Enterobacteriaceae (except Proteus, Providencia and Morganella) with reduced susceptibility (<23 mm inhibition zone diameter or MIC >1 mg/L) to any of the carbapenems (ertapenem, imipenem, meropenem) will be tested for the carbapenemase phenotype by the combined disc method (with EDTA or boronic acid). All strains with a positive phenotype will be sent to a reference laboratory for molecular testing. Hence, implementation of the new CLSI criteria would not simplify the laboratory testing and reporting procedure in our locality.

Although susceptibility of Proteus spp., Providencia spp. and M. morganii to imipenem is recognized to be lowered and could be caused by mechanisms other than carbapenemase production, the extent of the effect that applying the new interpretive criteria would have on clinical isolates has not been previously described. Here, we showed that susceptibility categorization for this group of organisms could change by up to 61.4%. Laboratories that choose to implement the new criteria should clearly inform infection control personnel so that there will not be any misunderstanding of outbreak occurrence.

In conclusion, this study showed that applying the new CLSI criteria to interpret carbapenem susceptibility in Enterobacteriaceae would drastically change the susceptibility rates for some isolate groups. Furthermore, the FDA-approved breakpoints have not been changed. This explains why many clinical laboratories continue to use the old breakpoints and perform phenotypic testing for carbapenemase production. Our findings emphasize the need to obtain more clinical outcome data.

**Funding**

This study was supported by a block grant from the Research Fund for the Control of Infectious Diseases (RFCD) of the Health and Food Bureau of the Hong Kong SAR Government.

**Transparency declarations**

None to declare.

**References**


was employed. Three days later, a combined liver–kidney transplant was performed. Repeat culture of the peritoneal fluid grew *E. faecium* with a daptomycin MIC by Etest of 16 mg/L. Confirmation showed a daptomycin MIC of 8 mg/L by broth microdilution and Etest (Table 1). Therapy was changed to 600 mg of linezolid intravenously every 12 h, but the patient expired after 6 days of treatment.

A third patient with acute myelogenous leukaemia received seven daily doses of 6 mg/kg daptomycin for abdominal wall cellulitis and a small, superficial abscess (whose drainage was later reported as growing only *Pseudomonas aeruginosa*). Five months later the patient was admitted with a draining ulcer on the abdomen and treated with 6 mg/kg daptomycin daily. Culture of the drainage grew DNSE (daptomycin MIC ≥16 mg/L by Etest). Confirmation revealed a daptomycin MIC of 32 mg/L by broth microdilution and 16 mg/L by Etest (Table 1). Therapy with 600 mg of linezolid orally twice daily for 14 days was completed uneventfully.

Daptomycin non-susceptibility among enterococci has rarely been reported. From the Daptomycin Surveillance Program, 99% of 203 vancomycin-susceptible *E. faecium* isolates and 99.7% of 640 vancomycin-non-susceptible *E. faecium* isolates were susceptible to daptomycin (with an MIC ≤4 mg/L), with the highest recorded MIC of 8 mg/L being seen for only four strains. In a recent literature review estimated the prevalence of daptomycin non-susceptibility among enterococci at 0.6%; however, several *E. faecium* isolates were shown by chromosomal testing to be clonally related. In this review, eight patients with DNSE were reported to have received a mean of 32.3 days of daptomycin exposure prior to the isolation of DNSE. Outcomes were documented in only eight cases of DNSE infection, with none achieving a clinical or microbiological cure despite treatment with alternative therapy.

All three of our isolates were *E. faecium*. Each had chromosomal DNA isolated, digested with the restriction enzyme Smal and analysed by PFGE. The isolates were found to be clonally unrelated and unique strains that had acquired daptomycin non-susceptibility.

While the mechanism of daptomycin non-susceptibility in enterococci has not been well characterized and no spontaneously resistant mutants of *E. faecium* have been isolated in vitro, alterations in genes for cardiolipin may be important. Factors that may influence the development of daptomycin non-susceptibility include a lengthy exposure to the drug, deep-seated infections with a heavy bacterial load and limited drug penetration, altered pharmacokinetics in some immunocompromised patients and inadequate dosing schedules due to renal replacement therapy. Each of our patients had at least one of the factors, including factors that could have resulted in the underdosing of daptomycin. Two patients had malignancies and one underwent SLED. Bubalo et al. determined that, in comparison with healthy volunteers, cancer patients had reductions in both the $C_{\text{max}}$ and $AUC_{0-\infty}$ of daptomycin while the volume of distribution and total clearance were increased. Few data are available on daptomycin dosing in extended dialysis, but two studies examining SLED and the clearance of daptomycin suggested that dosing daptomycin every 48 h would result in significant underdosing.

Until there is a better understanding of the mechanisms of altered daptomycin susceptibility, clinicians should be aware of its uncommon existence. Possible strategies to minimize its development could include limiting lengthy and repeated courses of the drug unless absolutely necessary, using higher doses in complicated infections or neutropenic patients with fever, or increasing the frequency of dosing in patients undergoing slow extended daily dialysis.

### Funding

This work was supported by Cubist Pharmaceuticals, Inc., who provided the confirmatory susceptibility testing and chromosomal analysis.

### Transparency declarations

K. H. is an employee and shareholder of Cubist Pharmaceuticals, Inc. All other authors have no declarations.

This work was reviewed and approved for submission by Cubist Pharmaceuticals, Inc.; however, the design, findings, conclusions and opinions are those of the authors and not of Cubist Pharmaceuticals, Inc.

### References


Telavancin for the treatment of methicillin-resistant Staphylococcus aureus osteomyelitis

Jennifer D. Twilla1,2, Michael S. Gelfand1,3*, Kerry O. Cleveland1,3 and Justin B. Usery1,2

1Methodist University Hospital, Memphis, TN, USA; 2Department of Clinical Pharmacy, University of Tennessee Health Science Center, Memphis, TN, USA; 3Department of Medicine, Division of Infectious Diseases, University of Tennessee Health Science Center, Memphis, TN, USA

*Corresponding author. Tel: +1-901-448-5770; Fax: +1-901-448-5940; E-mail: kcleveland@uthsc.edu

Keywords: vancomycin, linezolid, daptomycin, tigecycline, lipoglycopeptide

Sir,

With a rapid increase in invasive infections caused by methicillin-resistant Staphylococcus aureus (MRSA), there is a demand for antimicrobials with enhanced activity against MRSA. The concentration-dependent, bactericidal lipoglycopeptide telavancin was approved in 2009 for treatment of complicated skin and skin-structure infections due to susceptible organisms. The emergence of glycopeptidase resistance and clinical failures of vancomycin therapy in invasive MRSA infections, including osteomyelitis, has led to the unlabelled use of alternatives to vancomycin for treatment of these infections. We report four patients with MRSA osteomyelitis who failed standard vancomycin therapy and were successfully retreated with telavancin and surgical intervention.

A patient was admitted with inability to ambulate for 1 day. This was preceded by a 4 day history of progressive leg weakness and a 2 month history of lower back pain. There also was a history of multiple carbuncles of the face, neck and buttocks, but no antimicrobial therapy had been administered for these. No fever was present. White blood cell (WBC) count, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were elevated. Magnetic resonance imaging (MRI) revealed T4–7 vertebral osteomyelitis as well as T5–6 diskitis with an anterior epidural phlegmon and stenosis with spinal cord compression.

With the sudden onset of leg weakness and urinary incontinence was transferred from another hospital after a lengthy hospitalization with MRSA bacteraemia (vancomycin MIC 1 mg/L, linezolid MIC 2 mg/L and daptomycin MIC ≤0.5 mg/L) from cellulitis complicated by sepsis, respiratory failure with pneumonia, renal dysfunction and hepatic encephalopathy. Despite sequential treatment with adequate doses of vancomycin (14 days), linezolid (7 days) and daptomycin (14 days), the MRSA bacteraemia persisted with unchanged MIC values.

Fever was absent. WBC, ESR and CRP values were elevated. Transthoracic echocardiography and transesophageal echocardiography (TOE) did not reveal valvular vegetations. MRI showed an epidural abscess extending from T6 to L2, L1 vertebral osteomyelitis and a left psoas abscess. Telavancin 10 mg/kg iv daily was begun.

A patient with the sudden onset of leg weakness and urinary incontinence was transferred from another hospital after a lengthy hospitalization with MRSA bacteraemia (vancomycin MIC 1 mg/L, linezolid MIC 2 mg/L and daptomycin MIC ≤0.5 mg/L) from cellulitis complicated by sepsis, respiratory failure with pneumonia, renal dysfunction and hepatic encephalopathy. Despite sequential treatment with adequate doses of vancomycin (14 days), linezolid (7 days) and daptomycin (14 days), the MRSA bacteraemia persisted with unchanged MIC values.

Fever was absent. WBC, ESR and CRP values were elevated. Transthoracic echocardiography and transesophageal echocardiography (TOE) did not reveal valvular vegetations. MRI showed an epidural abscess extending from T6 to L2, L1 vertebral osteomyelitis and a left psoas abscess. Telavancin 10 mg/kg iv daily was begun.

T6–7 decompressive laminectomy was performed and the abscess was evacuated. Cultures of the blood and abscess grew MRSA with unchanged MIC values of vancomycin, linezolid and daptomycin. Telavancin MIC was 0.25 mg/L.

Telavancin was administered for 8 weeks with improvement in leg weakness and normalization of WBC, ESR and CRP values. There was no evidence of recurrence 7 months after completion of telavancin.

A patient presented with a 1 week history of right hip pain after a fall. Fever and leucocytosis were present. There was a remote history of a gunshot wound to the right hip.

CT revealed a 2 cm mass in the left upper lung and a large right hip effusion. MRI was consistent with right hip septic arthritis and osteomyelitis of the right acetabulum, femoral head, femoral neck and lesser trochanter. Blood cultures grew MRSA (vancomycin MIC 1 mg/L, linezolid MIC 1 mg/L and daptomycin MIC ≤0.5 mg/L). Ceftriaxone 2 g iv daily and vancomycin 13 mg/kg iv every 12 h were begun and continued for 5 days.

Telavancin for the treatment of methicillin-resistant Staphylococcus aureus osteomyelitis

Jennifer D. Twilla1,2, Michael S. Gelfand1,3, Kerry O. Cleveland1,3* and Justin B. Usery1,2

1Methodist University Hospital, Memphis, TN, USA; 2Department of Clinical Pharmacy, University of Tennessee Health Science Center, Memphis, TN, USA; 3Department of Medicine, Division of Infectious Diseases, University of Tennessee Health Science Center, Memphis, TN, USA

*Corresponding author. Tel: +1-901-448-5770; Fax: +1-901-448-5940; E-mail: kcleveland@uthsc.edu

Keywords: vancomycin, linezolid, daptomycin, tigecycline, lipoglycopeptide

Sir,

With a rapid increase in invasive infections caused by methicillin-resistant Staphylococcus aureus (MRSA), there is a demand for antimicrobials with enhanced activity against MRSA. The concentration-dependent, bactericidal lipoglycopeptide telavancin was approved in 2009 for treatment of complicated skin and skin-structure infections due to susceptible organisms. The emergence of glycopeptidase resistance and clinical failures of vancomycin therapy in invasive MRSA infections, including osteomyelitis, has led to the unlabelled use of alternatives to vancomycin for treatment of these infections. We report four patients with MRSA osteomyelitis who failed standard vancomycin therapy and were successfully retreated with telavancin and surgical intervention.

A patient was admitted with inability to ambulate for 1 day. This was preceded by a 4 day history of progressive leg weakness and a 2 month history of lower back pain. There also was a history of multiple carbuncles of the face, neck and buttocks, but no antimicrobial therapy had been administered for these. No fever was present. White blood cell (WBC) count, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were elevated. Magnetic resonance imaging (MRI) revealed T4–7 vertebral osteomyelitis as well as T5–6 diskitis with an anterior epidural phlegmon and stenosis with spinal cord compression.

Telavancin was administered for 8 weeks with improvement in leg weakness and normalization of WBC, ESR and CRP values. There was no evidence of recurrence 7 months after completion of telavancin.

A patient presented with a 1 week history of right hip pain after a fall. Fever and leucocytosis were present. There was a remote history of a gunshot wound to the right hip.

CT revealed a 2 cm mass in the left upper lung and a large right hip effusion. MRI was consistent with right hip septic arthritis and osteomyelitis of the right acetabulum, femoral head, femoral neck and lesser trochanter. Blood cultures grew MRSA (vancomycin MIC 1 mg/L, linezolid MIC 1 mg/L and daptomycin MIC ≤0.5 mg/L). Ceftriaxone 2 g iv daily and vancomycin 13 mg/kg iv every 12 h were begun and continued for 5 days.