# Meticillin-resistant *Staphylococcus aureus* pneumonia

***Meticillin-resistant* Staphylococcus aureus *causes an evolving clinical presentation of pneumonia. Health-care-acquired infection differs from community-associated disease, with important implications for treatment. Current antibiotics are less than ideal, and broader management strategies are crucial to prevent complacency.***

Although meticillin-resistant *Staphylococcus aureus* infection has declined markedly in the UK over the last 5 years, meticillin-resistant *S. aureus* pneumonia remains an important clinical entity (Health Protection Scotland, 2011; Health Protection Agency, 2012). The epidemiology of *S. aureus* pneumonia has been slowly changing over the last 25 years. Historically, *S. aureus* was considered to be an uncommon cause of community-acquired pneumonia accounting for less than 5% of all infections, and usually occurring in patients post influenza (Rogers, 1962). It was also recognized as an infrequent, although important cause of cases of hospital-acquired pneumonia, particularly among elderly patients (Oswald et al, 1958).

Several factors have influenced the pattern of disease seen today. First, the population in developed nations has become older, and expectations have been raised as a result of advances in health care. Prolonged ventilation of an aging and often chronically ill population has become much more commonplace. As a result of extensive invasive procedures, intensive care patients are known to be much more susceptible to infection (Brun-Buisson et al, 1995). Second, for a variety of reasons, including the increased use of antibiotics, resistance in *S. aureus* has also become an important problem globally. However, the prevalence rate of meticillin resistance in *S. aureus* varies greatly, not only worldwide, but even within Europe, with figures of <2% reported in the Netherlands to 54.4% in Portugal (Que and Moreillon, 2010). In the United States and Europe today, meticillin-resistant *S. aureus* accounts for 20–40% of all hospital-acquired pneumonia and ventilator-associated pneumonia (Rubinstein et al, 2008). Important increases in community-acquired meticillin-resistant *S. aureus* pneumonia are a significant addition to this disease burden (Salgado et al, 2003).

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## Hospital-acquired, health-care-associated and ventilator-associated pneumonia

Until recently meticillin-resistant *S. aureus* was confined to the hospital environment. There is a distinct aetiology between health-care-associated meticillin-resistant *S. aureus* strains and those found in the community. Health-care-associated meticillin-resistant *S. aureus* strains are usually described as containing the staphylococcal cassette chromosome (SCC) *mec* types I–III. These SCC*mec* types are resistance islands, and in health-care-associated meticillin-resistant *S. aureus* are quite large and confer resistance to many antimicrobial classes. These include the macrolides, lincosamides, tetracyclines, quinolones and sometimes the aminoglycosides.

Infectious Diseases Society of America guidelines described a new category of pneumonia, health-care-associated pneumonia (American Thoracic Society and the Infectious Diseases Society of America, 2005). In the USA, health-care-associated pneumonia appears to be similar in aetiology to hospital-acquired pneumonia and ventilator-associated pneumonia, with a considerable proportion of resistant organisms and increased mortality. In the UK and Europe, although patients with health-care-associated pneumonia do have a significantly higher mortality, this appears to be a result of the increased comorbidities found in this population, not a difference in causative organisms (Chalmers et al, 2011). In fact the organisms are more similar to those which cause community-acquired pneumonia, with around 1% meticillin-resistant *S. aureus*, 0.7% *Pseudomonas aeruginosa* and 2.9% other Gram-negative enterobacteriaceae (Chalmers et al, 2011). The predominant reason for inclusion of this new category was the need for broader empiric antibiotic cover to treat the more resistant organisms. This strategy looks to be unnecessary in the UK and Europe, and it may be that the term health-care-associated pneumonia is not useful outside of the USA (Chalmers et al, 2011).

Major risk factors for the acquisition of health-care-associated meticillin-resistant *S. aureus* pneumonia include residing in a nursing home, extended-care or rehabilitation facilities, being in hospital, particularly admission to intensive care or other units with high antibiotic use exerting selective pressure, or patients carrying an indwelling catheter or device. Patients with hospital-

acquired or ventilator-associated pneumonia tend to be elderly and often have significant comorbidities or underlying illness. The clinical features of this type of meticillin-resistant *S. aureus* pneumonia are very similar to those of Gram-negative infections. Often, despite early and appropriate antimicrobial therapy, mortality remains high at around 55%, especially in patients with associated bacteraemia (Rubinstein et al, 2008).

## Community-acquired pneumonia and Panton–Valentine leukocidin

Community-acquired meticillin-resistant *S. aureus* has a distinct epidemiology, it is not health-care-associated meticillin-resistant *S. aureus* that has spread outside the hospital setting. It has emerged separately and tends not to carry multiple antibiotic resistance genes, but is associated with toxin genes (Baba et al, 2001). In particular, community-acquired meticillin-resistant *S. aureus* has emerged as a pulmonary pathogen. Community-acquired meticillin-resistant *S. aureus* strains contains the SCC*mec* type IV (less often V or VI) and can also carry the gene that encodes for Panton–Valentine leukocidin (Vandenesch et al, 2003). Panton–Valentine leukocidin is a toxin that attacks and destroys polymorphonuclear leukocytes. In some reports it causes a particularly severe necrotizing pneumonia with a high mortality rate. In France an outbreak in 2002 involving 16 cases was described with an associated 48-hour survival rate of 63%, a phemonenon that has been consistently demonstrated in other parts of the world (Hyvernat et al, 2007; Rubinstein et al, 2008).

Community-acquired meticillin-resistant *S. aureus* pneumonia tends to have a different clinical presentation than health-care-associated meticillin-resistant *S. aureus.* Cases occur in young, previously healthy adults of whom up to 75% have a preceding influenza, or influenza-like illness (Gillet et al, 2002; Hageman et al, 2006; Vardakas et al, 2009). Respiratory symptoms are severe and often associated with high fever, haemoptysis, hypotension and a chest X-ray showing multilobular cavitating alveolar infiltrates. Blood results reveal leukopenia and a high C-reactive protein level (often >400 g/litre)(Morgan, 2007) (*Table 1*). The course is often rapidly progressive, necessitating intensive care unit admission in around 80% and ultimately causing death in around 20% (Gillet et al, 2002; Hageman et al, 2006). However, a recent report suggests that disease caused by community-acquired meticillin-resistant *S. aureus* may be milder now than previously (Qualls et al, 2012). Risk factors have been shown to be people with high intensity physical contact, particularly young men with an association with the military or gyms, men who have sex with men and injecting drug users (Salgado et al, 2003; Vardakas et al, 2009.

Unfortunately the epidemiology of community-acquired and health-care-associated meticillin-resistant *S. aureus* is becoming less distinct. Community-acquired meticillin-resistant *S. aureus* has moved into the health-care setting, but very variably by country, by region and even by hospital (Davis et al, 2006). This makes the differentiation between community-acquired- and health-care-associated-infection difficult, and with the potential of community-acquired meticillin-resistant *S. aureus* to be less resistant, but to cause more invasive disease, an important public health challenge.

## Diagnosis

Ideally diagnosis of infection should be based on both clinical and microbiological criteria. Diagnosis of ventilator-associated pneumonia is difficult and national guidelines are not always in concordance. Chest X-rays can miss up to a quarter of cases of ventilator-associated pneumonia, and blood cultures are only positive in 5–10% of patients. Unfortunately adequate microbiological sampling remains a challenge both in terms of sputum collection and more invasive respiratory sampling.

### Sputum

Sputum is often poorly collected, and meticillin-resistant *S. aureus* can colonize the upper respiratory tract and skin, particularly in the presence of foreign material (i.e. tracheostomy tubes) making evaluation of clinical significance complex and, in the inexperienced, sometimes resulting in overtreatment.

### Invasive sampling

Evidence suggests that quantitative sampling can also be useful in directing physicians between colonization and infection in ventilated patients. This requires invasive respiratory sampling in the form of spiral brushes, bronchoalveolar lavage or lung biopsy, necessitating added expense, expertise of the physicians and the microbiology laboratory and the risk of added complications for the patient. For largely unestablished reasons this occurs much less in the UK than in France, where most of the

**Table 1. British Thoracic Society guidelines for Panton–Valentine leukocidin infection when *Staphylococcus aureus* necrotizing pneumonia is strongly suspected or confirmed**

| | |
|---|---|
| Clinical features | Young previously healthy adults (often with preceding flu-like illness) |
| | Severe respiratory symptoms |
| | Haemoptysis |
| | Leukopenia |
| | Very high C-reactive protein (>400 g/litre) |
| | Cavitation on chest X-ray |
| In addition to the empirical antibiotic regimen* | Intravenous linezolid 600 mg twice daily plus |
| | Intravenous clindamycin 1.2 g four times daily plus |
| | Intravenous rifampicin 600 mg twice daily |
| Consider critical care admission | |

*Flucloxacillin should not be given as it has been associated with upregulation of Panton–Valentine leukocidin toxin production. From Lim et al (2009)

research in invasive sampling is carried out (Jung et al, 2010; Fagon, 2011). There is no established consensus on how frequently this should be performed, or whether surveillance cultures are helpful (Torres et al, 2009). Often the patients in whom results of invasive procedures would be useful are too unwell for them to be performed.

### Endotracheal aspirates

Endotracheal aspirates are often used as a substitute for more invasive sampling, but these are less representative of lower respiratory pathogens, and often tracheal tubes can become colonized with multi-resistant flora, making interpretation of results difficult.

As technology advances, diagnostic techniques for the detection of meticillin-resistant *S. aureus* have improved. Rapid diagnosis from clinical samples has become cost effective enough to be readily available, and technology like polymerase chain reaction which detects the presence of the *mecA* gene and fluorescent in situ hybridization (FISH) allow for real time detection of meticillin-resistant *S. aureus*. This should ensure appropriate and timely directed therapy for patients in whom meticillin-resistant *S. aureus* is detected, improving outcomes.

## Treatment options

### Vancomycin

The glycopeptide vancomycin remains the gold standard for treating meticillin-resistant *S. aureus* infections. Despite its increasing use there have still been very few isolates described with frank resistance, i.e. a minimum inhibitory concentration (MIC) of >16 mg/litre, but there are isolates classified as intermediate susceptibility with an MIC of 4–8 mg/litre, and the breakpoint for susceptible infections is now ≤2 mg/litre.

Despite lowered breakpoints, there are growing concerns about the efficacy of vancomycin in treating meticillin-resistant *S. aureus* infection for several reasons. Vancomycin is inferior to flucloxacillin in the treatment of meticillin-susceptible *S. aureus* infections, and it seems likely that this would translate to poorer efficacy in treating meticillin-resistant *S. aureus*. There are various concerns about getting high enough drug concentrations particularly in tissue, i.e. in order to achieve the pharmacokinetic/pharmacodynamic target area under the curve/MIC ratio of >400 (Kullar et al, 2011). Vancomycin is also a large molecule and penetrates slowly and poorly into lung tissue, which exacerbates this (Stein and Wells, 2010). There are concerns that the required therapeutic levels would necessitate vancomycin doses with unacceptable levels of renal toxicity. One reason this is important is because there have been reports of increasing MICs within the susceptible range, a phenomenon known as 'creep'. These higher MICs (of 1.5 mg/litre or 2 mg/litre) have pushed vancomycin trough target levels to 15–20 mg/litre, or if failure to achieve clinical response, to switch to alternative antimicrobial therapy. High MIC is also associated with loss of already poor cidal activity of vancomycin, possibly increasing risk of treatment failure (Sakoulas et al, 2004; Moise et al, 2007; Tsuji et al, 2009).

One of the proposed solutions to the problem of ascertaining high enough levels to achieve adequate bacterial killing is the use of continuous infusions of vancomycin. These have shown less toxicity than pulsed doses in treating serious meticillin-resistant *S. aureus* infections, although not specifically pneumonia (Cataldo et al, 2012). Although these require more involvement from nursing care, they are often helpful in avoiding missed or delayed doses as a result of difficulties with timely trough level sampling and physician prescribing.

MIC affects outcome in treatment with vancomycin, with patients with isolates with high MICs, yet still in the susceptible range, having poorer outcomes than those with isolates of ≤1 mg/litre (Haque et al, 2010). This has also prompted some experts to lower the vancomycin breakpoints still further (Gould, 2010). However, data from Australasia suggests that failure rates might be the result of other changes in the organism like in accessory gene regulation affecting virulence, or the type of patients now being treated, as meticillin-sensitive *S. aureus* with high vancomycin MICs treated with flucloxacillin also have the same poor outcome (Holmes et al, 2011). Nonetheless, despite all of these uncertainties, vancomycin still remains the benchmark against which all other therapy is measured.

The concurrent use of aminoglycosides or other nephrotoxic agents also increased the risk of nephrotoxicity during vancomycin treatment, making close monitoring vital (Rybak et al, 2009).

### Linezolid

Linezolid is an oxazolidinone with a licence for pneumonia, the first in the newest class of antibiotics to be developed in over 30 years. It acts by inhibiting protein synthesis at a very early stage of bacterial replication, unfortunately the *cfr* mobile gene gives cross resistance to pleuromutilins and chloramphenicol, among other antibiotics used for treating Gram-positive infections.

In systematic review and meta-analysis, linezolid is of equal efficacy to glycopeptides in the treatment of meticillin-resistant *S. aureus* pneumonia, both in terms of clinical and microbiological cure rates (Kalil et al, 2010). However, there is contention over the superiority of linezolid over vancomycin for treatment of meticillin-resistant *S. aureus* pneumonia. Only with post-hoc analysis of the original trials was the possibility of superiority suggested (Wunderink et al, 2012). This demonstrated superiority has since been brought into question by other groups, citing failure to achieve adequate vancomycin trough levels or course lengths in the vancomycin treatment arms, skewing the results in favour of linezolid (Masuta et al, 2012).

The side effects of linezolid are well documented, including bone marrow suppression and irreversible peripheral nephropathy. The meta-analysis noted a significant two-fold increase in thrombocytopenia and gastroin-

testinal upset, and importantly no difference in renal toxicity, although this remains contentious (Kalil et al, 2010). Infectious Diseases Society of America guidelines suggest linezolid should be considered as a more appropriate antibiotic choice in patients who have meticillin-resistant *S. aureus* isolates with an MIC in the high yet susceptible range (i.e. 1.5–2mg/litre), or who fail to respond clinically to vancomycin therapy (Haque et al, 2010).

In patients with pneumonia caused by meticillin-resistant *S. aureus* strains with a vancomycin MIC of ≥1.0 mg/litre who require concomitant nephrotoxic therapy or who have pre-existing renal failure linezolid 600 mg twice daily is advised (Rubinstein et al, 2011).

### Others

Teicoplanin, another glycopeptide used for the treatment of meticillin-resistant *S. aureus* infection, has also been compared to both vancomycin and linezolid. It is used more extensively in Europe and Asia than in America, and in systematic review (Kalil et al, 2010) has been shown to be of equivalent efficacy to either vancomycin or linezolid, although evidence is quite limited. At standard dosing it is less nephrotoxic than vancomycin (Svetitsky et al, 2009). However, there remains some doubt as to the adequacy of standard dosing in achieving adequate lung penetration, and it is probably as toxic as vancomycin if given at higher doses (Bal and Gould, 2005; Mimoz et al, 2006).

Co-trimoxazole (Septrin) is a combination of trimethoprim and sulfamethoxazole. It is an older antibiotic, relegated because of its side-effect profile and significant drug interactions, that has seen a revival in many health boards in the UK because many of the workhorse antibiotics were associated with an increased incidence of *Clostridium difficile* infection. Co-trimoxazole has been used to treat serious meticillin-resistant *S. aureus* infection (Goldberg et al, 2010), and has been found to be non-inferior to vancomycin, but studies are lacking. Providing the meticillin-resistant *S. aureus* strains locally remain susceptible, this could still be an alternative option for the treatment of both community-acquired and health-care-associated-meticillin-resistant *S. aureus* pneumonia (Diaz et al, 2012).

Quinupristin/dalfopristin (Synercid) is a semi-synthetic agent comprising of streptogramin A and streptogramin B, both of which produce an in-vitro synergistic effect against many Gram-positive bacteria. Streptogramins are members of the macrolide-lincosamide-streptogramin group which all have similar mechanisms of action (inhibiting protein synthesis). In one prospective randomized comparison, quinupristin/dalfopristin showed equivalent efficacy to vancomycin for the treatment of nosocomial pneumonia including that caused by meticillin-resistant *S. aureus* (Fagon et al, 2000). However, it did have a tendency to be associated with more adverse events, has not found common use (Fagon et al, 2000) and is still very much a reserve treatment option.

Daptomycin, a novel and rapidly bacteriocidal lipopeptide, is unfortunately not useful in the treatment of meticillin-resistant *S. aureus* pneumonia as it is inactivated in the presence of surfactant.

Televancin has a restricted license in Europe for meticillin-resistant *S. aureus* pneumonia, and together with registration studies suggesting significant nephrotoxicity, is unlikely to be widely used (Rubinstein et al, 2011). Oritavancin and dalbavancin are other glycopeptides currently in development to increase the anti-meticillin-resistant *S. aureus* antibiotic arsenal. Ceftaroline, an anti-meticillin-resistant *S. aureus* cephalosporin, has also passed Food and Drug Administration and European Medicines Agency approval for pneumonia, but there were limited meticillin-resistant *S. aureus* isolates in registration studies (File et al, 2010).

## Duration of therapy

With *S. aureus* infection, duration of therapy should be guided by the clinical picture. Some experts suggest 7 days of therapy would be sufficient providing there is an uncomplicated pneumonia with no associated bacteraemia or other deep source or collection, others suggest 10–15 days (Que and Moreillon, 2010; Liu et al, 2011). If an empyema is present antibiotics should be used in conjunction with drainage.

## Cost analysis

One of the main concerns over the use of linezolid empirically over vancomycin is cost. The raw drug cost of linezolid is more expensive than vancomycin. A cost-effectiveness study in a decision-analytic model based on clinical trial data from Germany showed a higher clinical cure (8.7%) and survival (13.2%) for linezolid compared with vancomycin at a increased cost of €420 per treatment episode. This was felt to support linezolid as a cost-effective alternative to vancomycin in the treatment of meticillin-resistant *S. aureus* pneumonia (De Cock et al, 2009).

## Reduction strategies

Given that *S. aureus* is now one of the most common causes of hospital-acquired pneumonia, and meticillin-resistant *S. aureus* accounts for a large part of this burden, meticillin-resistant *S. aureus* preventative strategies would help reduce the risk of infection. meticillin-resistant *S. aureus* in particular can benefit from a multifaceted approach to reduction, of which key elements are discussed below.

### Infection prevention and control

It is important for any programme attempting to reduce meticillin-resistant *S. aureus* to include administrative support to ensure adequate staffing levels and to try and prevent overcrowding among patients. Isolation of patients is paramount, decontamination needs to be performed appropriately and education must be sufficient among all grades of staff particularly with regards to hand hygiene.

### Meticillin-resistant *S. aureus* screening

Meticillin-resistant *S. aureus* colonized and infected individuals are still the biggest source of infection in the health-care setting. Screening for carriage and identifying patients early allows for appropriate infection prevention and control precautions to be implemented, decolonization of patients if appropriate, and early life-saving treatment (Lawes et al, 2012). Often, topical therapies such as mupirocin or chlorhexidine will be used to reduce the bacterial burden in patients who carry meticillin-resistant *S. aureus*. This kind of work requires input from the microbiology services, and adequate funding. Screening and decolonization has shown success in controlling or reducing transmission of meticillin-resistant *S. aureus* nationally, regionally and institutionally. In the UK particularly, there has been a huge fall in meticillin-resistant *S. aureus* bacteraemia (Health Protection Scotland, 2011; Health Protection Agency, 2012).

### Ventilator-associated pneumonia reduction strategies

Given that a substantial proportion of ventilator-associated pneumonia is caused by meticillin-resistant *S. aureus*, any strategies aimed at reducing the incidence of ventilator-associated pneumonia are particularly relevant. Although diagnosis of ventilator-associated pneumonia remains challenging, the implementation of care bundles comprising evidence-based elements of care or interventions can lead to a reduction in ventilator-associated mortality. The main elements of the Institute for Healthcare Improvement ventilator bundle are elevation of the head of the bed, deep vein thrombosis and peptic ulcer prophylaxis, daily 'sedation vacations' and 'readiness to extubate' assessments, and good oral care with chlorhexidine.

With more specific regard to the prevention of ventilator-associated pneumonia, selective decolonization of the digestive tract has also been attempted. This is a strategy whereby antibiotic prophylaxis is given, both systemically and topically as an oral paste, in order to reduce colonization of the patient's endotracheal tube and therefore reduce the likelihood of ventilator-associated pneumonia. Despite several trials showing a reduction in both respiratory tract infections and mortality, this still remains controversial, in part because of concerns over the driving of antibiotic resistance, and also because of *C. difficile* infection associated with antibiotic use (Liberati et al, 2010).

### Antimicrobial stewardship

The inappropriate use of antibiotics has multiple adverse consequences, not least of which is antimicrobial resistance. Often the relationship between the use of antibiotics and the resistance that results is logical, but some relationships are more difficult to understand. Use of cephalosporins, macrolides and quinolones can result in increased levels of meticillin-resistant *S. aureus* (Monnet et al, 2004). It is important that multidisciplinary teams comprising antimicrobial pharmacists, microbiologist and infectious diseases specialists are involved in ensuring antibiotic use is justified, and that the agent with the narrowest possible spectrum is chosen to treat the specific infection.

## The future

With the changing epidemiology of meticillin-resistant *S. aureus*, and its increasing prevalence in many countries, it remains important to be aware of its significance as a pathogen both in the health-care setting, and in the community. As *S. aureus* continues to evolve and acquire new resistances, new clones will arise causing new disease patterns. Limited new treatment options do not give great cause for optimism. Vigilance, clinical suspicion and surveillance will remain important to keep on top of this formidable pathogen. **BJHM**

### KEY POINTS

- Meticillin-resistant *Staphylococcus aureus* is a significant cause of hospital-associated pneumonia and ventilator-associated pneumonia, which carries a substantial mortality rate.
- The epidemiology of meticillin-resistant *S. aureus* pneumonia continues to evolve and as this happens so will the clinical presentation of disease.
- Panton–Valentine leukocidin-producing meticillin-resistant *S. aureus* should be considered in previously healthy young patients with severe, cavitating pneumonia.
- Treatment options are centred around vancomycin and linezolid with further studies still needed to confirm superior efficacy.
- Vancomycin minimum inhibitory concentration seems to be an important determinant of outcome, and so is important to consider when choosing antibiotic therapy.

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