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

A S Haddadin, S A Fappiano, P A Lipsett

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.

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 St 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.1,2 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.2 Most investigators have found a high prevalence of drug resistant bacteria in the hospital—and in the ICU—than in the community.1,3 However, MRSA strains are now found in the community in relatively large numbers, and MRSA is no longer only an ICU nosocomial disease.5 Recent studies have documented the increased costs associated with MRSA infection, as well as the importance of colonisation pressure.1,3 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.7 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.8 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.8 Also more than 95% of S aureus isolates produce...
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.9

METHICILLIN RESISTANCE

Resistance to β-lactam compounds that are not hydrolyzed 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.2 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.2−11 Harboring mecA gene is not sufficient for methicillin resistance; some S aureus (<2%) strains containing the mecA gene are susceptible to methicillin.11−14 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.12−15 In some strains, this includes a regulatory locus, mecR1-mec, 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, blaRI, blaZ) which, because of sequence similarities to the mecR1-mec I 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

GLYCOPEPTIDE INTERMEDIATE RESISTANCE

Several isolates of MRSA with intermediate resistance to vancomycin (>8–16 µg/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 1999.17−19 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.20

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.21 Staphylococci are found in the human body, on the skin, and mainly in the axillae, perianal area, inguinal area, and the anterior nares.22 Carrier rates are between 11% and 32% among healthy adults in the general population,23−25 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 intravenous catheters.

Carrier to a higher rate of infection than the non-carrier, the infection usually caused by the same colonising strain.7

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.22 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.23

Risk factors for community acquired infection included intravenous drug use, serious underlying illnesses, previous antimicrobial therapy, and previous hospitalisation.24 Risk factors associated with nosocomial acquired MRSA colonisation and infection are shown in box 3.25 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 wounds, 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.11

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.12 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.12 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.13

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.4 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.3

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.11 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.12 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.13 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.9 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.9 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.9 Somewhat surprisingly, without cohorting patients, neither of these commonly employed
methods was successful in decreasing MRSA colonisation. In another tertiary referral hospital, patients with MRSA colonisa-
tion were excluded from the orthopaedic and haematol-
ogy 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). Again, this emphasises the importance of
reinfection and re-exposure with MRSA.

Colonisation on environmental surfaces in the ICU can
serve as a reservoir for MRSA, including some previously
suspected 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. In an interesting recent report,
MRSA strains that had caused outbreaks had a significantly
longer survival period (1–3 months), and in higher concentra-
tions (×1000) when compared with strains causing sporadic
MRSA infection. 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. 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 transmis-
sion. 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 spo-
radic strains can be made by analysis of the coagulase gene by
single phage typing of S aureus.

Table 1 Infection control methods for MRSA

<table>
<thead>
<tr>
<th>Method</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening Patients</td>
<td>Effective if followed by isolation, cost effective for threshold values</td>
</tr>
<tr>
<td>Staff</td>
<td>Rates low, expensive</td>
</tr>
<tr>
<td>Handwashing</td>
<td>Effective, compliance poor</td>
</tr>
<tr>
<td>Antimicrobials</td>
<td>Mupirocin widely used, effective, resistance occurs</td>
</tr>
<tr>
<td>Topical agents</td>
<td>Resistance if used commonly used agents, other (rifampin and fusidic acid) with side effects</td>
</tr>
<tr>
<td>Systemic</td>
<td>Certain agents effective (povidone iodine, chlorhexidine, triclosan)</td>
</tr>
<tr>
<td>Body cleansing</td>
<td>Effective if changed between patients</td>
</tr>
<tr>
<td>Cohorting of patients</td>
<td>Nurses required to take care of a variety of patients, effective, disruptive</td>
</tr>
<tr>
<td>Complete separation/ward closure</td>
<td>With total isolation, effective</td>
</tr>
<tr>
<td>Preidentification of carriers and previously infected patients</td>
<td>Variable effectiveness, blocks of rooms may be helpful</td>
</tr>
<tr>
<td>Gowns</td>
<td>No proved value</td>
</tr>
<tr>
<td>Gloves</td>
<td>Effective</td>
</tr>
<tr>
<td>Environmental cleaning</td>
<td>Not effective in slowing outbreaks</td>
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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. 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. 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. 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. 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 48.8).

The risk factors identified by Rello et al for the development of ICU MRSA and mechanical ventilation included steriod
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). 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). Prior 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).

Mortality at 30 days in those infected with MRSA was 21%, was 86% when bacteraemic from a pulmonary or abdominopelvic 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. 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.

Chronic illness and acute critical illness may allow for the formation of resistance organisms on the skin or in the gastrointestinal tract. 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. Interestingly, the outpatients with chronic illness has a higher prevalence of micrococcus and Gram negative bacilli at both the forearm and sternum. Thus, not only current patient location but also past history may predispose the patient to certain microorganisms.

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.

### 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). 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. 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.
**Mechanism of action**

Vancomycin inhibits protein synthesis by binding to the 30S ribosomal subunit, thereby blocking the formation of the initiation complex at the 30S ribosome. This prevents the binding of tRNA to the ribosome, thereby inhibiting protein synthesis.

**Vancomycin**

- **Mechanism of action**: Vancomycin inhibits protein synthesis by binding to the 30S ribosomal subunit, blocking the formation of the initiation complex at the 30S ribosome.
- **Clinical use**: Vancomycin is used to treat infections such as endocarditis, pneumonia, cellulitis, osteomyelitis, and meningitis. It is effective against Gram-positive bacteria, including MRSA.
- **Adverse effects**: Vancomycin can cause allergic reactions, nephrotoxicity, and ototoxicity. It can also cause the development of resistant strains.

**Linezolid**

- **Mechanism of action**: Linezolid inhibits protein synthesis by binding to the 23S rRNA in the 50S ribosomal subunit, preventing the formation of the 70S initiation complex.
- **Clinical use**: Linezolid is used to treat infections caused by Gram-positive bacteria, including MRSA and VRE. It can be combined with quinupristin/dalfopristin to treat infections caused by enterococci.
- **Adverse effects**: Linezolid can cause nausea, vomiting, diarrhea, and hepatic dysfunction. It can also cause the development of resistance in some bacteria.

**Quinupristin/dalfopristin**

- **Mechanism of action**: Quinupristin/dalfopristin inhibits protein synthesis by binding to the 23S rRNA in the 50S ribosomal subunit, preventing the formation of the 70S initiation complex.
- **Clinical use**: Quinupristin/dalfopristin is used to treat infections caused by Gram-positive bacteria, including MRSA and VRE. It can be combined with vancomycin to treat infections caused by enterococci.
- **Adverse effects**: Quinupristin/dalfopristin can cause nausea, vomiting, diarrhea, and hepatic dysfunction. It can also cause the development of resistance in some bacteria.
Key references

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). 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. Newer agents such as LY333328 (glycopeptide), SCH27899, and newer semisynthetic tetracyclines (glyclyclines) are currently being investigated as treatment options.

Guidelines for the control and prevention of MRSA have been published by a number of societies throughout the US, Britain, and other European countries. 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, 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 endocardial 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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REFERENCES

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 infection and 33% for pneumonia.
7. True. 68% of patients are colonised with one or more of the above pathogens after head injury with an 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.