomycine était de 7,5 mg/kg q8h, administrée par infusion intraveineuse sur une durée de 30 minutes. L'infection a été éliminée chez les 7 chevaux avec une infection des tissus mous et chez 6 des 8 chevaux avec une infection impliquant un os ou une articulation, ou les deux. Aucun effet adverse associé au traitement à la vancomycine n'a été noté. Bien que le nombre de cas soit petit, nos résultats suggèrent que la vancomycine seule ou en combinaison avec un aminoglycoside est sécuritaire et efficace pour le traitement des infections associées aux staphylocoques résistants et aux entérocoques chez les chevaux et les poulains. Toutefois, compte tenu de l'importance des infections associées avec les staphylocoques et les entérocoques en médecine humaine de même qu'avec l'émergence des isolats résistants, nous recommandons que l'utilisation de la vancomycine chez les chevaux soit limitée à des cas où les résultats de la culture et des tests de sensibilité indiquent clairement que cet antibiotique serait efficace et qu'il n'y a pas d'alternative raisonnable.

(Traduit par Docteur Serge Messier)

Introduction

Vancomycin is a narrow-spectrum bactericidal antibiotic that is active at clinically achievable levels against most species of gram-positive cocci and bacilli, including many antimicrobial-resistant staphylococci (*Staphylococcus aureus* and *S. epidermidis*) and enterococci (1–3). After its introduction in the late 1950s, vancomycin became the antimicrobial agent of choice for the treatment of serious staphylococcal infections in humans. It remains the drug of choice for serious staphylococcal and enterococcal infections that are resistant to other antimicrobial agents and for patients who cannot tolerate cephalosporins or penicillins (2).

The incidence of nosocomial infections caused by methicillin-resistant *S. aureus* (MRSA) and enterococci in humans is rising, in part because of the significant and increasing resistance of these organisms to antimicrobial agents, which allows them to survive in settings in which antimicrobial agents are heavily used (2–5). These organisms are resistant to all currently marketed β-lactam antibiotics (3), and many isolates are now resistant to aminoglycosides, tetracyclines, erythromycin, clindamycin, fluoroquinolones, and rifampin (3,6). Vancomycin is active against most strains of MRSA, although higher dosages may be needed against the strains that show intermediate resistance to it (3,7).

An increasing percentage of *S. epidermidis* strains are resistant to cephalosporins and semisynthetic penicillins, yet this organism is susceptible to vancomycin (3). Enterococci are intrinsically resistant to cephalosporins and penicillins. They are also intrinsically resistant to low dosages of clindamycin and aminoglycosides and are

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acquiring resistance to higher levels of these 2 antimicrobials (2,3,8–11). Most enterococcal isolates are susceptible to vancomycin, although resistance has been reported in strains of *Enterococcus faecium* and *E. faecalis* (2,3).

In recent years there have been several reports of MRSA infections in horses (12–15) and 1 report of methicillin-resistant *S. epidermidis* infection in a horse (16). These reports suggest that the incidence of resistant staphylococcal infections in horses is on the rise, which would parallel the situation in humans. Vancomycin may thus become an important weapon for veterinarians faced with resistant staphylococcal infections in horses.

The pharmacokinetics of intravenously (IV) administered vancomycin in serum and synovial fluid have been studied in horses (17). Trostle et al (16) recently reported on the successful treatment with vancomycin of methicillin-resistant *S. epidermidis* infection in a horse. However, to our knowledge there are no other clinical reports of vancomycin use in equine patients. This retrospective study presents the findings and outcomes in 15 horses with antimicrobial-resistant staphylococcal and enterococcal infections in which vancomycin was used, alone or in combination with other antimicrobial drugs.

Materials and methods

Case selection

The study group was selected from horses presented at the George D. Widener Hospital for Large Animals, at New Bolton Center, Chester County, Pennsylvania, between January 1986 and March 2004. Selection criteria included documentation of antimicrobial-resistant infection with *Staphylococcus* or *Enterococcus* spp., or both, and subsequent treatment with vancomycin (alone or in combination with other antimicrobials). Fifteen horses fit the study criteria.

The medical records were reviewed. Signalment, site of infection, treatment before referral, clinical findings on presentation, results of bacteriologic culture and antimicrobial susceptibility testing, treatment, and outcome were recorded for each case. When available, peak and trough serum vancomycin concentrations, measured by polarization immunoassay (17), and serum creatinine concentrations were included. The outcome was considered successful if treatment resulted in a negative culture for the *Staphylococcus* or *Enterococcus* spp. and no recurrence of infection after cessation of all antimicrobial treatment.

All the horses underwent physical examination daily during their hospital stay. In addition to observations, detailed subjective assessments of the patient's condition were reported daily in the hospital record. When clinically indicated, a complete blood count or serum biochemistry panel, or both, was obtained periodically.

Bacterial culture and susceptibility protocols

All samples were collected on sterile swabs and immediately placed in Stuart's transport medium. Specimens presented to the Clinical Veterinary Microbiology Laboratory of New Bolton Center, a laboratory accredited by the American Association of Veterinary Laboratory Diagnosticians (AAVLD), were processed for aerobic and anaerobic bacterial culture and antimicrobial susceptibility testing as soon as possible, usually within several hours of collection.

The collection swabs were used to inoculate 5% sheep blood agar (trypticase soy agar base), colistin–nalidixic acid, and MacConkey plates. Swabs from wounds or abscesses were placed in thioglycollate broth, in accordance with AAVLD-acceptable standard operating procedures (18,19).

All media were incubated at 37°C for 18 to 24 h. The next day, single colonies were marked and transferred to identical media; in addition, a Gram's stain of each colony was prepared for microscopic evaluation. The media were incubated as before and isolated colonies used to prepare the inoculum for an AP-90 biochemical characterization strip (Trek Diagnostic Systems, Westlake, Ohio, USA) or a bile esculin and NaCl agar slope. The identification protocol was changed during the study period to a system that allows speciation (with the AP-90); hence, speciation was available for only 1 isolate.

Antimicrobial susceptibilities were determined with a Sensititre breakpoint plate for gram-positive organisms (Trek Diagnostic Systems). The plate is constructed according to the recommendations of the National Committee for Clinical Laboratory Standards for isolates from veterinary specimens, in accordance with the animal species guidelines (20). Standard American Type Culture Collection strains were used monthly to reference the identification techniques and the susceptibility results.

Results

Signalment for the 15 horses is summarized in Table I; 2 cases represented readmissions. The horses ranged in age from 1 mo to 25 y at the time of presentation. The breeds represented, and the number of horses of each breed, were as follows: Thoroughbred (5), standardbred (3), warmblood (4), quarterhorse (2), and Appaloosa (1). There were 5 females, 5 intact males, and 5 castrated males.

In all but 2 horses, the presenting complaint involved a forelimb (7 horses) or a hindlimb (6 horses). In 7 horses, the infection was confined to a soft tissue structure (Table II); the lesions included cellulitis with abscess formation (periarticular infection in 2 horses), surgical wound infection, septic calcaneal bursitis, septic peritonitis, and inguinal abscess/cellulitis. In the other 8 horses, the infection involved an appendicular bone or joint, or both (Table III); the lesions included septic arthritis with associated osteomyelitis or septic physitis, osteomyelitis at the site of internal fixation of a comminuted long-bone fracture, osteitis with overlying cellulitis or wound infection, and isolated septic arthritis.

In 7 of the 15 horses (47%), the infection was associated with a recent surgical procedure: internal fixation of a comminuted long-bone fracture (2 horses), metacarpophalangeal joint arthrodesis, superior check desmotomy, removal of an avulsed bone fragment, colic surgery, or exploration of the inguinal canal. In 4 of the remaining 8 horses, the infection was associated with a known event or condition: external trauma, peripartum sepsis, urachitis and omphaloarteritis, or chronic laminitis. The source of infection was unknown in the other 4 horses.

Antimicrobial therapy had been initiated before presentation in 6 horses (Tables II and III): systemic therapy with penicillin and gentamicin or ceftiofur in 5 horses and trimethoprim–sulfamethoxazole in 1 horse. For the remaining 9 horses, prior

Table I. Signalment, history, and presenting complaint in 15 horses with antimicrobial-resistant staphylococcal and enterococcal infections treated with vancomycin

Case number	Age	Breed[a]	Sex[b]	History/presenting complaint[c]
1	3 y	TB	F	Abscess/cellulitis 10 cm proximal to surgical site 2 wk after arthrodesis of MCP joint
2	4 y	SB	M	Osteomyelitis after surgical fixation of comminuted fracture of MC3; septic tenosynovitis in contralateral hindlimb
3	3 y	TB	F	Osteitis and cellulitis of distal MC3
4	1 mo	TB	F	Septic arthritis of elbow with osteomyelitis of proximal radial epiphysis and metaphysis; urachitis and omphaloarteritis
5a	5 y	SB	MC	Septic arthritis of TMT joint unresponsive to multiple antimicrobials
5b				Readmission 2 mo after discharge with septic osteitis of T3
6a	1 d	SB	M	Born at 337 d gestation; peripartum asphyxia and sepsis
6b	5 wk			Readmission 2 wk after discharge with acute bilateral hindlimb lameness caused by septic physitis of distal MT3 and septic arthritis of tibiotarsal joint
7	11 y	WB	F	During pregnancy, 360° volvulus of large colon, necessitating large-colon resection; severe septic peritonitis postoperatively
8	2 y	QH	MC	Wound dehiscence 6 d after bilateral superior check desmotomy for bilateral SDFT deformity
9	25 y	App	MC	Chronic laminitis with recurrent infection; admitted with periarticular infection of distal interphalangeal joint
10	10 y	WB	MC	Septic calcaneal bursitis
11	4 mo	TB	M	Draining tract/cellulitis of medial aspect of forearm, involving radius
12	1 mo	QH	M	Wound infection 5 d after surgical treatment of avulsion fracture at origin of long digital extensor tendon
13	10 y	WB	F	Partial wound dehiscence/infection 3 wk after surgical fixation of open comminuted fracture of MT3
14	3 y	TB	M	Cellulitis/abscess of lateral aspect of hock, unresponsive to oral TMPS
15	5 y	WB	MC	Left inguinal abscess/cellulitis

[a] TB — Thoroughbred; SB — standardbred; WB — warmblood; QH — quarterhorse; App — Appaloosa

[b] F — female; M — male; MC — castrated male

[c] MCP — metacarpophalangeal; MC3 — third metacarpal bone; TMT — tarsometatarsal; T3 — third tarsal bone; MT3 — third metatarsal bone; SDFT — superficial digital flexor tendon; TMPS — trimethoprim–sulfamethoxazole

antimicrobial therapy was either not given (to 4) or not recorded (for 5).

For 9 horses, only gram-positive organisms were identified on culture: *Enterococcus* spp. (for 4), *Staphylococcus* spp. (for 3), or both (for 2). The remaining 6 horses had a mixed infection that involved 1 or both of these organisms in addition to gram-negative bacteria (primarily *Enterobacter* spp. or *Escherichia coli*).

The decision to use vancomycin was based on culture and sensitivity results indicating *Enterococcus* or *Staphylococcus* spp., or both, that were susceptible to vancomycin but not to any other available antibiotic. When indicated by culture and sensitivity results, vancomycin was combined with an aminoglycoside (amikacin or gentamicin).

In every case, the calculated dose of vancomycin was added to sterile saline or other fluids and infused IV over 30 min. The dosage was typically 7.5 mg/kg q8h, although it ranged from 7.5 mg/kg q12h to 12.5 mg/kg q12h. Thus, although most of the horses received 22.5 mg/kg daily, the total daily dose ranged from 15 to 25 mg/kg, depending on whether the drug was given every 8 or every 12 h. In 1 horse, the dosage was adjusted after measurement of the peak and trough serum vancomycin concentrations.

The average duration of therapy with vancomycin was 10 d (range, 5 to 45 d). No adverse effects were reported, even in the horse that received vancomycin for 45 d. Concurrent administration of an aminoglycoside caused no adverse effects in the 8 horses receiving this combination. A transient elevation in serum creatinine concentration in 1 horse receiving amikacin and vancomycin responded to an adjustment of the amikacin dosage and to diuresis.

Vancomycin was the sole antimicrobial agent for 7 of the 9 horses from which only *Enterococcus* or *Staphylococcus* spp., or both, were cultured. In all but 1 case, the infection resolved with a single course of systemic vancomycin therapy and, when indicated, surgical drainage or debridement. In the 1 case in which initial therapy did not resolve the infection (case 5), further treatment with vancomycin was required. During the initial therapy, the horse's condition improved, and at the time of hospital discharge a synovial fluid culture was negative. However, the horse was readmitted 2 mo later with severe septic osteitis; culture yielded MRSA. The horse gradually recovered after surgical debridement, placement of vancomycin-impregnated polymethylmethacrylate (PMMA) beads at the site of infection, and a second course of systemic vancomycin therapy.

In the other 2 cases in which *Staphylococcus* or *Enterococcus* spp., or both, were the only organisms cultured, gentamicin was given along with vancomycin. Treatment, which included surgical debridement, was successful.

Table II. Treatment and outcome for the 7 horses with soft tissue infection

Case number	Treatment history[a]	Culture results	Treatment regimen[a]	Outcome
1	Penicillin and gentamicin	Gram-negative rods and *Enterococcus* spp.	Amikacin and vancomycin (7.5 mg/kg q12h) for 10 d	Recovered: infection resolved; MCP joint fused
7	Not recorded	*Enterococcus* spp. and *Escherichia coli* isolated from peritoneal fluid and incision site	Amikacin and vancomycin for 5 d; at discharge, therapy changed to TMPS for 14 d	Recovered from infection but euthanized when incision dehisced during unrestricted activity 3 wk after surgery
8	Not recorded	*Staphylococcus aureus, E. coli, Enterobacter cloacae, Pseudomonas aeruginosa*, α-hemolytic *Streptococcus* sp., and *Enterococcus* spp. isolated from right forelimb incision; *Staphylococcus* spp. susceptible only to vancomycin isolated from left forelimb	Penicillin and gentamicin; culture 7 d later yielded *P. aeruginosa* and *Klebsiella oxytoca* from right incision and *S. aureus* from left incision; on basis of susceptibility results, treatment changed to amikacin and vancomycin for 5 d	Recovered: rapid clinical improvement after therapy with amikacin and vancomycin
9	Not recorded	*S. aureus* susceptible only to vancomycin	Surgical debridement; vancomycin for 10 d	Recovered: negative culture 72 h after completion of therapy
10	Not recorded	*Enterococcus* spp. susceptible only to vancomycin	Surgical debridement; vancomycin	Infection resolved but laminitis in opposite limb necessitated euthanasia
14	Oral TMPS	MRSA	Systemic vancomycin	Recovered: horse raced successfully
15	Penicillin and gentamicin	*Enterococcus faecium* susceptible only to vancomycin; *E. coli* susceptible to amikacin	Systemic vancomycin and amikacin	Recovered: rapid clinical improvement after treatment with amikacin and vancomycin

[a] Unless otherwise stated, dosages were as follows: amikacin, 6.6 mg/kg IV q8h; ampicillin, 15 mg/kg IV q8h; ceftiofur, 2.2 mg/kg IV q12h; erythromycin, 44 mg/kg orally q6h; gentamicin, 2.2 mg/kg IV q8h; potassium penicillin G, 22 000 IU/kg IV q6h; rifampin, 2.5 mg/kg orally q6h; TMPS, 15 mg/kg orally q12h; vancomycin, 7.5 mg/kg IV q8h (infused over 30 min)
MRSA — methicillin-resistant *S. aureus*

Thus, vancomycin, alone or in combination with an aminoglycoside, was ultimately effective in all 9 cases in which staphylococci or enterococci were the only organisms isolated.

In the 6 cases involving mixed gram-positive and gram-negative infections, vancomycin was used in combination with amikacin and, when indicated, surgical drainage or debridement. In 4 of these cases (67%), the infection resolved. The remaining 2 cases are discussed below as treatment failures.

The infection resolved in all 7 horses with soft tissue infections (Table II) and in 6 of the 8 horses (75%) with infection involving a bone or a joint, or both (Table III). Overall, 11 horses (73%) recovered satisfactorily from the infection and associated lesions. The other 4 horses (27%) were euthanized because of treatment failure (2 foals) or for reasons not directly related to the infection (2 horses). A mare recovered from postoperative septic peritonitis only to experience wound dehiscence during unrestricted activity 3 wk after the surgery, and in a gelding with septic calcaneal bursitis, laminitis developed in the opposite limb. In both cases the infection was deemed to have resolved at the time of euthanasia.

The 2 cases considered vancomycin treatment failures (cases 6 and 12) involved infection of a bone or a joint, or both, in a young foal. Initial clinical improvement after commencement of vancomycin therapy was followed by the return of lameness or deterioration of the foal's condition, ultimately prompting euthanasia in both cases.

In case 6, the foal had asphyxia and sepsis in the first 24 h of life. Radiographic evidence of septic physitis of the distal third metatarsal bone was also noted. After 2 wk of antimicrobial therapy, culture of the physis yielded *Enterococcus* spp. The antibiotics were replaced with vancomycin and amikacin, and the physis was stabilized with pins and a cast. Despite initial improvement, the foal's condition deteriorated, prompting euthanasia. Necropsy revealed multiple abscesses in the physis.

The other foal was approximately 1 mo of age at initial presentation (case 12). A wound infection had developed 5 d after surgical removal of an avulsed bone fragment at the origin of the long digital extensor tendon. Culture yielded *E. coli, Enterococcus* spp., and a coagulase-negative *Staphylococcus* sp. The *E. coli* isolate was

Table III. Treatment and outcome for the 8 horses with bone or joint infection

Case number	Treatment history[a]	Culture results	Treatment regimen[a]	Outcome
2	Not recorded	*Enterococcus* spp.	Surgical drainage and debridement; vancomycin for 45 d, with dosage adjusted on basis of peak and trough serum levels from 7.5 to 10 and then 12.5 mg/kg IV q12h	Recovered: infections resolved, fracture considered healed radiographically 7 mo after injury
3	Not recorded	Coagulase-positive *S. aureus* and *Enterococcus* spp.	Surgical debridement; gentamicin and vancomycin (7.5 mg/kg IV q12h) for 5 d	Recovered; no further problems
4	Surgical resection of umbilical remnants, arthroscopic debridement and lavage of elbow; penicillin and gentamicin pending culture results	*Enterococcus* spp. isolated from umbilical artery; synovial fluid cultures negative	Antimicrobial therapy changed to erythromycin and rifampin and then to vancomycin and gentamicin because of poor clinical response; vancomycin given for 10 d	Recovered: BAR and afebrile within 24 h of start of vancomycin therapy; incisions and joint lesions healed uneventfully; horse healthy and sound 4 y later
5a	Arthrotomy for culture and debridement; penicillin and gentamicin pending culture results	*S. aureus* with limited susceptibility	Vancomycin for 10 d; discharged on 6-wk regimen of TMPS and rifampin	Improved initially; readmitted 2 mo later (case 5b)
5b	See treatment regimen of case 5a	MRSA	Surgical debridement, placement of vancomycin-impregnated PMMA beads; vancomycin IV; PMMA beads removed 3 wk later; discharged on oral TMPS regimen	Recovered: fully weight-bearing at time of discharge; no recurrence of lameness
6a	Colostrum, fluids and hyperimmune plasma given IV; oxygen given intranasally; ceftiofur and penicillin	*Enterobacter cloacae* cultured from nasotracheal tube	Amikacin added to regimen; discharged at 3 wk of age on ceftiofur, amikacin, and sucralfate (10 mg/kg orally q6h)	Improved initially; readmitted 2 wk later (case 6b)
6b	See treatment regimen of case 6a	*Enterobacter agglomerans* and *Clostridium* spp. isolated from physis; repeat culture yielded *Enterococcus* spp.	Curettage of distal MT3 physis; ceftiofur and amikacin; little improvement after 2 wk; when repeat culture yielded *Enterococcus* spp., therapy changed to vancomycin and amikacin; physis stabilized with pins and external coaptation	Improved initially, then deteriorated; euthanized; necropsy revealed multiple abscesses in distal MT3 physis
11	Not recorded	*S. aureus* (coagulase-positive, penicillin-resistant) and *Enterococcus* spp.	Surgical debridement; vancomycin for 12 d	Recovered: no further problems reported
12	Not recorded	*E. coli, Enterococcus* sp., and coagulase-negative *Staphylococcus* sp.	Wound drained; amikacin (15 mg/kg IV q24h) and vancomycin	Improved initially, but lameness and drainage persisted; euthanized; necropsy revealed necrotizing cellulitis, myositis, and fibrinous septic arthritis
13	Not recorded	*Enterococcus* spp. susceptible only to vancomycin	Vancomycin for 10 d	Recovered; 1 bone plate removed

[a] As in Table II

BAR — bright, alert, and responsive; PMMA — polymethylmethacrylate

susceptible to amikacin, and the other 2 isolates were susceptible to vancomycin. Treatment with amikacin and vancomycin was begun. The foal's condition initially improved; however, persistent lameness and wound infection ultimately prompted euthanasia. Necropsy revealed fibrinous septic arthritis with adjacent necrotizing cellulitis and myositis.

Peak and trough serum vancomycin concentrations during therapy were reported for 3 horses. The serum creatinine concentration, measured periodically during vancomycin therapy in all 15 horses, remained within the normal range for our laboratory (0.6 to 1.8 mg/dL) in all but 1 horse.

In 1 horse receiving vancomycin (7.5 mg/kg IV q8h) and amikacin (6.6 mg/kg IV q8h) concurrently, the peak and trough serum vancomycin concentrations 4 d after the start of therapy were 37.0 and 2.3 mg/L, respectively. The serum creatinine concentrations remained within the normal range during the 10 d of combination therapy.

In another horse receiving vancomycin (7.5 mg/kg IV q12h) and amikacin (19.8 mg/kg IV q24h) concurrently, the peak and trough serum vancomycin concentrations 3 d after the start of therapy were 45.0 and 4.4 mg/L, respectively. The 30-min peak serum amikacin concentration was 55 mg/L and the 12-h trough 5.6 mg/L (recommended trough, 2 to 5 mg/L). The serum creatinine concentration that day was more than 3.0 mg/dL. After an adjustment in the amikacin dosage and 48 h of fluid therapy IV, the serum creatinine concentration was again within the normal range.

In the 3rd horse, the peak and trough serum vancomycin concentrations were used to determine the most appropriate dosage of vancomycin. Therapy began with 7.5 mg/kg IV q12h. On the basis of the serum concentrations, the dosage was increased to 10 mg/kg IV q12h and then to 12.5 mg/kg IV q12h, at which point the peak and trough concentrations were 45.7 and 5.5 mg/L, respectively. The serum creatinine concentration, monitored every 3 d during the 45 d of vancomycin therapy in this horse, remained within the normal range.

Discussion

Although the number of cases in this study is relatively small, our findings suggest that vancomycin, alone or in combination with an aminoglycoside, is safe and effective for the treatment of resistant staphylococcal and enterococcal infections in horses and foals. Of course, systemic antibiotic therapy was only part of the overall treatment regimen, which included surgical drainage or debridement when warranted. In 1 case, systemic vancomycin therapy was augmented with local use of vancomycin-impregnated PMMA beads.

In only 2 cases was the infection not resolved by using vancomycin as part of the treatment regimen. Both cases were in foals with serious infections involving physeal cartilage or articular structures, or both. Initial improvement was noted in both cases once vancomycin therapy was instituted. However, persistence or deterioration of the foal's condition ultimately prompted euthanasia. The extent of physeal or articular damage found at necropsy suggests that either the damage was advanced before vancomycin therapy was initiated or that vancomycin does not penetrate well into infected physeal cartilage or articular tissues.

Therapeutic concentrations of vancomycin can be achieved and maintained in synovial fluid after IV administration in healthy horses (17). However, the concurrence of severe osseous or physeal lesions (multiple physeal abscesses) or severe joint disease (fibrinous septic arthritis) may have limited delivery of the drug to the site(s) of infection in these 2 foals. Vancomycin is effective in the treatment of acute hematogenous osteomyelitis caused by MRSA in children (21). In at least 1 of the foals (case 6), failure of passive transfer of immunity may have contributed to the establishment of what proved to be a polymicrobial infection, as this foal was septic at 24 h of age.

The 1 adult horse in which the initial course of vancomycin failed to resolve the infection (case 5) also had severe bone and joint involvement. In that case, and in a case reported by Trostle et al (16) in which a methicillin-resistant *S. epidermidis* infection developed at the site of fracture repair, surgical drainage and implantation of vancomycin-impregnated PMMA beads were necessary to resolve the infection with this vancomycin-sensitive organism. Thus, it may be prudent to augment systemic therapy with some form of local vancomycin delivery when severe infection with a resistant staphylococcal or enterococcal organism involves a bone or joint.

Most strains of MRSA and enterococci are susceptible to vancomycin. However, vancomycin resistance in these important pathogens is an increasing concern in human medicine (2,3). Vancomycin-intermediate *S. aureus* (VISA) strains have been reported in humans (2,3,7,22), and vancomycin-resistant enterococci (VRE) are widely reported in humans and farm animals, including horses (23–28). Of perhaps even more concern, vancomycin-resistant strains of *S. aureus* (VRSA) have begun to emerge (29–32).

For strains that are intermediate or frankly resistant to vancomycin, the minimum inhibitory concentration (MIC) or minimum bactericidal concentration (MBC) of vancomycin is high. Reported MIC/MBC values of vancomycin against VISA strains, for example, range from 6/6 to 8/12 mg/L (2,7). The MIC of vancomycin against VRE in farm animals may be 256 mg/L or more (23).

Thus, a further consideration when faced with apparent treatment failure is resistance, or at least intermediate susceptibility, of the causal organism(s) to vancomycin. To date, no clinical cases involving confirmed isolates of VISA, VRSA, or VRE in horses have been reported. Nevertheless, veterinarians should be mindful of the existence of these organisms and their increasing prevalence in the human population.

Unfortunately, MIC and MBC values were not determined for the *Staphylococcus* and *Enterococcus* isolates in the current study. In an earlier study, we found that the MIC of vancomycin for all clinical isolates of *S. aureus* cultured from equine patients in our hospital was 1 mg/L (17). The MBCs were not greatly different, the range being 1 to 4 mg/L, with 5 of 6 isolates having MBCs of 2 mg/L or less. The MIC of vancomycin for isolates of several *Enterococcus* spp. ranged from 0.5 to 2 mg/L; for 3 of 5 isolates the MIC was 1 mg/L or less. However, for all but 1 isolate, the MBC was at least 8 mg/L (range, 0.5 to >16 mg/L).

A similar divergence between MIC and MBC exists for penicillin G, cephalosporins, and other commonly used antibiotics to which enterococcal or staphylococcal resistance has developed (1). The MBC of the pathogen is thus an important consideration in

determining the vancomycin dosage and deciding whether to use another antimicrobial agent concurrently.

In our earlier study, we concluded that a vancomycin dosage of 4.3 to 7.5 mg/kg q8h, infused IV over 60 min, would result in peak and trough plasma vancomycin concentrations of 24 to 38 and 2 to 5 mg/L, respectively, and would maintain the synovial vancomycin concentration above 2 mg/L. These trough values met or exceeded the MIC for clinical isolates of *S. aureus* and *Enterococcus* spp. cultured at that time from horses in our hospital and would have been bactericidal for most of the *S. aureus* isolates tested in that study.

However, that study was published in 1992. As in human medicine, it is possible that VISA has made its way into the equine population since that time. Commonly used laboratory methods for determining antimicrobial susceptibility may be inadequate for detecting reduced susceptibility of *S. aureus* to vancomycin (22,33). This fact must also be considered when the clinical response to vancomycin used against an apparently susceptible organism is less than expected.

It could be argued that the case in which laminitis developed in the opposite limb (case 10) constitutes a treatment failure, as the ultimate outcome was euthanasia. However, the antibiotic-resistant enterococcal infection resolved, the criterion for a successful outcome of vancomycin therapy in this study. Also, the development of contralateral laminitis may have been inevitable, the chain of events having begun long before the horse was presented.

According to Peloso et al (34), clinical manifestations of laminitis in the weight-bearing limb may not become apparent until 3 to 6 wk after the onset of severe unilateral lameness, even though lamellar damage in the weight-bearing foot likely begins within hours of constant loading (35). Certainly, prompt resolution of the primary lameness is an essential component of preventing and managing contralateral limb laminitis. Unfortunately, time was not on our side in this case.

It could also be argued that the mare whose celiotomy incision dehisced 3 wk after colic surgery (case 7) constituted a treatment failure. But, again, the infection resolved before hospital discharge, so antibiotic therapy was considered successful. The mare was euthanized because the owner failed to restrict the mare's activity while the body wall was still compromised.

According to the daily physical examination and subjective assessments, as well as the periodic complete blood count and serum biochemistry panel, no adverse effects of vancomycin therapy were noted in any of the horses and foals, even with prolonged use or when an aminoglycoside was administered concurrently. Adverse effects of vancomycin in humans include ototoxicity (neurotoxicity primarily involving the auditory nerve), nephrotoxicity, thrombophlebitis after IV administration, fever, and an allergic reaction commonly referred to as "red neck" or "red man" syndrome (a pruritic erythematous or maculopapular rash involving the face, neck, and upper torso, accompanied in some cases by hypotension) after rapid IV administration (1,2,36). Impurities in early preparations of vancomycin are believed to be responsible for many of the adverse effects in the initial reports (1,37).

Nephrotoxicity and ototoxicity caused by vancomycin reportedly occur in approximately 5% of patients and perhaps only when trough serum concentrations exceed 10 mg/L (1,38) or when peak serum concentrations exceed 80 mg/L. In the horses in which serum vancomycin concentrations were recorded, trough levels were 5.5 mg/L or less and peak levels were 45 mg/L or less, both well below the suggested toxic levels in humans.

In our earlier study on the pharmacokinetics of IV vancomycin in horses, no adverse effects were noted in any of the 5 healthy horses used in the study, despite the fact that peak plasma vancomycin concentrations exceeded 75 mg/L in those receiving 15.4 mg/kg IV (17). However, ototoxicity (manifested as hearing loss) could easily be missed in horses. In human patients, ototoxicity has been reported at vancomycin concentrations as low as 25 mg/L. For this reason, we suggest that care be taken when using a vancomycin dosage greater than the recommended dosage of 4.3 to 7.5 mg/kg IV q8h (17).

Synergism between vancomycin and aminoglycosides has been reported against enterococci (11) and more recently against VISA (7). This effect appears to be the result of increased aminoglycoside uptake in the presence of vancomycin, a cell-wall-active agent (3). However, the clinical value of these observations is tempered by the possibility that the toxic effects of vancomycin and aminoglycosides may be additive (1,39).

In humans, the frequency of nephrotoxicity and ototoxicity with vancomycin may increase when aminoglycosides are administered concurrently. In fact, it is possible that the reported toxicity of vancomycin is primarily attributable to concurrent administration of an aminoglycoside (40). In all but 1 of the horses in our study, including several that were receiving an aminoglycoside concurrently, the serum creatinine concentration remained within the normal range for our laboratory throughout vancomycin therapy. In 1 horse that was receiving vancomycin and amikacin concurrently, a transient increase in the serum creatinine concentration was resolved by an adjustment in the amikacin dosage and 48 h of diuresis.

Although the vancomycin dosages used in our study, and the concurrent administration of an aminoglycoside, appeared to be safe, vancomycin is principally eliminated by the kidneys. Thus, it should be used with caution in patients with compromised renal function. Monitoring of the serum creatinine concentration and, if possible, the peak and trough serum vancomycin concentrations, is recommended when using vancomycin in horses with renal insufficiency (17).

In almost 50% of the cases in our study, infection occurred at the site of a recent surgical procedure. These data support the suggestion of Hartmann, Trostle, and Klohnen (12) that MRSA should be considered in horses with postoperative *S. aureus* infections that do not respond to routine antimicrobial treatment. We would add that resistant enterococci should also be considered when dealing with serious postoperative gram-positive infections. Bacterial culture and sensitivity testing are advised in any case that does not respond to therapy as expected.

In at least 4 other cases in our study, it is conceivable that the infection resulted from human intervention of some other type, such as wound management or handling of the neonatal foal's umbilicus. In a recent report of an outbreak of MRSA in a veterinary teaching hospital, the microbiologic, biochemical, and genetic characteristics of the equine isolates were compared with those of isolates cultured

from the nasal cavities of hospital staff members. It was concluded that the hospital staff were likely the primary source of the equine infections (14).

Because MRSA has become such a common pathogen, and treatment options are limited, good hygiene should always be practised when handling equine wounds and other breaks in the integument, for the protection of both the human caregiver and the equine patient. In noting the increasing reports of MRSA infections in horses, veterinarians, and equine personnel, Weese (15) urged the institution of appropriate surveillance and other infection control measures in an attempt to limit the impact of MRSA in veterinary medicine.

The following observations by Mascaretti (3) are sobering: "MRSA has become one of the most important nosocomial pathogens worldwide and poses serious infection control problems because of its tendency to accumulate additional unrelated resistance determinants and incorporate them into its genome. The adaptability and quick response of MRSA strains to antibiotic selection has led, in less than 40 years, to the evolution of strains that are multiresistant to many antibiotics, including in many cases glycopeptides such as vancomycin and teicoplanin."

In an effort to slow the spread of vancomycin-resistant bacteria, the American Medical Association has recommended that the use of intravenous vancomycin be restricted to serious infections caused by susceptible gram-negative bacteria when other antibiotics are ineffective or not tolerated (3). It would be prudent for the veterinary profession to follow suit. We thus recommend that vancomycin use in horses be limited to only those situations in which culture and susceptibility results clearly indicate that vancomycin is likely to be effective and for which there are no other reasonable alternatives.

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