REVIEW

Methicillin resistant *Staphylococcus aureus* (MRSA) in the intensive care unit

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Methicillin resistant *Staphylococcus aureus* (MRSA) is a major nosocomial pathogen that causes severe morbidity and mortality worldwide. MRSA strains are endemic in many American and European hospitals and account for 29%–35% of all clinical isolates. Recent studies have documented the increased costs associated with MRSA infection, as well as the importance of colonisation pressure. Surveillance strategies have been proposed especially in high risk areas such as the intensive care unit. Pneumonia and bacteraemia account for the majority of MRSA serious clinical infections, but intra-abdominal infections, osteomyelitis, toxic shock syndrome, food poisoning, and deep tissue infections are also important clinical diseases. The traditional antibiotic therapy for MRSA is a glycopeptide, vancomycin. New antibiotics have been recently released that add to the armamentarium for therapy against MRSA and include linezolid, and quinupristin/dalfopristin, but cost, side effects, and resistance may limit their long term usefulness.

investigators have found a high prevalence of drug resistant bacteria in the hospital—and in the ICU—than in the community.³ However, MRSA strains are now found in the community in relatively large numbers, and MRSA is no longer only an ICU nosocomial disease.³

Recent studies have documented the increased costs associated with MRSA infection, as well as the importance of colonisation pressure.^{4,5} Surveillance strategies have been proposed especially in high risk areas such as the ICU. Pneumonia and bacteraemia account for the majority of MRSA serious clinical infections, but intra-abdominal infections, osteomyelitis, toxic shock syndrome, food poisoning, and deep tissue infections are also important clinical diseases. New antibiotics have been recently released that add to the armamentarium for therapy against MRSA. None the less, prevention of infection and control of endemic rates are critically important features of MRSA control today. In this paper, we will discuss the microbiology, epidemiological features and risk factors, surveillance strategies, costs, treatment, and outcomes of patients with MRSA in the ICU.

MORPHOLOGY AND IDENTIFICATION

Microscopically *S aureus* is a Gram positive organism characterised by individual cocci measuring 0.5–0.7 µm in diameter. The organisms can occur singly, in pairs, or in short chains with a strong tendency to form clusters.⁶ The three main species considered clinically important include *S aureus*, *S epidermidis*, and *S saprophyticus*. To differentiate *S aureus* from the other species the following tests can be done: (a) catalase, which differentiates *S aureus* from catalase negative streptococci, and (b) bound coagulase (often referred to as clumping factor as it reacts with fibrinogen to cause aggregation of organisms), which differentiates between *S aureus* and *S epidermidis*, the latter being negative.⁶ Another extracellular coagulase, also referred to as free coagulase, reacts with prothrombin to form staphylothrombin which converts fibrinogen to fibrin (an effect similar to thrombin). About 97% of the human *S aureus* isolates possess both forms of coagulase.^{7,8} Also more than 95% of *S aureus* isolates produce

Each year about two million patients acquire nosocomial infections in US hospitals.¹ About 60% of these infections involve antibiotic resistant bacteria. About 40% of nosocomial *Staphylococcus aureus* infections in the United States are methicillin resistant; and vancomycin resistant enterococci have increased 25-fold (up to 16%) since 1987 in our nation's intensive care units (ICUs). Estimated excess costs related to antibiotic resistance range from \$100 million to \$30 billion annually in US hospitals. Methicillin resistant *S aureus* (MRSA) is a major nosocomial pathogen that causes severe morbidity and mortality worldwide. MRSA strains are endemic in many American and European hospitals and account for 29%–35% of all clinical isolates.^{1,2} In 1992, MRSA accounted for 57% of all ICU acquired *S aureus* infection recorded in the European Prevalence of Infection in Intensive Care (EPIC) study.³ However, infection rates varied from 1% to 80% and were dependent on location, emphasising the need to be cognisant of the local microbial resistance patterns.³

The major reservoir of MRSA in institutions are colonised and infected inpatients, while transient hand carriage of the organism on the hands of health care workers account for the major mechanism for patient-to-patient transmission.⁴ Most

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Abbreviations: GISA, glycopeptide intermediate *S aureus*; ICU, intensive care unit; MIC, minimal inhibitory concentration; MRSA, methicillin resistant *Staphylococcus aureus*; MSSA, methicillin sensitive *S aureus*, RR, relative risk; VISA, *S aureus* with intermediate resistance to vancomycin

Box 1: Key points

- Two million patients acquire nosocomial infections in US hospitals.
- About 60% of these infections involve antibiotic resistant bacteria.
- Estimated excess costs related to antibiotic resistance range from \$100 million to \$30 billion annually in US hospitals.
- About 40% of *S aureus* infections in the US are methicillin resistant.
- MRSA strains are endemic in many American and European hospitals and account for 29%–35% of all clinical isolates. MRSA accounted for 57% of all ICU acquired *S aureus* infection.
- The major reservoir of MRSA in institutions are colonised and infected inpatients.
- Transient hand carriage of the organism on the hands of health care workers accounts for the major mechanism for patient-to-patient transmission.

protein A which may be cell associated and/or extracellular.^{7,9} This protein has a special affinity for the Fc moiety of IgG.

Peptidoglycan is the main constituent of the cell wall of *S aureus*; it confers shape and stability to the micro-organism and represents 50% of the cell wall weight. Teichoic acid is another cell wall constituent made of phosphate containing polymers, and represents 40% of the cell wall weight. Other constituents include fibronectin binding proteins, clumping factors, and collagen binding proteins.⁶ *S aureus* produces a number of toxins and enzymes that are implicated as possible pathogenic factors. The enzymes include catalase, coagulase, clumping factor, hyaluronidase, β -lactamase, and others.⁶

MECHANISMS OF RESISTANCE

Antibiotic resistance may be termed natural or acquired. Natural resistance refers to the inherent lack of activity of an antibiotic beyond its usual spectrum. If organisms previously sensitive to an antibiotic become resistant, this is referred to as acquired antibiotic resistance. Relative acquired resistance refers to the gradual increase over time of the minimal inhibitory concentration (MIC) of an organism to a particular antibiotic. Acquired high grade or absolute resistance occurs when there is a single step mutation that occurs during or after therapy and increases the MIC of a previously susceptible isolate to extremely high levels unachievable using therapeutic doses.¹⁰

METHICILLIN RESISTANCE

Resistance to β -lactam compounds that are not hydrolysed by β -lactamase such as methicillin, oxacillin, nafcillin, cloxacillin, and dicloxacillin is termed “intrinsic” or “methicillin” resistance. MRSA isolates and methicillin resistant coagulase negative staphylococci isolates are broadly resistant to penicillins and cephalosporins.⁷ Methicillin resistance is most commonly mediated by the *mecA* gene, which encodes for a single additional penicillin binding protein, PBP2a, with low affinity for all β -lactams.^{11,12} Harboring *mecA* gene is not sufficient for methicillin resistance; some *S aureus* (<2%) strains containing the *mecA* gene are susceptible to methicillin.^{13,14} The *mecA* gene is widely distributed in both coagulase positive and coagulase negative staphylococci, is carried on a transposon, and appears to integrate into a single site in the staphylococcal chromosome along with an additional 30 kb of DNA, the *mec* locus.¹⁵ In some strains, this includes a regulatory locus, *mecR1-mecI*, and may include an insertion element that is a potential integration site for unrelated resistance determinants. Expression of *mecA* can be either constitutive or inducible. Other regulatory components that control the expression of the gene are the β -lactamase genes (*blaI*, *blaR1*, *blaZ*)

Box 2: Key points

- Methicillin resistance is most commonly mediated by the *mecA* gene, which encodes for a single additional penicillin bind protein, PBP2a, with low affinity for all β -lactams.
- Expression of *mecA* can be either constitutive or inducible.
- MRSA MICs vary from 3–200 $\mu\text{g/ml}$, isolates of MRSA with intermediate resistance to vancomycin (>8–16 $\mu\text{g/ml}$) are called VISA and glycopeptide intermediate resistance, GISA.

which, because of sequence similarities to the *mecR1-mecI* genes, also can down regulate *mecA* gene transcription. Expression of resistance also depends, in part, on other chromosomal genes where there are a series of five auxiliary genes that can modify expression of methicillin resistance, these are the *fem* (factor essential for the expression of methicillin resistance) A to E genes where they affect different steps in the synthesis of peptidoglycan; they are part of cellular peptidoglycan metabolism and can regulate the degree of resistance without altering levels of PBP2a.¹⁶

The phenotypic expression of methicillin resistance shows great variability. MRSA isolates can be divided into four arbitrarily defined expression classes according to methicillin MIC, which varies from 3–200 $\mu\text{g/ml}$, and the resistance phenotype, that is, homogeneous or heterogeneous.¹⁷ In a heterogeneous bacterial population, all cells carry the genetic markers of methicillin resistance, but the resistant phenotype occurs only in a small fraction of the population.¹⁸ The proportion of the population that is resistant to higher concentrations of methicillin is a strain specific characteristic under genetic control and varies from 10^{-2} to 10^{-8} .^{17,18} The least frequent phenotype is homogeneous resistance, with a single population of cells that is inhibited by high levels of antibiotic concentration.^{18,19}

GLYCOPEPTIDE INTERMEDIATE RESISTANCE

Several isolates of MRSA with intermediate resistance to vancomycin (>8–16 $\mu\text{g/ml}$) (VISA) have been identified. Since 1996, VISA has been identified in Europe, Asia, and the US. The fourth case of VISA in the US was reported in April 1999.²⁰ More than eight cases are known worldwide. Since the original naming and description of VISA, these pathogens have also been known to be resistant to teicoplanin; thus the term glycopeptide intermediate *S aureus*, or GISA, is more appropriate. These pathogens as yet, have not been “vancomycin methicillin resistant” *S aureus*. However, in the laboratory, this genetic material has been easily transferred. In the cases thus described in the literature, a common feature is prolonged vancomycin exposure. Optimal therapy for this condition has not yet been determined.²¹

EPIDEMIOLOGICAL FEATURES OF S AUREUS, MRSA, AND RISK FACTORS

S aureus has been known as a causative agent of infection since 1882, when Ogston identified its role in sepsis and abscess formation.²² Staphylococci are found in the human body, on the skin, and mainly in the axillae, perianal area, inguinal area, and the anterior nares.²³ Carrier rates are between 11% and 32% among healthy adults in the general population,^{24,25} and a prevalence of 25% was found among hospital personnel.²⁶ Approximately 85% of carriers can be identified with a swab taken from the anterior nares. Higher carrier rates are seen in injection drug users, persons with insulin dependent diabetes, patients with dermatological conditions, and in patients with long term indwelling intravascular catheters. The carrier state is of clinical importance because any surgical intervention or exudative skin condition will predispose the

Box 3: Risk factors for MRSA colonisation and infection

- Advanced age.
- Male gender.
- Previous hospitalisation.
- Length of hospitalisation.
- Stay in an ICU.
- Chronic medical illness.
- Prior and prolonged antibiotic treatment.
- Presence and size of a wound.
- Exposure to colonised or infected patient.
- Presence of invasive indwelling devices.

Box 4: Key points

- Staphylococci are found in the human body, on the skin, and mainly in the axillae, perianal area, inguinal area, and the anterior nares.
- Carrier rates of 25% were found among hospital personnel.
- Approximately 85% of carriers can be identified with a swab taken from the anterior nares.
- Higher carrier rates are seen in injection drug users, those with insulin dependent diabetes mellitus and dermatological conditions, and those with long term indwelling intravascular catheters.

carrier to a higher rate of infection than the non-carrier, the infection usually caused by the same colonising strain.⁶

In the last 20 years, the National Nosocomial Infection Surveillance data show that within all hospitals, there was an increase from 2% to 29% in the proportion of methicillin resistance among *S aureus*, and an increase to 38% in those hospitals with more than 500 beds.²⁷ MRSA has been isolated within 48 hours of admission to urban hospitals, mostly in patients with prior hospitalisation, outpatient hospital visits within the previous six months, recent antibiotic use, or transfer from a long term care facility. These pathogens are described as community strains, but not necessarily true community acquired methicillin resistance. Sporadic occurrences of community spread of MRSA do occur and future surveillance may detect a further change in epidemiology. Long term care facilities have become reservoirs of MRSA with mean monthly patient colonisation rates as high as 23% with 5%–15% of colonised long term care facility residents subsequently develop MRSA infections.²⁸

Risk factors for community acquired infection included intravenous drug use, serious underlying illnesses, previous antimicrobial therapy, and previous hospitalisation.²⁸ Risk factors associated with nosocomial acquired MRSA colonisation and infection are shown in box 3.^{29–30} Transient or persistent (as long as three years) colonisation may occur at multiple body sites, and with multiple strains. The most common body sites are wound, nasopharynx, trachea (especially if intubated), and perineum. Transmission from environmental surfaces or by airborne route occurs in special circumstances, as in burn units or among intubated patients.³¹

The transmission of MRSA from temporary colonisation of the hands of health care workers is the major mechanisms of spread of MRSA in hospitals today. The impact of colonisation pressure (the number of MRSA carrier patient days/total number of patient days) was the only independent predictor of MRSA infection in a recent study.³² Above a colonisation pressure of 30%, the risk of acquisition of MRSA was approximately fivefold times higher (relative risk 4.6, 95% confidence interval 1.2 to 19.9, $p < 0.001$). This factor outweighed severity of illness, omega 3 score, and the number of imported MRSA cases.³² Jerinigan and colleagues estimated that the transmission rate from patients in contact isolation was significantly

lower (0.009 transmissions/day) than in patients not in isolation.³³

MRSA infections appear to occur in patients with decreased susceptibility to infection. Singh *et al* reported that patients with both cirrhosis and early following liver transplantation are at an increased risk of MRSA infection when colonisation is present in the anterior nares.³⁴ Patients in an ICU, especially a surgical ICU, have wounds, drains, and invasive monitoring devices that breach the skin and increase the risk of developing infections. Additionally, impaired neutrophil function as a result of chronic liver disease, diabetes, or corticosteroid therapy may render these patients more susceptible to MRSA. Specific defects associated with granulocyte function, such as decreased chemotaxis and impaired phagocytosis associated burst activity have been documented with liver disease and diabetes.³⁵

MRSA in the setting of foreign devices tends to be more virulent because the foreign body appears to facilitate infection by shielding these normally low virulence organisms from being attacked by host defences possibly through (1) alteration in bacterial metabolism, alteration in leucocyte function, or creation of a permeability barrier and (2) attachment, adherence, and slime production are factors which make coagulase negative staphylococci especially adept at surviving on various biomaterials.

Several authors have addressed the question of whether MRSA is more virulent than methicillin sensitive *S aureus* (MSSA). Soriano and colleagues performed a retrospective case control study of 908 (225 MRSA) episodes of bacteraemia and matched 163 pairs. When multiple factors about the patients such as shock, source of bacteraemia, acquisition of the infection in an ICU, and inappropriate empirical therapy were among the factors considered, MRSA was not an independent factor for mortality. However, methicillin was an independent predictor for shock.³⁵ In a similar study of 504 patients (188 MRSA, 316 MSSA), overall mortality was 22%. Death was significantly greater in the MRSA group (odds ratio 1.68), although these patients were found to be more likely to die due to underlying disease during treatment of bacteraemia, rather than from the MRSA bacteraemia itself.³⁶ These authors suggest that differences in patient comorbidities in different centres, true virulence differences, or aggressiveness of treatment may explain the variance in the literature about whether or not MRSA is more virulent than MSSA.

With the whole genomic sequencing of MRSA, most of the antibiotic resistant genes are carried on plasmids or by mobile genetic elements including a unique resistance island. Three classes of pathogenicity islands were identified in the genome: a toxic shock syndrome toxin island, and clusters of exotoxin and enterotoxin genes were found closely linked with other gene clusters encoding for putative pathogenic factors. These authors also identified 70 candidates for new virulence factors.³⁷ These newly identified factors may help to explain the biology of staphylococci and the processes of infections caused by *S aureus*.

INFECTION CONTROL METHODS

Since MRSA is endemic in most referral hospitals in the developed world, strategies to reduce further spread are needed. Commonly employed strategies for the control of MRSA spread are shown in table 1 and proved methods to treat colonisation and infection are discussed in detail by Boyce.³⁸ In a surgical ward with a rate of 21.6 per 1000 admissions, refurbishment was followed by a new isolation rate of 20.4 per 1000 admissions.³⁹ New MRSA rates before flagging as notification was 6.4 per 1000 hospital admissions versus 6.2 per 1000 admissions after, thus concluding that neither ward refurbishment or introduction of flagging significantly reduced rates of colonisation.³⁹ Somewhat surprisingly, without cohorting patients, neither of these commonly employed

Table 1 Infection control methods for MRSA

Method	Comment
Screening	
Patients	Effective if followed by isolation, cost effective for threshold values
Staff	Rates low, expensive
Handwashing	Effective, compliance poor
Antimicrobials	
Topical agents	Mupirocin widely used, effective, resistance occurs
Systemic	Resistance if use commonly used agents, other (rifampin and fusidic acid) with side effects
Body cleansing	Certain agents effective (povidone iodine, chlorhexidine, triclosan)
Cohorting of patients	
Complete separation/ward closure	Nurses required to take care of a variety of patients, effective, disruptive
Single room isolation	Variable effectiveness, blocks of rooms may be helpful
Preidentification of carriers and previously infected patients	With total isolation, effective
Gowns	No proved value
Gloves	Effective if changed between patients
Environmental cleaning	Not effective in slowing outbreaks

methods was successful in decreasing MRSA colonisation.⁴⁰ In another tertiary referral hospital, patients with MRSA colonisation were excluded from the orthopaedic and haematology wards. The incidences on the 39 wards ranged from 0 to 75 per 1000 admissions, highest in the ICU and in services that frequented the ICU such as the liver transplant service. Using a policy of screening and complete isolation and separation of the orthopaedic and haematology wards, the incidence remained low in orthopaedics (<1 per 1000) and haematology (3 per 1000).⁴¹

Colonisation on environmental surfaces in the ICU can serve as a reservoir for MRSA, including some previously unsuspected surfaces. In a recent study, 26% of computer key-boards and 15% of sink faucet handles were colonised with MRSA. This rate was substantially higher than that reported for other ICU environmental surfaces, and suggests a pattern of environmental contamination and patient infection not limited to the patient's room.⁴² In an interesting recent report, MRSA strains that had caused outbreaks had a significantly longer survival period (1–3 months), and in higher concentrations ($\times 1000$) when compared with strains causing sporadic MRSA infection.⁴³ Again, this emphasises the importance of reinfection and re-exposure with MRSA.

Though endemic rates of MRSA isolation and infection can be successfully controlled in some areas, some individuals have questioned both efficacy and costs of these infection control programmes.⁴⁴ Chaix and colleagues examined the ICU costs attributable to MRSA infection from therapeutic intensity, and compared this to the costs of the infection control programme. They determined that the mean cost attributable to MRSA infection was US\$9275 dollars, while the infection control programme costs ranged from \$340 to 1480 per patient. A 14% reduction in MRSA, not replaced by MSSA infection, resulted in the programme being beneficial by reducing both costs and morbidity. Critical determinants of these results were the MRSA carriage rate on ICU admission (1%–7%), costs of control measures, and MRSA transmission, when infection rates were greater than 50% after transmission.⁴⁴ Thus these authors documented that selective screening of high risk patients and isolation of carriers on ICU admission was beneficial compared with no isolation.

Differentiation of epidemic methicillin resistant strains, for example EMRSA-03, EMRSA-15, and EMRSA-16 and sporadic strains can be made by analysis of the coagulase gene by single phage typing of *S aureus*.

Box 5: Key points

- Above a colonisation pressure (the number of MRSA carrier patient days/total number of patient days) of 30%, the risk of acquisition of MRSA was approximately five times higher (relative risk 4.6, 95% confidence interval 1.2 to 19.9, $p < 0.001$).
- The transmission rate from patients in contact isolation was significantly lower (0.009 transmissions/day) than in patients not in isolation.
- Infection control methods have proved cost effectiveness when rates of colonisation and infection are significant.

CLINICAL FEATURES OF MRSA INFECTIONS IN THE ICU

In a medical ICU, over a four year period, 293 (7.9%) of 3686 admissions developed new MRSA. Cases were "imported" in 4.1% and the remaining cases were acquired in the ICU.⁴⁵ Surprisingly, in this study, only a few MRSA carriers (26%) acquired secondary colonisation or infection, and only 26 (19.5%) of 133 had secondary infection. Pujol *et al* showed that nasal carriage of MRSA in ICU patients was associated with an MRSA bacteraemia rate of 38%, fourfold higher than MSSA.⁴⁶ In the hospital, one third of colonised patients becomes infected and one half of these have pneumonia or bloodstream infection. Mortality rates for nosocomial acquired MRSA infections may reach 50% for bloodstream infections and 33% for pneumonia.

Among ICU patients with hospital acquired pneumonia, *S aureus* was identified as the most frequent pathogen in the EPIC study.³ The distribution of infecting species in the 836 cases of nosocomial infection is shown in table 2. Specific patient populations of critically ill, mechanically ventilated patients seem to be a high risk for *S aureus* related disease including recent cardiopulmonary arrest, and early onset pneumonia after trauma, neurological disease, or neurosurgery. A recent study by Sirvent *et al* examined the role of tracheal colonisation on ICU admission for head trauma in the production of early onset ventilator associated pneumonia.⁴⁷ They found that 68% of patients were colonised with *S aureus* (35%), *Haemophilus influenzae* (31%), and *Streptococcus pneumoniae* (11%). The odds ratio for developing an early ventilator associated pneumonia if colonised within 24 hours was 28.9 (95% confidence interval 1.59 to 48.5).

The risk factors identified by Rello *et al* for the development of ICU MRSA and mechanical ventilation included steroid

Table 2 Distribution of infecting species in nosocomial (ICU) pneumonia³

Species	% Nosocomial pneumonia
<i>Staphylococcus aureus</i>	31.7
<i>Pseudomonas aeruginosa</i>	29.8
Yeasts	14
<i>Acinetobacter</i> species	9.9
<i>Escherichia coli</i>	6.8
Enterococci	5.4

Box 6: Key points

- In a medical ICU, over a four year period, 293 (7.9%) of 3686 admissions developed new MRSA.
- Nasal carriage of MRSA in ICU patients was associated with a MRSA bacteraemia rate of 38%, four times higher than MSSA.
- One third of colonised patients become infected and one half of these have pneumonia or bloodstream infection.
- Mortality rates for nosocomial acquired MRSA infections may reach 50% for bloodstream infections and 33% for pneumonia.
- The odds ratio for developing an early ventilator associated pneumonia if colonised within 24 hours was 28.9 (95% confidence interval 1.59 to 48.5).
- Risk factors identified for the development of ICU MRSA and mechanical ventilation included steroid treatment (RR 3.45), ventilator >6 days (RR 2.03), prior chronic obstructive pulmonary disease (RR 2.76), or age >25 years (RR 1.50). The most important risk factor seen was previous treatment with antibiotics ($p=0.000001$).

treatment (relative risk (RR) 3.45), ventilator >6 days (RR 2.03), prior chronic obstructive pulmonary disease (RR 2.76), or age >25 years (RR 1.50).⁴⁸ However, the most important risk factor seen was previous treatment with antibiotics ($p=0.000001$). This suggests, as has many other studies, that prior use of antibiotics contributes to the development of MRSA infection. In addition to the use of systemic antibiotics, patients undergoing selective digestive decontamination have increased oropharyngeal colonisation with staphylococci.

Liver transplant recipients are increasingly infected with resistant species including MRSA and vancomycin resistant enterococci. In 1990 through 1998, 23% of liver transplant recipients developed MRSA infections particularly during their early postoperative course (32% within 14 days).³⁴ Predominant sources of infection were intravascular catheters (39%), wound (18%), abdomen (18%), and lung (13%). Risk factors noted in this study included more recent time period, cytomegalovirus seronegativity, or conversion postoperatively. Mortality at 30 days in those infected with MRSA was 21%, but was 86% when bacteraemic from a pulmonary or abdominal source, compared with 6% with infection from an intravascular catheter. These data underscore the virulent nature of MRSA infection in postoperative liver transplant patients unless an immediately remediable source of infection is identified, treated, and removed.

The question of whether methicillin resistance confers a more immediate deterioration or more severe outcome is debated. Chaix found a four day increase in overall length of stay and 8.5 days increase in length of ICU stay in survivors, lower than the estimate of some previous studies.⁴⁴ However in 908 consecutive episodes of *S aureus* (225 MRSA) bacteraemia and 163 case-control patients matched for comorbidities, prognosis of the underlying disease, length of hospitalisation and age, the authors could not demonstrate a poorer outcome for patients with MRSA when prior antibiotic therapy,

inappropriate treatment, ICU residence, and female gender were considered.³⁵

Chronic illness and acute critical illness may allow for the formation of resistance organisms on the skin or in the gastrointestinal track. Differences were seen in the concentration and location of colonising species, with ICU patients having greater concentration of MRSA on the forearm (odds ratio 2.48; 95% confidence interval 1.34 to 4.43; $p = 0.004$) when compared with other inpatients and outpatients.⁴⁹ Interestingly, the outpatients with chronic illness has a higher prevalence of micrococcus and Gram negative bacilli at both the forearm and sternum.⁴⁹ Thus, not only current patient location but also past history may predispose the patient to certain micro-organisms.

Postoperative infection with MRSA is a serious and significant problem as noted in liver transplants above, but also in prosthetic devices such as endovascular implants, orthopaedic devices, and sternal infections. Identification and amelioration of possible risk factors would be of significant benefit. Surgical site infections, superficial, deep, and organ space, can be caused by MRSA. In a recent study of intra-abdominal infection with MRSA, a single organ system failure (odds ratio 6.12, 95% confidence interval 1.41 to 26.6) in the presence of nasal carriage with MRSA (odds ratio 4.72, 95% confidence interval 1.17 to 19.0) was a significant risk factor for the subsequent acquisition of an intra-abdominal infection with MRSA. In addition, patients with an MRSA infection had a longer ICU stay and more reoperations than those free of MRSA infections.⁵⁰

THERAPEUTIC STRATEGIES

Epidemiological studies suggest that an empiric approach to the treatment of suspected nosocomial infection with possible MRSA should be based on the presence of coexisting illness, prior treatment (including antibiotic therapy), and the duration of hospitalisation. The selection of an empiric agent for treatment of suspected MRSA infection should depend on the knowledge of MRSA incidence in the patient location, and evidence of patient colonisation. When systematic screening was performed, MRSA was a more frequent cause of infection when compared with MSSA (13 infections in 63 colonised patients (20.6%) v seven infections in 477 non-colonised patients (2%), odds ratio 18).⁵¹ The median delay between colonisation and infection was five days. The positive predictive and negative predictive values for previous colonisation with MRSA to predict infection in the presence of a positive specimen were 81% and 84% respectively. This suggests the potential value of screening and limiting empiric vancomycin treatment of suspected Gram positive organisms to those colonised with MRSA. Additional authors have suggested that failure to use vancomycin as highly empiric treatment would be associated with minimal risk.

In the guidelines for empiric management of patients with hospital acquired pneumonia published by the American Thoracic Society patients who develop mild-moderate pneumonia and have specific risk factors, and those with severe disease, risk factors and are within four days of admission, or without risk factors and beyond five days, are at potential risk of MRSA as a pathogen.⁵² Treatment under these guidelines should include an antibiotic described below, until MRSA is excluded. An alternative method for selection of agent would be focused at more intensified investigation such as bronchoalveolar lavage, or the protected brush specimen technique. This strategy could allow for limiting broad spectrum antibiotic therapy, and may avoid the risk of inappropriate treatment. This strategy is advocated by many intensivists.

Vancomycin and teicoplanin

Vancomycin is the drug of choice for the treatment of established MRSA. Though early preparations contained fermentation by-products, today preparations are highly purified

Box 7: Key points

- Empiric decisions to utilise antibiotics with coverage for MRSA should be based on either culture information or knowledge and consideration of risk factors.
- Vancomycin remains the drug of choice for critically ill patients with MRSA infections.
- Linezolid and quinupristin/dalfopristin are newer alternatives.

(although not completely pure) and hence less toxic. Vancomycin is bactericidal for most Gram positive organisms. However, against enterococci it is only bacteriostatic. Though commonly believed to be true and used in clinical practice, the vancomycin/aminoglycoside combinations do not have proved synergy for the majority of *S aureus* strains, including both MSSA and MRSA.

Vancomycin is used to treat infections including bacteraemia, endocarditis, pneumonia, cellulitis, osteomyelitis, and meningitis. Although vancomycin has a large volume of distribution, it penetrates poorly into bile and aqueous humor. Penetration into cerebrospinal fluid is poor except when the meninges are inflamed, when cerebrospinal fluid concentrations range from 7% to 21% of concomitant serum levels.^{53 54} The desired cerebrospinal fluid level is 25 µg/ml and levels should be monitored, as penetration into cerebrospinal fluid varies. The bone to serum ratio of vancomycin concentration is 10%, which can increase up to 25% in infected bone.⁵⁵ Vancomycin retains activity between pH of 6.5 and 8 with achievable concentration in abscess fluid that approach serum concentrations. Vancomycin is eliminated by glomerular filtration, with 80%–90% of the administered dose appearing in the urine within 24 hours. The serum half life in adults with normal renal function is 4–8 hours after intravenous injection. In anuric patients it may be prolonged to about nine days and the drug may be detected in serum for as long as three weeks after a single 1 g dose. From 10%–55% of vancomycin is protein bound in serum. However, this is believed to have a negligible effect on clinical results. Vancomycin cannot be given intramuscularly because of severe pain at the injection site. Orally administered vancomycin is poorly absorbed from the gastrointestinal tract and should not be used for systemic illness. Vancomycin may be inactivated by high concentrations of heparin if the two agents are administered through the same intravenous line.⁵⁶

Teicoplanin (formerly teichomycin A) is a glycopeptide antibiotic that is chemically similar to vancomycin and is widely used in Europe but is not available in the US. It has greater lipophilicity than vancomycin, long elimination half life, slow release from tissues, water solubility at physiological pH, and few if any inactive metabolites. Thus in some European centres it has been a viable if not preferred alternative to vancomycin. However, in England and other parts of Europe as has been true with vancomycin, resistant strains have been found.

Mechanism of action

Vancomycin inhibits synthesis and assembly of the second stage of cell wall peptidoglycan polymers by complexing with the D-alanyl-D-alanine portion of peptide precursor units, which fits into a “pocket” in the vancomycin molecule, thereby preventing its binding to peptidoglycan terminus that is the target of transglycolase and transpeptidase enzymes. Like penicillin, however, vancomycin requires actively growing bacteria to exert its effect. In addition, vancomycin is capable of injuring protoplasts by altering the permeability of their cytoplasmic membrane and selectively inhibiting RNA synthesis. Vancomycin continues to exert its antibacterial activity after concentrations fall below inhibitor levels, with a postantibiotic effect of about two hours.⁵⁶ In 41 US hospitals involv-

ing 108 adult ICUs, vancomycin use was most closely linked to endemic isolation of MRSA, type of ICU, and central line associated bloodstream infections. No single restriction effort was associated with lower rates of vancomycin use.⁵⁷

Linezolid

Linezolid is in a new class of antimicrobial agents, discovered in 1987, known as oxazolidinones. Linezolid has inhibitory activity against a broad range of Gram positive bacteria, including MRSA, VISA, vancomycin resistant enterococci, and penicillin resistant *S pneumoniae*. Characteristics of linezolid include 100% oral bioavailability, renal elimination, and a short postantibiotic effect of about one hour. No synergy exists with aminoglycosides for Gram positive bacteria. Maximum peak plasma levels are achieved within 1–2 hours after administration. MIC values over 32 µg/ml are considered resistant.⁵⁶

Mechanism of action

Linezolid exerts its effects early in protein synthesis by inhibiting the initiation complex at 30S ribosome. Linezolid interacts with a translational component that is either directly or indirectly involved in binding mRNA during the start of translation. Because of this unique action, no cross resistance with other currently available antimicrobials occurs.⁵⁶ Linezolid resistance due to a 23S rRNA mutation may emerge in enterococci during therapy with this antimicrobial, and may be associated with clinical failure.

Linezolid is indicated for adults in the treatment of nosocomial pneumonia, hospitalised patients with serious community acquired pneumonia, and complicated and uncomplicated skin and skin structure infections due to appropriate pathogens. In controlled phase III trials, linezolid was as effective as vancomycin in the treatment of MRSA. Though effective against MRSA, randomized double blind controlled large trials in ICU patients for the treatment of any significant anatomic site of infection are not currently published except in abstract form.

Quinupristin/dalfopristin

Quinupristin/dalfopristin is derived from the streptogramins pristinamycin IA and IIB; they are macrolactones that belong to the family of macrolides-lincosamides-streptogramins. The drugs are present in a fixed 30:70 ratio, are synergistic, and have in vitro activity similar to that of pristinamycin. Neither component is extensively protein bound, and the combination has a postantibiotic effect of 6–8 hours. High intracellular concentrations are seen and excretion is primarily through the biliary tract. The drug combination is a potent inhibitor of cytochrome P450 enzymes. Both drugs are metabolised quickly after intravenous administration.⁵⁶ In an open labelled trial for patients failing therapy for MRSA, the overall success rate (defined as a clinical outcome of either cure or improvement, and a bacteriological outcome of eradication or presumed eradication) was 71.1% in the all-treated population (n = 90) and 66.7% in patients who were both clinically and bacteriologically evaluable (n = 27).⁵⁸ Success rates for endocarditis, respiratory tract infection and bacteraemia of unknown source were below the population mean and could not be determined.⁵⁹

Mechanism of action

Quinupristin/dalfopristin exerts activity through inhibition of protein synthesis. The drugs sequentially bind to different sites on the 50S ribosome, resulting in a stable ternary drug-ribosome complex. Newly synthesised peptide genes cannot be extruded from this complex. When resistance to only one of the components of quinupristin/dalfopristin occurs, the organism may continue to be inhibited but not killed.⁵⁸

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Other agents

Efficacy studies of cotrimoxazole against clinical MRSA isolates in Europe and the US have reported resistance rates of 47%–76% and 100%, respectively. Similar resistance results have been obtained with clindamycin (30%–97% in Europe and 98% in the US) and erythromycin (38%–97% in Europe and 92% in the US).^{51–58} Rifampin is a potent bactericidal antistaphylococcal agent, but high level resistant strains occur early in vivo if it is used alone so that rifampin must be used only in combination with another antistaphylococcal agent. Rifampin has a high concentration in the bone and tissue, therefore, may be particularly helpful for infections outside the endovascular system. Doxycycline and minocycline seem to be active in vitro and bactericidal for some isolates. Aminoglycoside modifying enzymes produced by many MRSA strains make aminoglycosides not useful in this setting.⁶⁰

Newer agents such as LY333328 (glycopeptide), SCH27899, and newer semisynthetic tetracyclines (glycylcyclines) are still considered investigational drugs which are in preclinical or clinical phase II–III evaluation.

Guidelines for the control and prevention of MRSA have been published by a number of societies throughout the US, Britain, and other European countries.^{61–64} The reader is referred to these manuscripts for further details.

CONCLUSIONS

S aureus is a formidable pathogen with significant morbidity and mortality. MRSA is a commonly found in the community, and hospital, especially in the ICU. Patients who are elderly, are immunosuppressed, have been exposed to antibiotics and prolonged ICU care, and exposed to a MRSA carrier or infected patient are at risk of colonisation and subsequent infection. Pneumonia and bacteraemia are the most common causes of MRSA infection but soft tissue, bone, and endovascular disease cannot be ignored. Treatment is traditionally with a glycopeptide, vancomycin, or in Europe, teicoplanin. Newer alternatives are linezolid and quinupristin/dalfopristin but side effects, costs, and resistance may limit the usefulness of these agents.

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Questions (true/false; answers at end of paper)

1. Of the two million nosocomial infections in US hospitals annually, more than 70% are caused by MRSA, and account for \$100 billion annually in cost.
2. Major reservoirs of MRSA in institutions include colonised infected patients as well as health care workers.
3. Methicillin resistance is most commonly mediated by the *mecA* gene which changes the cytoplasmic vacuoles.
4. Carrier rates for MRSA among hospitalised patients is between 11% and 32%, and the most common and reliable way to identify these individuals is by rectal swab.
5. Infection control methods such as selective high risk screening, contact isolation, and typical agents such as mupirocin are all cost effective for intensive care unit patients.
6. One third of colonised patients with MRSA become infected and one half of these have bloodstream infections and pneumonia.
7. Tracheal colonisation is *S aureus*, *Haemophilus influenzae*, and *Streptococcus pneumoniae* within 24 hours after head injury is associated with early onset ventilator pneumonia.
8. Vancomycin penetrates well into cerebrospinal fluid and should be used as a primary agent for all Gram positive infections.

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Answers

1. False. 40% of infections are caused by MRSA. Cost of antibiotic resistant infections range from \$100 million to \$30 billion.
2. True. Patients serve as the reservoir while health care workers are believed to be the vector.
3. False. The *mecA* gene encodes for single additional penicillin binding protein, PBP2a, with low affinity for all β -lactams.
4. False. Prevalence rates for MRSA commonly is 25%, and is best identified (85%) by cultures of the anterior nares. High carrier rates are seen in injection drug users, persons with insulin dependent diabetes, patients with dermatological conditions, and in patients with long term indwelling catheters.
5. True. See table 1. Chaix *et al* demonstrated that a modest reduction in infection rate (14%) can be beneficial in reducing both costs and morbidity.
6. True. Mortality rates may reach 50% of bloodstream infections and 33% for pneumonia.
7. True. 68% of patients are colonised with one or more of the above pathogens after head injury with and odds ratio of 28.9 (95% confidence interval 1.59 to 48.5) for early onset nosocomial pneumonia.
8. False. Cerebrospinal fluid penetration for vancomycin is poor except when the meninges are inflamed with concentration ranging between 7% and 21% of concomitant serum levels.