CURRENT PRACTICE

Antibiotic therapy of surgical infections

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We face a crisis with regard to antibiotic resistance. Highly pathogenic, pan-resistant Gram-negative (GN) or highly resistant Gram-positive (GP) infections are increasingly prevalent in the intensive care unit and in the general wards. Whereas no intervention will eradicate resistance, it is essential that antibiotic management be optimised both to improve efficacy and to extend the lifespan of drugs that are currently available.[1]

Therapy of severe community-acquired (CA) infections (those with organ dysfunction and/or hypotension) are treated according to the site, local resistance patterns, the presence or absence of factors associated with resistance, and the pharmacokinetics and pharmacodynamics of the specific drug and its ability to penetrate into the infected tissue. Whatever the type of infection, the principles of antibiotic therapy remain the same. Therapy should be initiated as soon as possible via the parenteral route,[2] and 5 - 7 days is the recommended duration.[3,4] Therapy should be directed towards clinical response, which limits duration – prolonged duration of antibiotic treatment and overuse of antibiotics being the most important factors causing resistance. If features of sepsis persist after 2 - 3 days, the first consideration should be that there has been inadequate source control rather than that the infection is resistant or that a prolonged course of antibiotics is required.[5]

In general, monotherapy according to established protocols should be employed for CA infections unless anaerobic cover is required and the chosen antibiotic has no anaerobic activity, or all the likely organisms in a specific infection are not covered. There is no evidence that combinations or broad-spectrum agents increase efficacy in severe CA infections.[6,7] For example, regimens that would be considered for CA intra-abdominal infection include monotherapy with amoxicillin/clavulanate, piperacillin/tazobactam and ertapenem (the latter especially when antibiotics have recently been used, in patients from long-term care facilities, or where *Pseudomonas* is not suspected) and moxifloxacin.[8] Combinations that are frequently used are cefuroxime or third- or fourth-generation cephalosporins with metronidazole, amoxicillin/clavulanate with an aminoglycoside, or cipro-/levofloxacin plus metronidazole.[9]

With regard to skin and soft-tissue infection, the considerations that would determine whether therapy is appropriate would be the requirement for GP cover and the likelihood of a methicillin-resistant *Staphylococcus aureus* (MRSA) or a vancomycin-resistant *Enterococcus* (VRE). Similarly, the necessity for GN cover and also the potential for resistant organisms, such as *Pseudomonas* spp. as in macerated ulcers, wounds of long duration, previous broad-spectrum antibiotic therapy and wounds that have extensive necrosis or gangrene or are malodorous, would have to be considered. One other factor that will be discussed further on is the need for virulence factor inhibition.[10]

Inappropriate initial therapy is associated with increased mortality; however, routine use of broad-spectrum empiric antibiotics that would cover all possible organisms ensures selection of an increasingly resistant ambient flora.[11] In a recent study of 5 715 patients with septic shock, the overall survival rate was 43.7%. Survival with initial appropriate therapy was 52.0%, and with inappropriate therapy (where the organism is not covered by the chosen antibiotic) it was only 10.3% (odds ratio (OR) 9.45, confidence interval (CI) 7.74 - 11.54; $p<0.000$ and OR 8.99, CI 6.60 - 12.23, after adjustment for APACHE II, co-morbidities, hospital site, and other risk factors).[12]

The factors that are associated with resistance are:

- hospitalisation
- immunosuppression
- postoperative infection
- recent antibiotic therapy
- residence in long-term care facilities.

If these factors are not present, an antibiotic that covers CA organisms such as amoxicillin/clavulanate is usually sufficient. It is important to note that the anaerobic cover of the latter, piperacillin/tazobactam

and the carbapenems including ertapenem exceeds that of metronidazole and clindamycin, and as such these agents should not be added to the therapy to increase anaerobic cover.[13]

Resistant organisms

The organisms that are most frequently found in resistant nosocomial sepsis are the GNs, i.e. enterobacteriaceae (*Escherichia coli*, *Klebsiella*, *Enterobacter*), *Acinetobacter* spp., *P. aeruginosa*, *Proteus* spp. and *Stenotrophomonas maltophilia*, and the GPs, i.e. enterococci, MRSA, coagulase-negative staphylococci (CoNS) and *Candida*. Resistant flora are unit specific and influenced mainly by antibiotic usage, and large variations exist between hospitals and units and from country to country.[14,15] Currently, according to data from the National Antibiotic Surveillance Forum, 50% of the *Klebsiella* spp., 22% of the *Enterobacter* spp. and 8% of the *E. coli* that are cultured in Johannesburg are extended-spectrum beta-lactamase (ESBL) producers, and these figures are similar to those from elsewhere in the country.[16] With regard to *P. aeruginosa* blood cultures in Johannesburg, only 65% are susceptible to ceftazidime, 73% to cefepime, 61% to piperacillin/tazobactam, 69% to amikacin, 59% to imipenem, 58% to meropenem and 62% to cipro- and levofloxacin. Only polymyxin (colistin) can be said to be reliable with 97% susceptibility. The figures for *Acinetobacter* spp. are even worse, with suscetibilities to ceftazidime, cefepime, piperacillin/tazobactam, amikacin, meropenem/imipenem and polymyxin of 32%, 38%, 36%, 52%, 51% and 94%, respectively. It should be noted that if polymyxin is excluded, the carbapenems are no longer the best agent for either of these organisms. This not the case with the ESBL producers, however, where 100% remain susceptible to the carbapenems but significant resistance to other antibiotics has developed. ESBL organisms are resistant to all beta-lactams with the exception of the carbapenems, and 69.9% of *Klebsiella pneumoniae* are resistant to the quiolones, 38% to gentamicin and >40% to piperacillin/tazobactam.[16] The nightmare scenario is that the *Klebsiella* spp. will, in addition to the ESBL enzymes, acquire a carbapenemase, the KPC enzyme, which renders them resistant to all beta-lactams including the carbapenems. In Greece, 25 - 50% of *Klebsiella* spp. currently have KPC enzymes, and these organisms have been already been identified in isolated cases in South Africa.[17,18]

Twenty-six per cent of *S. aureus* and 65 - 70% of CoNS are methicillin resistant, and there is increasing resistance to vancomycin among staphylococci and enterococci. With regard to vancomycin resistance among staphylococci, two patterns are seen, 'MIC creep' and 'hetero-resistance'. The former is indicative of a gradual increase in minimum inhibitory concentrations (MICs) as a whole, and the second is a phenomenon in which organisms of differing sensitivity are found within the same culture.[19-21] The importance of this lies in the fact that if the MICs are 2 or greater, the clinical failure rate is in the region of 50%. It has therefore become mandatory for laboratories to provide MIC values with the antibiogram in order to determine whether therapy with vancomycin will be effective.[22]

With resistance levels as they are currently, a different strategy is necessary to ensure optimal outcome. This includes early, effective therapy using broad-spectrum antibiotics followed by de-escalation once the culture is available, the rationale being to minimise resistance but retain efficacy.[23] The antibiotic used for empiric therapy will depend on the principles described above.

The choice, dose and method of delivery have become an extremely specialised area; as a consequence, regimens for hospital-acquired infection must be chosen with the assistance of a clinical microbiologist. It is also critical not merely to treat a culture but to ensure that there is evidence of sepsis, i.e. pyrexia, elevated white cell count, increasing need for inotropes, and in addition an elevated C-reactive protein and/or procacitonin level. *Pseudomonas* and in particular *Acinetobacter* are frequently colonisers and as such do not require therapy. Similarly, a positive blood culture of a CoNS requires only that the lines be removed unless there is a prosthesis and it is suspected that this has become infected.

Regimens for nosocomial infections

Regimens for nosocomial infections can include:

- ESBL producers: carbapenem, tigecycline
- *Acinetobacter*: aminoglycoside, colistin, tigecycline (if MIC ≤1; whether it will be effective for MIC ≤2 is not known)
- *Pseudomonas*: monotherapy: cefepime, piperacillin/tazobactam, meropenem/imipenem; colistin (should always be used with another agent, see below)
- MRSA: vancomycin, teicoplanin, linezolid, tigecycline.

The use of meropenem/imipenem

Monotherapy is suitable where the sensitivity is known. Combinations should be considered with empiric therapy where resistant infections or GP infections are suspected. Appropriate additions for GN bacilli (GNB) are amikacin or ciprofloxacin and for GP cocci (GPC) vancomycin, teicoplanin or linezolid. Appropriate dosing and administration are essential; meropenem and imipenem should be administered by extended infusion over 3 hours.[24] Metronidazole or other anti-anaerobic agents are not necessary except for *Clostridium difficile*. Unnecessary use, as with all

antibiotics, results in collateral damage, specifically an increase in ESBLs, MDR *Pseudomonas*, *Acinetobacter*, *Stenotrophomonas* and KPC-producing *Klebsiella*.[25]

The use of colistin

This is an old agent originally withdrawn due to nephro- and neurotoxicity. It acts by binding to phosphate moieties on lipid A, where it displaces magnesium and destabilises endotoxin on the GN cell wall. It is effective against GNB except for *Proteus* spp., *Burkholderia cepacia, Providencia* spp., *Serratia marcescens* and *Morganella* spp. For maximum efficacy and to reduce the possibility of resistance, it must be used appropriately. It must not be used as a daily dose and must never be used alone. It should be administered as follows:

With normal renal function: 9 million units loading dose, then 3 million units three times daily.

In renal failure: 1 - 2 million units loading dose, then 1 million units BD (creatinine clearance <30 (ml/min) and 2 million units BD (30 - 50 ml/min).[26-30]

In both circumstances, colistin should always be used with another agent such as rifampicin 600 mg BD IVI or ceftazidime 2 g 6-hourly.

Because colistin disrupts the bacterial cell membrane, antibiotics to which an organism is resistant are rendered susceptible. This includes antibiotics that are usually only active against GP organisms, such as rifampicin. The combination of colistin plus rifampicin increases killing of *A. baumannii by more than* 100-fold and similar synergy is apparent for *P. aeruginosa*, *S. maltophilia*, *K. pneumoniae* and *S. marcescens*. This practice may also delay emergence of resistance, which has already been documented in *Acinetobacter*, *Pseudomonas* and *Klebsiella*. Synergy has also been observed with imipenem, ciprofloxacin and ceftazidime.[26-33]

The use of glycopeptides

Because MICs have been increasing, higher therapeutic levels in the range of 15 - 20 µg/ml are desirable. As opposed to the aminoglycosides, levels should be maintained at this level without a trough. Time to therapeutic level may also be an important determinant of efficacy, and a bolus is therefore essential.[34]

GP organisms produce peptide products that function as virulence factors: 39.9% of *S. aureus* produce one or more toxins that cause tissue damage and shock and promote tissue spread.[35] Oxacillin enhances toxin release whereas clindamycin, linezolid, fucidin and rifampicin inhibit and vancomycin, tetracyclines and flouroquinolones have no effect. As a consequence, inhibition of protein synthesis is essential for serious infections.[36]

The use of tigecycline

This is a new drug derived from the tetracyclines. It is minimally metabolised and primarily excreted by the liver (renal 22%). It has no effect on cytochrome P450, no clinically relevant drug interactions, and is not influenced by renal impairment or removed by

MRSA treatment

- Drainage and debridement.
- Removal of foreign bodies: catheters, pacemakers, orthopaedic hardware.
- Glycopeptides remain the primary therapeutic option.
- However, if it is a hospital-acquired pneumonia or the patient is intolerant or allergic to vancomycin or fails therapy, linezolid is the most appropriate option.
- Tigecycline is an option for skin and soft-tissue infection or can be used as directed therapy in renal dysfunction or if there is resistance to the other agents.

Doses of Gram-positive antibiotics

Normal renal function:

Teicoplanin: 800 mg BD, then 400 mg BD × 3 days, then 400 mg daily

Vancomycin: 1 g stat then 2 g infused over 24 hours titrated to <15 - 20 µg/ml.

Renal dysfunction:

Teicoplanin: 400 mg BD × 1, then daily

Vancomycin: 1 g initially and then maintain levels at <15 - 20 µg/ml

Linezolid: 600 mg BD.

Tigecycline: registered at 100mg stat then 50 mg BD. It is possible, however, that critically ill patients, with an increased volume of distribution, may require at least 100 mg BD.

haemodialysis.[37] It has relatively low serum values but concentrates in various tissues: 38-fold in the gallbladder, 2.3-fold in the colon, 78-fold in pulmonary alveolar cells, and 0.58-fold in synovial fluid.[38]

The spectrum includes potent activity against all staphylococci including enterococci, as well as *Acinetobacter* spp. (the most active after colistin), *S. maltophilia*, ESBL producers including KPC producers, and anaerobes. Importantly, it has no activity against *Pseudomonas*.[38]

Tigecycline is registered for treatment of intra-abdominal sepsis and skin and soft-tissue infection, and appropriate use of this agent would include the following:

- ESBL (with or without carbapenem resistance) or *Acinetobacter* (MIC ≤1 and possibly MIC ≤2)
- MRSA but other agents are available
- vancomycin-resistant *S. aureus* (VRSA) (vancomycin MIC ≥2), VRE or MRSA with renal dysfunction as an alternative to linezolid
- polymicrobial MDR infection where *Pseudomonas*, *Proteus*, *Providencia* and *Morganella* spp. are unlikely.

The use of linezolid

This agent has no activity against GN organisms but it is highly effective against GPC inclusive of MRSA and vancomycin-resistant strains of staphylococci and enterococci. No adjustment is necessary for renal or hepatic dysfunction.[39]

Conclusion

Surgeons are important prescribers of antibiotics, and like other disciplines frequently make ill-informed decisions regarding antibiotic use. It is essential that all disciplines apply the principles of antibiotic stewardship to preserve this precious resource.

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