Superbugs in ICU: Is there Any Hope for Solution?

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Bacterial infections that are resistant to multiple antibiotics are major cause of morbidity and mortality among critically ill patients. Medical community is in continuous search for new agents to combat these organisms. The search for more potent agents appears to be futile presently as nature has equipped these microbes to evade bactericidal efforts with efficient mechanisms. Despite rise in percentage of patients with sepsis due to Gram-positive pathogens and fungi, Gram-negative organisms still account for most of the nosocomial infections, including pneumonia, skin infections, intraabdominal sepsis, and urosepsis, and are re-emerging as a significant cause of bloodstream infections.6,7 There has been limited development of new antibiotics with Gram-negative activity, which has made the treatment of Gram-negative bacteremia more difficult.8,9 As noted by the Infectious Diseases Society of America’s “Bad Bugs, No Drugs” campaign, during the next decade, no new antimicrobial classes are expected to be developed to target some of these multidrug-resistant Gram-negative bacilli.

In light of emerging Gram-negative resistance combined with an empty pharmaceutical pipeline in the foreseeable future, we must make appropriate use of both newer (e.g., tigecycline, doripenem) and older (e.g., polymyxin, ampicillin-sulbactam) antibiotics so that therapeutic options are still available for years to come. It is plausible that the treatment of infections caused by these bacteria will soon require combinations of antibiotics and individual dosages based on pharmacodynamics to achieve requisite exposures at higher MICs. Antibiotic stewardship and adequate infection control practices should be reinforced in order to control the further spread of these nearly untreatable Gram-negative bacteria.5

In this issue of the journal, Shanthi and Sekhar have discussed the risk factors and outcomes of multi-drug resistant (MDR) Pseudomonas aeruginosa and Acinetobacter baumannii infections among hospitalised patients in their institute.6 Although variations exist between institutes, this article reflects the general trend of antimicrobial resistance in metropolitan hospitals and is quite worrisome. Although, distinction of an isolated MDR strain as coloniser from infection remains major clinical problem, use of markers of sepsis like C-reactive protein (CRP), cytokines, procalcitonin may be useful in this regard.7 Severity of illness, mechanical ventilation, neutropenia, prior antimicrobial exposure, blood transfusion and multiple trauma are reported risk factors for infection with MDR Acinetobacter infections.8 P. aeruginosa is well recognised cause of nosocomial infections like ventilator-associated pneumonia (VAP), device-related bacteremia, infections of burn wounds or surgery in both immunocompromised and immunocompetent hosts.8,9 MDR strains of P. aeruginosa are associated with increase in mortality, length of hospital stay and treatment cost.10

Multidrug resistance in these non-fermenting Gram-negative bacilli is defined as resistance to three or more of the following antibiotic classes: (β-lactams, including penicillins, cephalosporins, and monobactams- carbapenems; fluoroquinolones; and aminoglycosides. Resistance to most antipseudomonal agents has increased by >20%, over the last five years. Even more concerning, these bacteria can be pan-resistant, defined as resistant to all available antibiotic options.11 Gram-negative bacilli can develop resistance to most antibiotics through four general methods: production of enzymes that destroy the integrity of the antibiotic; mutations at the binding site, thereby preventing some antibiotics from binding tightly; downregulation of outer membrane proteins, thus preventing the antibiotic from getting into the periplasmic space; and efflux pumps that efficiently remove an antibiotic from the cell. Often for multidrug resistance to occur, several mechanisms of resistance are contained in the same strain. Both P. aeruginosa and Acinetobacter produce chromosomally encoded β-lactamases and also have the ability to acquire genes that encode other β-lactamases.12 The specter of acquisition of genes encoding metalloenzymes is a particularly important one, because these encode resistance to all β-lactam antibiotics except aztreonam. Hyperproduction of chromosomally encoded β-lactamases can lead to aztreonam resistance and, thereby, to resistance to all β-lactam antibiotics. Target site mutations in quinolone resistance-determining regions, acquisition of genetic elements encoding aminoglycoside resistance, and the presence of outer membrane protein deficiencies and overexpressed efflux pumps can result in P. aeruginosa or Acinetobacter species becoming truly “panresistant.” There is also the threat of transferable genetic elements that encode proteins that block the active site of quinolones. Finally, resistance to colistin and polymyxin B is now very real, eliminating all options from the antibiotic formulary.

The treatment of patients with serious Gram-negative infections must be both prompt and correct. Numerous studies have demonstrated that mortality risk is significantly increased when the initial antibiotic regimen does not adequately cover the infecting pathogen.14 Selecting such a regimen is complicated by the increasing prevalence of resistance to commonly used antibiotics. Moreover, multidrug-resistant pathogens, once limited to hospital-acquired infections, are increasingly being detected in community-acquired infections, especially those involving the urinary and gastrointestinal tracts in immunocompromised patients. In general, carbapenems are reserved at most hospitals for the sickest patients or for those who are infected with MDR Gram-negative bacilli. The carbapenem class includes imipenem-cilastatin, meropenem, ertapenem, and doripenem, the latter of which has recently been approved by the United States Food and Drug Administration (FDA). These antibiotics have broad-spectrum Gram-positive and Gram-negative activity, including activity against P. aeruginosa and Acinetobacter sp, with the exception of ertapenem, which lacks reasonable activity against non fermenting Gram-negative bacilli. There is improved efficacy or decreased mortality with imipenem or meropenem compared with other classes of antibiotics against...
ESBL-producing infections. This β-lactam class is particularly stable to hydrolysis by the ESBL enzymes. Meropenem and imipenem are routinely used as therapy for P. aeruginosa and A. baumannii infections. Between the two carbapenems, meropenem is noted to be more potent against P. aeruginosa and imipenem is more potent against Acinetobacter. Polymyxins are older agents that have extensive Gram-negative coverage but have been flawed with risks of nephrotoxicity and neurotoxicity. The increasing problem of multidrug-resistant Gram-negative bacteria causing severe infection and shortage of new antibiotics to combat them has led to re-evaluation of polymyxins. Since their discovery from Bacillus polymyxa in 1947, only two of them-polymyxin B and E (colistin) have been used clinically. Commercially available intravenous preparations are polymyxin B and colistimethate sodium. Recent data suggest less severe toxicity compared to that reported in old literature however caution in the form of dose adjustment, monitoring of renal functions and neurological status is needed when administered in patients with renal dysfunction. Though proven clinically efficacious against Acinetobacter and P. aeruginosa infections, there are reports of emerging resistance. Tigecycline is a glycylcycline agent that has in vitro activity against Gram-positive and most Gram-negative organisms and is indicated for complicated intraabdominal and skin and soft tissue infections. Although a broad-spectrum agent, P. aeruginosa, Proteus sp, Providencia sp, Burkholderia sp, and Morganella sp are commonly resistant to the antibiotic. Though not very effective by themselves, drugs like rifampin, minocycline, azithromycin and sulfactam have been used in combination with polymyxins in treating MDR Gram-negative sepsis in selected cases.

Acute severe bacterial infections have become cosmopolitan with P. aeruginosa and Acinetobacter sp leaders amongst difficult to treat infections. The cumulative impact of resistant bacteria on outcome is enormous. The most important goal is to increase adherence to basic infection control policies and procedures. These include isolating colonized or infected patients, staff education, hand washing, using disposable items, disinfecting the environment properly and fully incorporating the most current laboratory techniques to detect antibiotic-resistant organisms. Initial enthusiasm for antibiotic cycling or rotation in ICUs is being replaced by the reality that antibiotic cycling is not a practical option in the “real world.” Insistence on the use of the scheduled antibiotic may be at odds with providing appropriate and adequate empirical antibiotic therapy. Applying de-escalation to empirically started therapy helps prevent misuse of antibiotics. Though Selective Digestive Decontamination (SDD) has shown survival benefit in ICU, it can lead to emergence of resistant strains of micro-organisms. Isolation practices, antibiotic policies, effective surveillance, maintenance of epidemiological trends of infections and, rapid molecular diagnosis are the need of hour in improved and speedy management of infections with resistant organisms.

Antibiotic resistance is increasing at an alarming rate, leading to increased morbidity, mortality and treatment costs in ICU setting. Also, emergence of resistance in out of ICU and community setting demands increased awareness of MDR pathogens in physicians other than intensivists as well. A key factor in the development of antibiotic resistance is inappropriate use of antibiotics. The medical fraternity needs to understand that antibiotics constitute a precious and finite resource. Unless conscious efforts are made to contain the menace of drug resistance, MDR organisms, untreatable by every known antibiotic, may emerge, reversing the medical progress made by mankind and throwing us back to the pre-antibiotic era. The collective findings of the studies suggest that Gram-negative bacterial resistance increases the burden in the ICU as measured by mortality, length of stay, and costs. More prospective studies are needed to explore methods for combating Gram-negative resistance, including prevention, education, and better antimicrobial therapy.

References


