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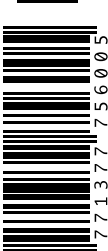
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Antibiotic Resistance in the ICU

Time to Take Things Seriously!

Multidrug resistance (MDR) is increasing worldwide and has been acknowledged as one of the major threats to healthcare by the World Economic Forum and the World Health Organization (World Health Organization 2014). Intensive care unit (ICU) patients seem to be particularly susceptible for acquiring MDR organisms, either just as colonisers, or as pathogens causing invasive infection. This increased risk is due to both patient factors as well as environmental factors such as antibiotic exposure, hospitalisation and environmental contamination with MDR bacteria (Bassetti et al. 2015a). Whereas Gram-positive pathogens were considered the major threat in the 1990s, the focus now is much more on Gram-negative micro-organisms that have developed resistance to many of our currently used antibiotics. Combined with the fact that no new antibiotic classes and only few new agents are becoming available in the near future (Harbarth et al. 2015), this offers only a grim preview on what we can expect in the next decades. A report from the Department of Health in the UK estimated that 300 million people will die over the next 35 years from MDR infections (Lancet 2014).

All critical care healthcare workers need to be aware of the problem of antimicrobial resistance (AMR) and the immediate threat associated with MDR isolates in the ICU. There are two specific challenges to intensivists when it comes to MDR: first, early identification and appropriate treatment of patients at risk as well as patients with confirmed MDR infections, and second, avoiding spread and development of antibiotic resistance to other patients. In this respect, controlling one of the major contributors to MDR development, antibiotic use, is critical. In this article, we will discuss the different aspects of treating patients

with MDR infections. Appropriate antibiotic use will be covered by another article in this series (see p. 20).

Historical Perspective on Antibiotic Resistance

AMR is not a new phenomenon. In fact, it has been present ever since antibiotics were discovered (Perry et al. 2016). For all antibiotic classes, AMR was described soon after the introduction of the drugs. AMR may have been present even before antibiotics were discovered and used in clinical practice. This however does not mean that recent trends in AMR should be taken lightly and discarded as a phenomenon that is implicit to the use of antibiotics and a natural, evolutionary event. The increase in MDR infections and difficult-to-treat pathogens is happening in many ICUs worldwide.

It is also a reality, however, that the lack of susceptibility to our current antibiotics causes patients to die in the ICU, many of them primarily admitted for other reasons than infections. In others, protracted and recurrent infections—often due to inappropriate initial therapy associated with MDR infections—and prolonged antibiotic exposure, leads to increased morbidity and prolonged hospital stays.

This phenomenon is not likely to go away, but a fatalist attitude is not appropriate here either. Although the antibiotic options may be limited, adequate antibiotic treatment is possible for most infections, through an improved use of older antibiotics, as well as new agents coming to the market. While early identification is difficult, new techniques are becoming available that allow early identification of infected and colonised patients. Although infection control is tough to implement and maintain, knowledge is increasing and prevention of MDR spreading to other patients is feasible.

Defining Antimicrobial Resistance

Whereas AMR is a common occurrence, with many micro-organisms being naturally resistant against certain antibiotics, the real problem is MDR, the situation where there is acquired resistance against an increasing number of antibiotics. According to the definition proposed by an international expert panel in 2012, MDR refers to resistance to one or more antibiotics in three or more antibiotic classes. Extensive drug resistance (XDR) is defined as resistance to at least one antibiotic in all but 2 or fewer antibiotic classes, and pan-drug resistance (PDR) is defined as non-susceptibility to all agents in all antibiotic classes (Magiorakos et al. 2012). This conceptual framework can be applied to all pathogens, but is limited to the need for extensive antibiotic susceptibility testing (AST) to appropriately classify all pathogens—Gram-positive or Gram-negative. In clinical practice this detailed information is rarely available, and as a result this classification is interesting for epidemiological studies and benchmarking, but not useful at the bedside. Also the fact that resistance to only one drug in a certain antibiotic class is enough as one of the three criteria for MDR, may not reflect the real-life challenges in antibiotic selection for MDR pathogens. Therefore in many studies a more practical approach is used where often the focus is on the resistance mechanism or resulting phenotype e.g. extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae, carbapenem resistant Enterobacteriaceae (CRE), MDR *Pseudomonas aeruginosa*, among others. These are also the pathogens that are most challenging to treat, and focusing on a pathogen rather than the MDR/XDR/PDR classification is probably a more rational and clinically oriented approach. There clearly is a difference in approach from a clinical perspective compared to the microbiological perspective.

Epidemiology in Critical Care

Large-scale, detailed, epidemiological data on AMR in our ICUs worldwide are scarce. Most studies in the literature are either single centre reports (often before-after studies on a particular intervention), or focus on an outbreak and the management thereof. Large-scale epidemiological data exist, but ICU-specific data are rarely available, and are mostly limited to a small number of centres contributing to the database. Moreover, there are limited longitudinal data available, so it is hard to make any statements on the current status of AMR in ICUs. This is an area that requires urgent attention.

What is clear from these limited data is that there is important geographical diversity when it comes to MDR and the mechanisms involved. This further challenges external validity of many of the epidemiological studies. This geographical diversity may not only be at the country level, but even within the same area or city, important variations may be present; hospital and unit specific data are required.

Gram-negative pathogens clearly are the major threat to patients in our ICUs today; it seems that the Gram-positive resistant pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) are more or less controlled and not perceived as an immediate threat by many clinicians. The most urgent challenges in the ICU are ESBL-producing Enterobacteraceae, CRE, MDR *Pseudomonas aeruginosa* and *Acinetobacter*. For many of these pathogens, the southeast of Europe seems to be a hotspot, but also elsewhere in Europe ESBL and CRE incidence is increasing. For CREs there seems to be considerable variability in enzyme distribution. Recently, colistin resistance has been identified as an emerging threat, which is particularly problematic as colistin is the backbone of many antibiotic schemes to treat MDR pathogens in severely ill patients (Marston et al. 2016).

Whereas in many countries these pathogens are found only in isolated cases or related to hospital-acquired infections and outbreaks, it is more worrying that they are becoming endemic in some countries. In the first case this poses few challenges for empiri-

cal therapy, but this is different when MDR pathogens spread in the community and may be involved in community-acquired infections as well. In these situations, more broad-spectrum antibiotics may be used, fuelling the problem of MDR and accelerating a vicious circle of increased antibiotic consumption, antibiotic resistance and increased length of stay.

Diagnostics and Risk Stratification – the Need for Speed

MDR infections pose specific problems not only to clinicians, but also to the microbiology lab. Classic microbiological techniques require multiple days until full AST can be reported and this is no longer acceptable with our current challenges. Rapid identification and susceptibility reporting are now the goal of many new techniques that are becoming available. New techniques such as matrix-assisted laser desorption/ionisation time-of-flight (MALDI-TOF) analysers, and polymerase chain reaction (PCR) based techniques drastically reduce time to reporting of problematic pathogens or particular resistance patterns (Mitsuma et al. 2013). While interesting in terms of performance, the true value of these systems should be assessed on the time to adequate therapy, overall antibiotic consumption and incidence of MDR infections in the unit as a whole. A strategy based on PCR to identify and isolate patients colonised with MDR pathogens could not reduce acquisition rates of multidrug-resistant bacteria in a large, international study (where hand hygiene compliance was high) (Derde et al. 2014).

This does not mean that trying to identify the patient at risk for infection with MDR pathogens should not be pursued. However, it is plausible that risk factors for MDR involvement are not uniform for all different MDR pathogens, which further complicates things. Common risk factors for MDR involvement include antibiotic exposure, previous stay in an acute or chronic care facility, the presence of comorbidities and chronic kidney disease requiring RRT (Martin-Loeches et al. 2015). The problem is that these factors are quite common these days, not only in hospital-acquired infections but also in community-acquired disease.

Antibiotic Therapy—Continued Efforts Necessary

As for all pathogens, antibiotic therapy remains the cornerstone of infection treatment. Empirical antibiotic therapy is especially challenging in endemic situations; this is where early risk stratification, probably combined with rapid diagnostic techniques, has its highest merits. This will allow selective targeting of patients at risk for infection with MDR pathogens while avoiding antibiotic overuse in the overall population. Whereas this may be more easy outside the ICU, we need to apply the same concept in critically ill patients.

Generally, combination therapy is recommended for MDR infections, particularly in the empirical phase but also for directed therapy for many pathogens.

Although resistance is increasing, many of our ‘old antibiotics’ are still of use in the treatment of MDR pathogens (Theuretzbacher et al. 2015). Based on our current knowledge though of antibiotic pharmacokinetics (PK) and pharmacodynamics (PD) in critically ill patients, dosing and antibiotic administration certainly are to be considered when treating MDR infections. Not only the dose itself is important—with doses generally higher compared to non-severe infections—but optimising PK/PD of antibiotics may also include the use of prolonged infusion e.g. for beta-lactam antibiotics. One critical limitation in this approach is the lack of detailed information about the susceptibility of the pathogen; the minimally inhibitory concentration (MIC) is important but not routinely available, and certainly not in the early phase of therapy using current technology. Additionally, for many drugs that are crucial for managing MDR infections, there are no solid PK and PD data available on which we can base solid dosing advice (colistin, fosfomycin, among others). To fully compensate for the changed PK in critically ill patients, therapeutic drug monitoring (TDM) may be a logical solution; this fits the trend towards personalised medicine, but up until now no study has demonstrated an advantage of TDM guided therapy in MDR infections.

New drugs are coming to the market that are specifically targeting MDR pathogens (Bassetti et al. 2015b). All of these are further developments in known antibiotic classes, and

there is a real risk of AMR developing against these newly developed drugs, particularly if these will be used on a large scale and in settings where basic concepts of infection prevention are lacking. It is our responsibility to use these antibiotics wisely, that is for the right indication (and pathogen), and for the correct duration.

Antibiotics that are of particular interest here are ceftolozane/tazobactam, avibactam combinations (ceftazidime, ceftaroline, aztreonam), plazomicin, new beta-lactamase-inhibitor plus carbapenem combinations and eravacycline. Until now most of these new drugs have been tested in complicated urinary tract infections and intra-abdominal infections only, but studies in infected critically ill patients are being performed and will inform us of their value in this precise setting.

Irrespective of the above, it is imperative to control antibiotic use in all patients through an integrated, multidisciplinary approach aimed at reducing antibiotic exposure and improving patient outcomes, commonly referred to as 'antimicrobial stewardship' (De Waele et al. 2016), which is discussed more extensively by Schouten on page 20.

Infection Control – a Crucial Cornerstone

Controlling transmission of MDR pathogens in the hospital is the main goal in infection control strategies, focusing mostly on hand hygiene, surveillance, patient isolation and environmental measures. Hand hygiene is one of the primary strategies of infection control measures, and indeed impacts transmission of high-risk pathogens such as MRSA or VRE (Derde et al. 2014). Equally important is environmental cleaning, which has long-time been ignored, particular-

ly of beds and equipment that have had MDR-infected or -colonised patients in them.

Decontamination of the skin and GI tract, two important potential reservoirs of MDR pathogens, is more controversial. While selective digestive decontamination (SDD) and selective oral decontamination (SOD) have been proved to improve outcome in setting with low incidences of MDR, concerns about the effect of antibiotics used in SDD in high-MDR prevalence prevent wide adoption of this approach (Plantinga et al. 2015). Large-scale studies in these settings are currently underway. Skin decontamination with chlorhexidine (chlorhexidine bathing) remains controversial, and was found to reduce central line-associated bloodstream infections and MRSA infection, and to have the most effect when baseline infection rates are high (Frost et al. 2016).

One topic drawing much attention now is the impact of the microbiome on acquiring MDR pathogens. Faecal microbiota transplantation has been suggested as a possible strategy in the treatment of relapsing *Clostridium difficile* infections (Youngster et al. 2014) but may also be helpful to combat MDR colonisation. Many studies in this field are underway.

All of the above strategies however do not prevent transmission of mobile genetic elements encoding for AMR in the GI tract of our patients. Combined with widespread antibiotic use that greatly affects the microbiome and takes down our natural defence against colonisation with pathogens (Brooks and Brooks 2014), this exchange of resistance mechanisms in the gut is probably the biggest threat in Gram-negative MDR infections.

Conclusion

AMR has become a major concern in critical care medicine, and impacts the daily manage-

ment of severe infections in many ICUs. Maximising appropriateness of antibiotic therapy in patients with infections due to MDR pathogens while minimising antibiotic exposure in all patients in the ICU and avoiding transmission of MDR pathogens are the main goals for which all healthcare workers in the ICU are responsible. Antibiotic therapy, while challenging, is still possible for most pathogens using both older antibiotics and the new drugs that will become available in the next years. An individualised approach incorporating PK/PD principles and also considering antibiotic susceptibility will further improve antibiotic effectiveness. Infection control measures remain important with hand hygiene as the key element; other interventions may be pathogen- or unit-specific. ■

Conflict of Interest

Jan De Waele declares Consultancy for AtoxBio, Bayer Healthcare, and Merck. He is Infection section Chair at the European Society of Intensive Care Medicine, President of the Belgian Society of Intensive Care Medicine, Past President of WSACS - the Abdominal Compartment Society and Senior Clinical Investigator at the Flanders Research Foundation.

Abbreviations

AMR antimicrobial resistance
AST antibiotic susceptibility testing
ESBL Extended-Spectrum beta- Lactamase
ICU intensive care unit
MDR multidrug resistance
MRSA methicillin-resistant <i>Staphylococcus aureus</i>
PCR polymerase chain reaction
PD pharmacodynamics
PK pharmacokinetics
PDR pan-drug resistance
TDM therapeutic drug monitoring
VRE vancomycin-resistant enterococci
XDS extensive drug resistance

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