Staph aureus [created by Paul Young 02/10/07]

antimicrobial therapy - general

MSSA:
- Penicillin, in high doses, is the drug of choice for penicillin- sensitive S. aureus, although these strains are rare.
- Strains that produce penicillinase but are methicillin sensitive should be treated with semisynthetic compounds (e.g. flucloxacillin, dicloxacillin, nafcillin, oxacillin) which have bactericidal activity.
- Alternatives that are active against methicillin-sensitive S. aureus include first generation cephalosporins (e.g. cephalothin, cefazolin) and beta-lactam/beta-lactamase combinations such as amoxycillin-clavulanic acid.
- Anti-pseudomonal agents such as piperacillin-tazobactam, ticarcillin-clavulanic acid and the carbapenems are also active against MSSA although of course their spectrum of activity is far broader than necessary for this

MRSA:
- Methicillin-resistant isolates are frequently cross-resistant to many antimicrobials including aminoglycosides, macrolides, lincosamides, tetracyclines, co-trimoxazole, cephalosporins, carbapenems and beta-lactam/beta-lactamase combinations.
- Fluoroquinolone resistance is now widespread, particularly in MRSA isolates. Although newer agents (e.g. levofloxacin, gatifloxacin, sparfloxacin and moxifloxacin) have improved Gram-positive activity, the mechanism of cross-resistance amongst fluoroquinolones is such that susceptibility cannot be assumed
- Antibiotics with potential or proven activity against MRSA include vancomycin, teicoplanin, quinupristin-dalfopristin, linezolid, rifampicin and fusidic acid.

VISA:
- vancomycin-intermediate strains have all been sensitive to chloramphenicol, gentamicin, rifampicin, co-trimoxazole and tetracycline.
- The role of the recently approved antibiotics quinupristin / dalfopristin and linezolid in the treatment of vancomycin-intermediate S. aureus infections is still unclear.

vancomycin

General:
- Vancomycin remains the drug of choice for MRSA, although it is intrinsically less active against Staphylococci than beta-lactams.

Tissue distribution and tissue penetration:
- has a wide volume of distribution but penetration into cerebrospinal fluid is poor.
- penetration into peritoneal dialysis fluid is unpredictable and may necessitate an intraperitoneal route of administration for treatment of MRSA peritonitis in patients with a peritoneal dialysis catheter

Dosage adjustment in renal impairment
- intervals must be adjusted in patients with reduced creatinine clearance as renal excretion is the main route of drug elimination.

teicoplanin

- Teicoplanin is a glycopeptide similar to vancomycin and is widely used in Europe, often in preference to vancomycin.
- It is usually active against both MSSA & MRSA.

quinupristin: dalfopristin

General:
- These agents are streptogramins and are presented in combination at a fixed ratio of 30 : 70 (quinupristin: dalfopristin).
- The two compounds act synergistically on different sites of the 50S subunit of the bacterial ribosome to inhibit protein synthesis

Activity:
- It has good activity in vitro against a range of Gram-positive bacteria, including methicillin-resistant and vancomycin-intermediate S. aureus.
- decreased in vivo susceptibility to quinupristin / dalfopristin has been noted with some erythromycin-resistant MRSA

Trials:
- Controlled trials indicate that quinupristin / dalfopristin and vancomycin are of comparable efficacy for a range of MRSA infections, including skin infections, pneumonia and bacteraemia

linezolid

General:
- Linezolid belongs to a new class of drugs called the oxazolidinones.
- It acts by inhibiting protein synthesis at an early stage of bacterial replication.

Activity:
- No cross resistance from other classes of antibiotics has been reported.
- It has inhibitory activity against a broad range of Gram-positive bacteria including MRSA and VISA
- Linezolid-resistant isolates have been recovered during clinical use, although reports are still rare

Trials:
- Clinical trials comparing vancomycin and linezolid in the treatment of infections caused by MRSA have shown equivalent clinical and bacteriological success rates.

rifampicin

General:
- Rifampicin is a potent bactericidal agent which penetrates well into tissues and abscesses.
- High levels of resistance develop early if it is used alone; hence, it must only be used with another antistaphylococcal agent to which the isolate is susceptible.

Trials:
- The role of rifampicin as an adjunctive drug in patients with S. aureus infections remains controversial. Nonetheless, it is recommended in combination with gentamicin and either vancomycin or a semisynthetic penicillin for prosthetic valve endocarditis.

fusidic acid

Activity:
- Fusidic acid inhibits protein synthesis and is active in vitro against MSSA and MRSA. However, resistance develops if it is used alone and, like rifampicin, it must be administered with another antistaphylococcal agent to which the strain is susceptible.

Trials:
- There are only case reports or small studies evaluating the clinical efficacy of combinations of fusidic acid with other antibiotics, including vancomycin, flucloxacillin, teicoplanin, rifampicin and gentamicin; results have been varied. Nonetheless, it remains frequentpractice to add either rifampicin or fusidic acid to the regimen in patients who are either failing to respond to treatment or who have a deep-seated infection such as osteomyelitis

laboratory diagnosis

- S. aureus is arranged in grape-like clusters when viewed through the microscope.
- It is distinguished from other species by 'gold pigmentation' of colonies and by positive results for coagulase, mannitol fermentation and deoxyribonuclease tests

epidemiology & development of resistance

- First described in the 1880s, S. aureus has adapted rapidly in the modern environment.
- Shortly after penicillin was first introduced, resistant strains of S. aureus producing penicillinase were reported.
- The development and use of semisynthetic penicillins (e.g. flucloxacillin, oxacillin, cloxacillin and dicloxacillin) was quickly followed by new resistance identified as early as 1961 in the United Kingdom
- Currently, in most USA and European hospitals, MRSA represents about 30% of all S. aureus isolates. However, rates of up to 55% may be found in some ICUs.
- Furthermore, in some countries, methicillin-resistant S. aureus is no longer confined to the hospital environment, having established itself as an important community pathogen, particularly in long-term nursing care facilities in the USA
- Since the emergence of MRSA, the glycopeptide vancomycin has been the only uniformly effective treatment for staphylococcal infections.
- Strains with reduced susceptibility to vancomycin referred to as vancomycin-intermediate or glycopeptide intermediate S. aureus, have emerged, initially in 1996 in Japan, and subsequently in many areas including the USA, UK, Europe, Australia and Asia.
- It is postulated that vancomycin-intermediate S. aureus arises from methicillin-resistant S. aureus clones with 'heteroresistance', strains that are categorised as susceptible by conventional minimum inhibitory concentration breakpoints but that generate vancomycin- intermediate S. aureus cells at high frequency in their daughter populations when exposed to vancomycin
- a truly vancomycin-resistant strain of S. aureus (minimum inhibitory concentration greater than 32 microg/ml has been isolated in the USA from a renal dialysis patient with a history of prolonged exposure to multiple antibiotics including vancomycin.
- This strain possesses the enterococcal vanA gene, an acquisition that had previously only been observed in vitro

colonisation & infection

- Humans are natural reservoirs for S. aureus and, as a surface commensal, it is most commonly found in the anterior nares. - About 30% to 50% of healthy adults are colonised with S. aureus at any given time; 10–20% are persistently colonised

Higher rates of nasal S. aureus carriage are found in
(i) intravenous drug users,
(ii) diabetics,
(iii) those with long-term indwelling catheters
(iv) patients with acquired immunodeficiency syndrome
(v) inflammatory skin disorders

- Colonisation with either methicillin-sensitive or methicillin-resistant S. aureus increases the risk of subsequent infections with the same colonising strains, particularly in wound infections and central venous catheter-related bacteraemia

- Nasal de-colonisation reduces the rate of infections by S. aureus, particularly surgical site infections and bacteraemias in haemodialysis patients.
- The most effective agent available for eradication of S. aureus nasal carriage is topical mupirocin

clinical infections

- S. aureus causes many illnesses, including pneumonia, bacteraemia and sepsis, superficial and deep skin and soft tissue infections and toxin-mediated disease.
- It remains one of the commonest pathogens isolated in ventilator-associated pneumonia and catheter-related bacteraemia.
- S. aureus bacteraemia has a propensity to seed to other sites including the heart valves, bones, joints and spinal canal.
-Secondary abscesses formed at distant sites may act as foci for recurrent infections.
- It is worth noting that S. aureus is a common pathogen for native and prosthetic valve endocarditis and that intravenous catheters remain the commonest source of innoculation.
- endocarditis may be under-diagnosed and all patients with S. aureus bacteraemia should be investigated by echocardiography, as a diagnosis of endocarditis determines the duration of therapy