Antibiotics and the critically ill burns patient

Infection is the leading cause of death after extensive burn injuries, with the most common infectious syndromes being pneumonia, bacteremia and wound infection.

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IN CENTRES WHERE the principles of early excision of the burn eschar coupled with early skin grafting and the use of topical antibiotics are implemented, the incidence of burn wound infections rates have decreased. However, the growing challenge of antimicrobial resistance is making it increasingly difficult to treat sepsis in this patient population.

ORGANISMS OF INTEREST

During the first week of hospitalisation infections are usually caused by relatively sensitive organisms such as methicillin sensitive *Staphylococcus aureus, Haemophilus influenzae* and *Streptococcus pneumoniae.* Thereafter Gram-negative organisms from the order Enterobacterales (enteric Gram-negative bacilli) as well as *Pseudomonas aeruginosa* and *Acinetobacter baumannii* become the dominant isolates, and these have become increasingly resistant to even broad-spectrum antibiotics over the last few decades. Fungal infections can be seen as the 'third wave' and usually manifest after two weeks of hospitalisation in patients who had been on broad-spectrum antibiotics. *Candida species* are the most common fungal isolates in this setting, with azole-resistant species such as *Candida parapsilosis* and *Candida auris* dominating in certain centres.

THE SCOURGE OF ANTIMICROBIAL RESISTANCE

The term 'multidrug-resistant organism' or MDRO usually refers to Gram-negative bacilli resistant to at least three of the following four drug classes:

- Penicillins/cephalosporins
- Carbapenems
- Aminoglycosides
- Fluoroquinolones

Of special concern is resistance to the beta-lactam group of antibiotics, which encompasses the penicillins, cephalosporins and carbapenems. Beta-lactams are rapidly bactericidal drugs and were traditionally the 'backbone' of therapy for the vast majority of bacterial infections due to their efficacy and relatively low incidence of adverse effects.

In the Enterobacterales, production of enzymes (termed beta-lactamases and carbapenemases) is the main mechanism of resistance. The term CRE commonly used in infection prevention is short for 'carbapenem resistant Enterobacterales'. The loss of the carbapenems which had been our 'catch-all' antibiotics for years has dealt a massive blow to our ability to treat nosocomial sepsis with regards to both empirical- and organism directed therapy. We now have to resort to combination therapy with often more toxic, less efficacious, more expensive and often hard to obtain antibiotics to treat these infections.

Acinetobacter baumannii has the ability to survive on wet as well as dry surfaces, contributing to its reputation for causing nosocomial outbreaks. Descriptions of outbreaks in burn units are plentiful and often necessitates closure of the unit due to the extensive environmental contamination caused by this organism.

It is not uncommon now to find isolates that are resistant to all antibiotics in our Gram-negative armamentarium, including last resort antibiotics such as colistin. The same is true for *Pseudomonas aeruginosa* where multiple resistance mechanisms, including changes in outer membrane permeability, production of beta-lactamases and efflux pumps, can lead to the emergence of pan-resistant organisms.

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Multidrug resistance in Gram-positive organisms appears to be less of a problem in South Africa than elsewhere in the world and the incidence of methicillin resistant *Staphylococcus aureus* (MRSA) and vancomycin resistant enterococci (VRE) remain low.

Amongst the nosocomial fungal infections *Candida auris* is of particular concern due to its ability to develop resistance to multiple classes of antifungals and its propensity for causing outbreaks in the healthcare setting. Not only are most *Candida auris* isolates resistant to the azoles, but resistance to amphotericin B and the echinocandins can develop during therapy.

EMPIRICAL ANTIBIOTIC THERAPY AND SURVEILLANCE CULTURES

It has become increasingly challenging to establish an empirical antimicrobial regimen for units in which MDROs are prevalent. We cannot, as in the past, rely on carbapenem monotherapy, knowing it will cover most nosocomial infections caused by Gram-negative bacilli (with the exception of *Stenotrophomonas maltophilia*).

Surveillance cultures may be of assistance in the form of weekly tracheal aspirates for example. Cultures of tissue after debridement, wound swabs taken during dressing changes and central line tips could also assist in making choices regarding empirical therapy for sepsis. However, it is most important to discriminate between colonisation and infection. The purpose of these cultures should be purely to provide information regarding the organisms a patient is colonised with and their antibiotic susceptibilities, and positive cultures should not prompt commencement of antibiotic therapy in the absence of a diagnosis of infection/sepsis. Units should carefully consider the costs, risks, and benefits of various screening approaches.

PROPHYLACTIC SYSTEMIC ANTIBIOTICS

Recommendations regarding prophylactic systemic antibiotics to prevent infections in burn patients as well as perioperative prophylaxis for excision and grafting procedures are hampered by an absence of good quality trials. Available studies use different drugs, doses and duration of treatment and, importantly, were usually designed to evaluate efficacy but not safety. In our current world of increasing antimicrobial resistance it seems counter-intuitive to flood our units with an even greater load of antibiotics. Multiple studies have failed to provide sufficient evidence to recommend their usage.

DOSING

The hypermetabolic state of patients with large burn injuries results in increased renal clearance of commonly used antibiotics. Strategies to optimise dosing include using higher doses, increasing administration frequency and prolonging intravenous infusion times.

The limiting factor with dose increases is the risk of toxic effects. Standardising dosing recommendations is difficult given the intrapatient and interpatient variability of this hyperdynamic state. In an ideal world individualised antibiotic dosing would be possible through the use of real-time therapeutic drug monitoring for all antimicrobials. However,

in South Africa this is only readily available for the aminoglycosides and vancomycin. For this reason no official guidelines for dosing in burn patients exist at this time.

TREATING MDROs

There are currently no official guidelines for the treatment of infections caused by extensively drug resistant Gram-negative bacteria. Treatment is often complex, consists of antimicrobial combinations and should be individualised, taking into account the identity of the organism, MICs of antibiotics such as the carbapenems, colistin and tigecycline, drug toxicities and limiting factors such as renal/hepatic failure or bone marrow suppression.

Ideally a multi-disciplinary team including the clinician, microbiology lab and clinical pharmacist is needed. The Infectious Diseases Society of America recommend the novel antibiotics ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam and cefiderocol. Of these only ceftazidime-avibactam is currently available in South Africa as a section 21 drug and it is costly.

CONCLUSION

Preventing and treating infections in a burn unit depends on teamwork. Antimicrobial stewardship without the rigid application of infection prevention principles is a futile endeavour. Our approach is a collaborative effort between nursing staff, clinicians, infection prevention practitioners, pharmacists, laboratory staff and microbiologists. We cannot wait for the arrival of miracle drugs to cure our increasingly resistant population of r esistant microbes.

We have to work with the antibiotics that we currently have and use them responsibly, wisely and sometimes creatively. MC