

# ICU

## MANAGEMENT & PRACTICE



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# Antibiotic Resistance

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# Antibiotic Resistance

Infections occur frequently in critically ill patients in the ICU. They may be the reason for admission and could also be due to immunosuppression associated with critical illness. Antibiotics are essential tools for treating both common and complex infections. It is recommended that antibiotics should be administered as soon as possible once an infection is identified. However, managing these infections continues to become more and more challenging because of the increasing prevalence of antibiotic-resistant strains. Nearly [50% of isolates in ICUs](#) are resistant to at least one antibiotic. Antibiotic-resistant infections are difficult to treat and increase morbidity and mortality. They also add costs to healthcare systems. Addressing this threat is essential and requires infection prevention and slowing the progression of antibiotic resistance.

In our latest cover story, our contributors discuss the problem of **antibiotic resistance**, the frequency, type and extent of antibiotic-resistant bacteria, the impact of this problem on patient outcomes, the importance of effective antimicrobial stewardship programmes to facilitate responsible use of these drugs and their proper implementation in ICUs, the role of rapid diagnostic testing, and important strategies to reduce the spread of antimicrobial resistance.

Sofie Dhaese, Jerina Boelens, and Jan De Waele discuss pharmacodynamic and pharmacokinetic principles and how they play a central role in antimicrobial dose-optimisation to combat antimicrobial resistance. Miriam Machado, Benoit Guery, and Jordi Rello provide an overview of antimicrobial stewardship in critical care units and emergency departments and highlight the key aspects of reducing multidrug resistance.

Gabriela Bautista-Aguilar, Jorge Peña-Juárez, Edgar Pérez-Barragán and co-authors discuss the frequency of severe infections by antibiotic-resistant gram-negative bacteria in ICU patients and their impact on patient morbidity and mortality. Iaswarya Ganapathiraju and Ryan Maves highlight the need to address the problem of antimicrobial resistance and talk about the importance of faster diagnosis of bacterial infections and an overview of rapid diagnostic testing.

Sara Haddad, Johnny Zakhour, Anthony Kerbage and Souha Kanj define diagnostic stewardship and discuss how it can be implemented in intensive care units to improve patient outcomes. Ines Lakbar, Gary Duclos, and Marc Leone provide an overview of antimicrobial resistance and its impact on clinical outcomes in the ICU. Haifa Algethamy reviews practices currently available to reduce the spread of antimicrobial resistance and novel therapies presently being developed.

In other feature articles, Etrusca Brogi, Chiara Piagnani, Marta Pillitteri, and Francesco Forfori discuss the importance of clearly defining sepsis, improving early recognition strategy, and increasing the understanding of innate and adaptive immune system derangements that facilitate the development of sepsis.

Antibiotic resistance continues to be one of the most significant public health challenges today. The increasing prevalence of antibiotic-resistant strains makes the management of infection in critically ill patients a difficult task. Responsible antibiotic prescribing can help control the development of antibiotic resistance but how well antimicrobial stewardship programmes are designed and implemented is extremely important. There is also a need to develop new and improved antibiotics to improve patient outcomes, but this must be supported by efforts dedicated to preventing infections and slowing the development of antibiotic resistance.

As always, if you would like to get in touch, please email [JLVincent@icu-management.org](mailto:JLVincent@icu-management.org).

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### Antimicrobial Resistance in the ICU

The use of antimicrobial drugs in the hospital is very common with approximately 35% of the patients on an adult ward and up to 70% of the patients in the intensive care unit (ICU) receiving an antimicrobial drug on any given day (Versporten et al. 2018). This large antimicrobial burden exposes the patient to the risk of acquiring multidrug resistant (MDR) organisms. These MDR organisms are either the result of exogenous cross-contamination (i.e., transfer of MDR organisms from other patients or the healthcare environment) or from selection-pressure applied to the patient's own microbiome, resulting in a competitive advantage for mutated strains (Arulkumaran et al. 2020).

ICU patients are specifically at risk for infections with MDR organisms because antimicrobial use, and therefore selection pressure, is highest in the ICU; these patients also often have advanced co-morbid illnesses and undergo invasive procedures which

# Pharmacokinetic/Pharmacodynamic Principles to Combat Antimicrobial Resistance

Pharmacodynamic and pharmacokinetic principles play a central role in antimicrobial dose-optimisation to combat antimicrobial resistance. In the future, research focused on the integration of preclinical and clinical data is paramount.

further exposes them to an increased risk for MDR-infections (Timsit et al. 2019). Antimicrobial resistance leads to excess deaths, prolonged hospitalisation, increased costs and the inability to perform procedures that rely on effective prophylactic antibiotic therapy (Laxminarayan et al. 2013). In response to the surge of antimicrobial resistance, antimicrobial stewardship programmes (ASP) were introduced in many hospitals around the world. The aim of an ASP programme is to improve patient outcome by ensuring optimal use of the available antimicrobial drugs. One of the core ASP interventions is antimicrobial dose-optimisation, i.e., informed decision making regarding the optimal dose and dosing regimen for the individual patient (Dyar et al. 2017; Roberts et al. 2019).

### Pharmacokinetics/Pharmacodynamics of Antimicrobial Drugs

Dose-optimisation of antimicrobial drugs mainly relies on pharmacokinetic (PK) and pharmacodynamic (PD) principles. PK/PD relates the effect of the drug exposure (PK) to an outcome measurement (PD) (Nielsen and Friberg 2013). For antimicrobial drugs specifically, PK/PD describes the drug exposure necessary to achieve bacterial cell kill, while limiting toxicity and antimicrobial resistance. Three summary PK/PD indices have been defined for antimicrobial drugs. For fluoroquinolones for example, the efficacy is mainly related to area under the concentration curve of the free ( $f$ ) or unbound drug, inversely related to the MIC ( $fAUC/MIC$ ). Other antimi-

crobial drugs, for example beta-lactam antibiotics, are considered time-dependent drugs and the PK/PD index of choice for this group is the percentage of the dosing interval the free concentration is above the MIC ( $fT > MIC$ ). Finally, the efficacy of a third group of antibiotics, such as aminoglycosides, is best described by the peak free drug concentration inversely related to the MIC ( $C_{max}/MIC$ ) (Mouton et al. 2012). By convention, the magnitude of the PK/PD index necessary to achieve a certain outcome (for example a  $3\text{-log}_{10}$  reduction in colony forming units (CFU/mL)) is called the PK/PD target (Nielsen and Friberg 2013).

Ideally, achieving the PK/PD target ensures a high probability of successful treatment and therefore our dosing regimens have been designed to achieve a certain predefined PK/PD target. However, a perfect dosing regimen not only ensures maximal bacterial cell kill but also tries to minimise drug toxicity and antimicrobial resistance. Unfortunately, the vast majority of preclinical PK/PD studies designed to decipher the optimal PK/PD target focused on targets linked to bacterial efficacy alone, i.e., reduction in CFU/mL, and not the drug exposure necessary to avoid antimicrobial resistance. For example, a conventional PK/PD target for intermittent infused beta-lactam antibiotics is 40-70%  $fT > MIC$ . Achieving this PK/PD target should ensure a  $3\text{-log}_{10}$  reduction in CFU/mL after 24 hours of treatment (Dhaese et al. 2020). However, Sumi et al. (2019) have emphasised the importance



of higher PK/PD targets to suppress the emergence of antimicrobial resistance (as opposed to more conventional targets to achieve a  $3\text{-log}_{10}$  reduction in CFU/mL after 24 hours). For example, Tam et al. (2017) found that a  $C_{\text{min}}/\text{MIC}$  (trough concentration/MIC) ratio of  $\geq 3.8$  (instead of 40–70%  $fT > \text{MIC}$ ) was necessary to suppress resistance development in a 120h *in vitro* hollow-fibre *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* infection model, although biofilm development in such an *in vitro* infection model may influence observations (Tam et al. 2017). Also, the majority of preclinical PK/PD experiments are only of 24-hour duration and with an initial inoculum of  $10^5$  cells (Craig 1998). Yet, clinical infections may have much higher inocula (i.e.,  $10^{10}$ ) (Feldman 1976; Wimberley et al. 1979; Low 2001) and preclinical experiments with longer treatment durations (for example 5 days instead of 24h) have clearly shown selection of mutant strains beyond the first day of treatment, even when an initial  $3\text{-log}_{10}$  reduction after 24 hours was achieved (Tam et al. 2005).

### The Mutant Selection Window

Mutant prevention concentration (MPC) based indices as opposed to MIC-based indices have also been explored to describe the risk of bacterial resistance with any given dosing regimen. The MPC is the concentration that prevents growth of first-step resistant mutants. This concentration is seen as the upper limit of the mutant selection window (MSW). Above this concentration, cell growth would require two mutations. This is deemed unlikely given that the theoretical size of the inoculum with bacteria harbouring two mutations (approximately  $10^{14}$ ) far exceeds the inocula found in clinical infections ( $10^{10}$ ) (Feldman 1976; Wimberley et al. 1979; Low 2001). The lower limit of the MSW is the lowest concentration that inhibits the growth of the majority of the drug-susceptible organisms, since below this concentration mutant strains do not have a growth advantage (Drusano et al. 2015; Firsov et al. 2003; Drlica 2003). This lower limit is approximated by the  $\text{MIC}_{99}$ ,

or the minimal inhibitory concentration that results in growth inhibition of 99% of the cells. Concentrations within the MSW are expected to promote selection of resistance (Figure 1) (Drusano et al. 2015; Firsov et al. 2003).

The advantage of using the MPC instead of the MIC and denominator in the PK/PD equation is that the MPC is determined using an inoculum of  $10^{10}$  instead of  $10^5$  as is common for MIC determination (Blondeau et al. 2001; Mouton et al. 2018). Using a higher inoculum has the advantage that the risk of a first-step mutant is accounted for; moreover, it also better mirrors clinical infections. However, to date, studies comparing MIC-based and MPC-based targets have not been able to clearly demonstrate superiority of one over the other (Firsov et al. 2003; Drlica 2003; Blondeau et al. 2001; Mouton et al. 2018; Olofsson et al. 2006).

did not achieve the PK/PD target of 50%  $fT > \text{MIC}$ . The observation of low target attainment rates in ICU patients fuelled the search to optimise the PK/PD of beta-lactam antibiotics in the ICU and maintaining beta-lactam antibiotic concentrations above the MIC for a prolonged period by extending the duration of infusion (i.e., prolonged infusion). The goal of prolonged infusion has always been to reduce the mortality of patients suffering from infection but little attention has been paid to differences in antimicrobial resistance with different modes of infusion (Wang et al. 2014; Lyu et al. 2017; Dulhunty et al. 2013; Abdul-Aziz et al. 2016; Bao et al. 2017; Wang 2009; Chytra et al. 2012; Vardakas et al. 2018; Roberts et al. 2016; Rhodes et al. 2018). From a theoretical point of view, continuous infusion drug concentrations may remain in the MSW for either 0 or 100% of the time, which makes it difficult

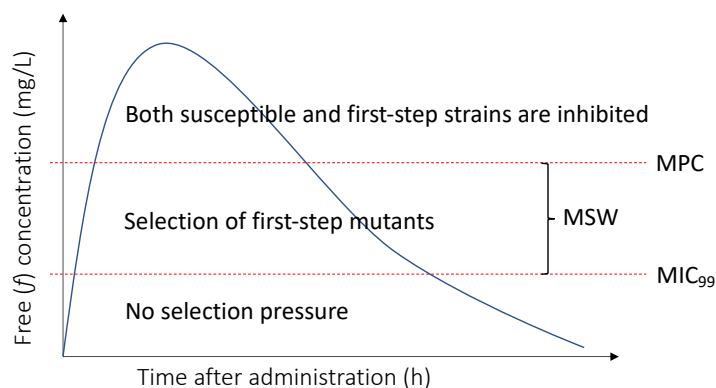


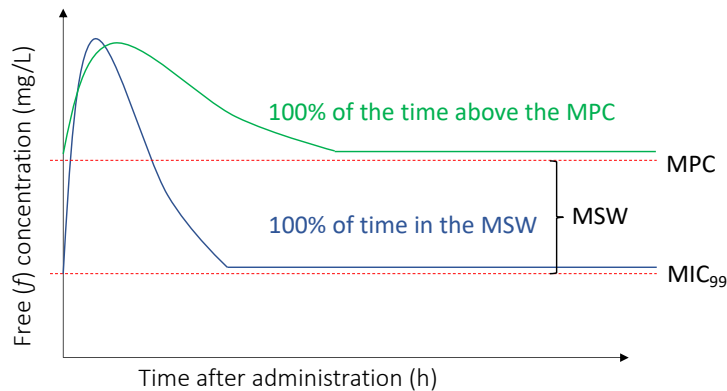
Figure 1. Concentration-time curve after an intermittent infusion of antibiotic drug

$\text{MIC}_{99}$  = minimal inhibitory concentration that results in growth inhibition of 99% of the cells; MSW = mutant selection window; MPC = mutant prevention concentration

### Prolonged Infusion of Beta-Lactam Antibiotics and Antimicrobial Resistance

The PK of beta-lactam antibiotics is highly unpredictable in critically ill patients, mainly because of changes in kidney function and volume of distribution (Gonçalves-Pereira and Póvoa 2011). In 2013, a landmark study by Roberts et al. (2014) demonstrated that approximately 16% of the patients treated for infection with beta-lactam antibiotics administered via intermittent infusion

to assess the impact of prolonged infusion on the risk of antimicrobial resistance (Figure 2). New acquisition, colonisation, or infection with a multi-resistant organism (MRO) is a secondary outcome of the BLING III study, a large multicentre trial with primary outcome 90-day-all-cause mortality of ICU patients receiving either intermittent or continuous infusion of piperacillin or meropenem. Study enrollment is now finished and the results are eagerly awaited (Lipman et al. 2019).



**Figure 2.** Concentration-time curve after a continuous infusion of antibiotic drug  
 MIC<sub>99</sub> = minimal inhibitory concentration that results in growth inhibition of 99% of the cells; MSW = mutant selection window; MPC = mutant prevention concentration

### PK/PD and Antimicrobial Drug Synergism in the Treatment of Resistant Infections

PK/PD experiments have also been used to investigate synergism between two antimicrobial drugs. Synergism in PK/PD experiments is defined as a  $\geq 100$ -fold increase in killing with the combination at 24h compared to the most active single agent and compared to the starting inoculum (Karakonstantis et al. 2022). This strategy is increasingly used to evaluate drug combinations for the treatment of infections with resistant microorganisms. For example, Lenhard et al. (2017) performed time-kill experiments with polymyxin and escalating doses of meropenem against carbapenemase-resistant *Acinetobacter baumannii* (CRAB). Meropenem monotherapy did not result in significant cell kill; however, in combination with polymyxin, a meropenem dose-dependent reduction in CFU/mL was seen. Synergism in this specific combination is mainly due to the mechanism of action of

polymyxin which acts as a detergent making holes in the gram-negative cell wall. Synergism has also been evaluated for several other MDR organisms such as *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Enterobacteriales* (Oh et al. 2021). Unfortunately, the evidence supporting synergism is mainly based on preclinical time-kill or PK/PD experiments and the recent European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines suggest the use of combination therapy for treatment of resistant organisms, although the level of evidence is low (Paul et al. 2022). Convincing *in vivo* data on combination of antibiotics are still missing.

### Future Perspectives

In the future, dose ranging and dose fractionating studies with a clinically relevant initial inoculum (at least  $10^7$ ) and a clinically relevant treatment duration (at least 5 days) will be very important to determine the antibiotic exposure necessary to avoid selection of mutant strains. Based on

available literature, this likely implies the need for higher PK/PD targets (or higher drug exposures). This is not without risk, given that the levels of drug toxicity for antimicrobial drugs are ill-defined. Hence, navigating on PK/PD targets for suppressing resistance alone may imply a higher risk of drug toxicity. Using a maximum tolerable dose (MTD, i.e., the highest dose possible without a risk of toxicity) may provide a more practical approach to this clinical problem (Dhaese et al. 2022). Indeed, this MTD should maximise bacterial cell kill whilst minimising the growth of first-step mutants and the adverse effects of high drug concentrations in our patients. The pitfall of this approach is the lack of strong toxicodynamic data, i.e., data describing the relationship between drug concentrations and drug toxicity. Therefore, research aimed at not only defining PK/PD targets for antimicrobial resistance but also at drug levels associated with toxicity will be paramount to optimise our current dosing regimens to suppress the emergence of resistance.

### Conclusion

Pharmacokinetic/pharmacodynamic principles should aid the clinician in dose-selection, not only to improve outcomes but also prevent antimicrobial drug resistance development. However, more data are needed regarding the optimal dose exposure necessary to avoid selection of resistant strains, as well as drug levels associated with drug toxicity. Also, clinical data are urgently needed to define the role of prolonged infusions and combination therapy in infections with resistant organisms.

### Conflict of Interest

None. ■

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# Pancreatic Stone Protein Biomarker for Sepsis, Anti-microbial Resistance and Nosocomial Infections

The problem of antimicrobial resistance and the use of a clinical decision score and point-of-care testing biomarkers, such as CRP and PSP, to help solve this problem.

## Introduction

Infectious diseases are a public health issue around the world, with bacterial, viral, parasitic, or fungal-related diseases responsible for 26% of mortality worldwide, and the remaining 74% attributed to non-communicable diseases (cardiovascular diseases, cancers, diabetes, trauma, etc.) (WHO 2018). The COVID-19 pandemic highlighted the high mortality of infectious diseases, with 5.94 million deaths in two years and nearly 18.2 million deaths worldwide (as measured by excess mortality) (COVID-19 Excess Mortality Collaborators 2022).

Among infectious diseases, sepsis is a major public health threat, responsible for 11 million deaths yearly (Rudd et al. 2020). Sepsis and septic shock are also the leading cause of death among children worldwide (Rhodes et al. 2017). Bacterial infections and sepsis can be effectively treated with antibiotics. However, the overuse of broad-spectrum antibiotics has led to bacterial antimicrobial resistance (AMR). Today, AMR is another major public health problem, with an estimated 4.95 million deaths associated with bacterial AMR in 2019 (Antibiotic Resistance Collaborators 2022). Sepsis and AMR together are responsible for more than 12.3 million deaths each year. The WHO has declared AMR one of the top ten global public health threats (WHO 2021).

Hospital Acquired Infections or Healthcare Associated Infections (HAIs) occur in 7-8% of hospitalised patients in Europe and 56% of patients in the ICU (Vincent et al. 2017). The main causes of nosocomial infections include bacterial AMR, lack of adherence to infection control and prevention procedures.

Bacterial infections can be complicated by sepsis and septic shock (Singer et al. 2017). In developing countries, the incidence of sepsis and septic shock is much higher than in high-income countries (Rudd et al. 2020). In addition, the administration of antibiotics is broad spectrum and leads to AMR (WHO 2011; Flandrin 2019; WHO 2020). For example, in India, the incidence rate of sepsis is the second highest in South Asia after Afghanistan (WHO 2011; Belagere 2020), and the incidence of nosocomial infection represents 11-60% (Choudhuri et al. 2017) of hospitalised patients. India also leads the world in human antibiotic use (Van Boeckel et al. 2014).

While the incidence of sepsis is higher in developing countries, the mortality rate is nearly 20-25% in developed countries. Sepsis-related costs in U.S. hospitals surpass US\$24 billion annually, making it the most expensive disease to manage (Torio and Moore 2016). Mortality from sepsis increases by about 8% per hour of delayed appropriate administration of antibiotics (Kumar et al. 2006). Hence, sepsis and septic shock can be prevented if diagnosed and treated early with appropriate treatment, in particular, antibiotics.

## Sepsis and Antimicrobial Resistance

The 2021 Surviving Sepsis Campaign (SSC) guidelines recommend starting antibiotics as soon as possible (ideally <45-60 minutes of recognition) (Evans et al. 2021). The determination of procalcitonin (PCT), with a specificity of 79% and sensitivity of 77% (Wacker et al. 2013), is not recommended because it has not demonstrated significant benefit for the patient. However, in a medical survey with 40 Swiss intensive care physicians, 92.3% test C-reactive protein (CRP), 84.6% PCT, 100% lactate and 89.7% leucocytes in case of suspicion of sepsis (Ventura 2021). Only 35.9% use the Sepsis-3 definition alone, while 34.2% calculate the qSOFA and 44.7% the SOFA. These data suggest that, in current practice, biomarkers are used more than scores. In addition to CRP and PCT, many biomarkers have been studied; however, none of them are included in the guidelines for early diagnosis of infection or sepsis because of the lack of consistent data.

There is a need to develop and optimise tools to manage sepsis and decrease the unnecessary use of antibiotics and the spread of AMR. Developing new antibiotics and searching for accurate solutions for early diagnosis of sepsis are also a priority. One possible solution could be using biomarkers combined with clinical decision support algorithms. The positive predictive value of biomarkers/algorithms could allow judicious and timely initiation of antibiotics, while

negative predictive values could indicate that antibiotics need not be administered.

Several research projects are already under way. For example, a point-of-care testing (POCT) solution using CRP and PCT has been integrated into algorithms. The e-POCT solution is an innovative electronic algorithm using host biomarker POCTs, including CRP and PCT. It could potentially improve clinical outcomes among children with febrile illnesses while reducing the use of antibiotics through improved identification and better targeting of children in need of antibiotics (Keitel et al. 2017).

### Pancreatic Stone Protein

Another possible diagnostic tool could be a solution based on clinical algorithms and the use of biomarkers with the combination of CRP and a new early biomarker of sepsis, the Pancreatic Stone Protein (PSP). Two literature reviews (Eggimann et al. 2019; Fidalgo et al. 2022) suggest that PSP could be an innovative tool for the detection of pre-symptomatic sepsis. PSP is a 16 kDa C-type lectin protein produced mostly by the pancreas and the intestine. PSP is measured in less than 10 minutes, from a drop of capillary or venous whole blood, at the point-of-care (POC) by an innovative nanofluidic technology (abioSCOPE, Abionic, Epalinges, Switzerland) CE certified since January 2020. PSP can be used to diagnose sepsis even in severe inflammatory states, such as in trauma patients (Keel et al. 2009; Klein et al. 2020a), postoperative patients (Klein et al. 2020a; Klein et al. 2015), severely burned patients (Klein et al. 2020b), and in acute respiratory distress syndrome (ARDS) after inhalation (Klein et al. 2020c).

A meta-analysis shows that PSP is more

sensitive and specific than CRP and PCT for the diagnosis of infection. The combination of CRP with PSP further enhances its accuracy with higher sensitivity and specificity for discriminating infection from non-infection (Prazak et al. 2021). PSP increases early, nearly 48-72 hours before manifestation of clinical suspicion of nosocomial sepsis, organ dysregulated response onset and elevation of CRP and PCT. Findings from a study conclude that "while the diagnostic accuracy of PSP, CRP and PCT for sepsis were similar in this cohort, serial PSP measurement demonstrated an increase of this marker the days preceding the onset of signs necessary to clinical diagnose sepsis" (Pugin et al. 2021). The kinetics of PSP allow early diagnosis of nosocomial sepsis, even before manifestation of clinical signs and symptoms. Daily measurement of this biomarker is, therefore, routinely proposed in the ICU (Pugin et al. 2021). The CRP/PSP combination is also more specific and sensitive than CRP, PCT, and PSP alone for diagnosing sepsis. Moreover, CRP and PSP dosages are accessible from a drop of blood in less than 10 minutes at the POC.

### Conclusion

Overall, it is evident that there is a need for better tools to guide the initiation of antibiotics in managing sepsis. These tools can also lead to the appropriate use of antibiotics and help decrease the burden of AMR. Using PSP in combination with other biomarkers (CRP) can provide a useful and practical approach in patients presenting with sepsis with a major impact on AMR. Moreover, integrating this combination of biomarkers (CRP/PSP) with a clinical decision support algorithm could represent an innovative solution to help overcome the

challenges related to sepsis and AMR. The savings for public health would also be major, and an estimated 1 million lives could be saved by 2030 (Ventura 2020). Hence, the use of a clinical decision score and POCT biomarkers, such as CRP and PSP, can help solve several major health problems: sepsis, AMR, and nosocomial infections. ■

### Key Points

- Sepsis is a major public health threat and responsible for 11 million deaths annually.
- Antimicrobial resistance (AMR) is another major public health problem, with an estimated 4.95 million deaths associated with bacterial AMR in 2019.
- The WHO has declared AMR one of the top ten global public health threats facing humanity.
- The 2021 Surviving Sepsis Campaign (SSC) guidelines recommend starting antibiotics as soon as possible, ideally within one hour of recognition.
- There is a need to develop and optimise tools to manage sepsis and decrease the unnecessary use of antibiotics and the spread of AMR.
- The use of biomarkers such as pancreatic stone protein (PSP), a new biomarker shown to detect pre-symptomatic sepsis up to 72 hours before the current standard of care, could be used in combination with clinical decision support algorithms as a possible solution to improve the diagnosis of sepsis and ultimately help overcome the global challenges related to sepsis and AMR.

### Disclaimer

Point-of-View articles are the sole opinion of the author(s) and they are part of the ICU Management & Practice Corporate Engagement or Educational Community Programme.

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## Introduction

Infections caused by resistant bacteria are associated with higher treatment costs and increased morbidity and mortality, and bacterial resistance represents a major challenge in global health (Antimicrobial Resistance Collaborators, 2022; WHO 2019). Antibiotic stewardship programme (ASP) is one of the interventions aimed at improving the appropriate use of antimicrobials and reducing the incidence of multidrug-resistant (MDR) bacteria (UN 2016). The EPIC II study, a one-day prevalence study, showed that 71% of ICU patients were receiving antibiotics (Vincent et al. 2009). The EPIC III study demonstrated the prevalence of *Klebsiella* resistant to third generation cephalosporin, *Pseudomonas* and *Acinetobacter* reaching rates close to 20% each (Vincent et al. 2020). The main infectious syndromes associated with MDR bacteria are respiratory, bloodstream and intra-abdominal infections (WHO 2021). The Top Ten resistant microorganisms' study (TOTEM) provides a priority pathogen list

# Antibiotic Stewardship in Critical and Emergency Care

An overview of antimicrobial stewardship in critical care units and emergency departments, highlighting aspects to reduce multidrug resistance focusing on antibiotic optimisation in respiratory infections and sepsis.

of the most serious MDR bacteria presenting in the ICU. Carbapenem-resistant (CR) *Acinetobacter baumannii*, *Klebsiella pneumoniae*-expressing carbapenemase (KPC), and MDR *Pseudomonas aeruginosa* were identified as critical organisms (Rello et al. 2019). The other bacteria are listed in Figure 1. Therefore, intensive care units (ICU) are suitable places for the implementation of ASP measures. Similarly, emergency departments (ED) are gateways for community-acquired infections and have unique features of uncertain diagnosis and

## Antibiotic Stewardship Programme

Antimicrobial stewardship refers to optimised antibiotic prescription to prevent the emergence of antimicrobial resistance (Dyar et al. 2017). Appropriate use of antimicrobials in critical areas as ICUs and EDs means the right drug, at the right time, the right dose, for the right bug, for the right duration (Wunderink et al. 2020). Despite positive evidence with ASP (Atamna-Mawassi et al. 2021; Jover-Sáenz, 2020; Karanika et al. 2016; Lee et al. 2018), in critically ill patients, clinical outcomes remained the

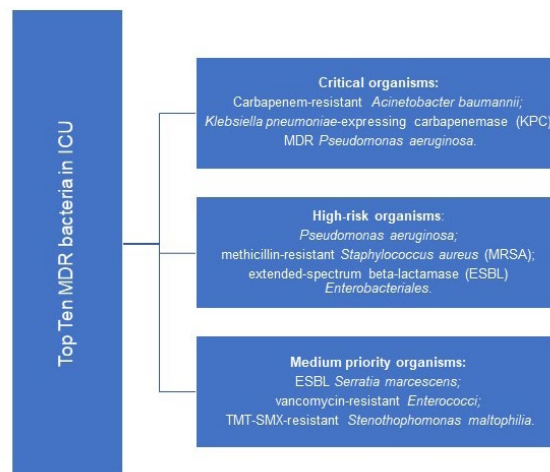


Figure 1. Top Ten MDR bacteria in the ICU. Source: Rello et al. 2019. MDR: multidrug-resistant; ICU: intensive care unit

time pressure that are favourable to misuse of antibiotics (May et al. 2014). This overview aimed to highlight the main aspects related to respiratory infection and sepsis and management in the context of intensive care units and emergency departments.

primary concern, even with the recognition that antibiotics prescribed for one patient can have ecological negative results. The balance between correct empirical choice and narrow-spectrum antibiotic use may be a challenge, especially in cases of septic

shock. Fear of missing causative pathogen or adverse clinical outcomes and aspects regimen (May et al. 2014; Denny et al. 2019). Important details to note when

Doctors factors	Patients factors	Commercial factors
Empiric judgement, using signs and symptoms to guide treatment choice.	Perceived patients' satisfaction – antibiotic as a standard of care in any kind of infection.	Promotional activities by pharmaceutical companies.
Outbreaks of diseases.	Accessibility to medical facilities.	The choice of antibiotics is often affected by promotional activities by medical representatives.
Lack of continuing medical education on antibiotic usage.	Advancing age.	
Fear for litigation.	Likelihood of drug resistant infections.	
Growing lack of trust between doctors and patients, leading doctors to opt for defensive practices by prescribing "higher" and more "critical" antibiotics.		

Table 1. Challenges in implementing antimicrobial stewardship - Factors for inappropriate use of antibiotics

Critical care and emergency practitioners are essential for solutions to the crisis of antibiotic resistance.
Antibiotic stewardship should be considered a core competency and theme of continuing medical education.
Antibiotic stewardship must address the fear of inadequate empirical treatment in the critically ill to be effective.
The adverse effect of excessive antibiotic treatment on the individual patient needs greater emphasis, with a focus on population outcome.
Antibiotic stewardship programs must ensure that improving overall antibiotic use is the primary focus.
The hope of rapid diagnostics is currently largely unfulfilled.
A shift in emphasis to an individualised approach to antibiotic therapy is needed.

Table 2. Major topics of ASP in intensive care units and emergency departments

concerning patients are important barriers to antibiotic optimisation (Alghamdi et al. 2020; Mathew et al. 2020) (Table 1). Antibiotic optimisation should be a core competency of ICU and ED physicians. Education focused on the appropriate use of antibiotics is key to changing the antimicrobial resistance (AMR) scenario (Wunderink et al. 2020) (Table 2).

### Antibiotic Stewardship Programme in Emergency Department

Antibiotics treatment in emergency department (ED) is predominantly empirical and about 30% are inappropriate (Denny et al. 2019; Oomen et al. 2020). The main aspect related to inappropriateness is the indication when there is no need for antibiotics and the broad-spectrum antibiotic

prescribing antibiotic in ED are that the first dose of antibiotic should always be given as a bolus to ensure that the time to peak concentration is not delayed (Vardakas et al. 2018), and should also check that the second dose is administered at the correct interval. Thirty-three per cent of patients with sepsis or septic shock experience a delay in the second dose, and it is more common with frequent dosing intervals (every 8 or 6 hours) as well as hospital admission in the ED (OR 2.67; 95% CI 1.74-4.09) (Leisman et al. 2017). The first infectious syndrome in ED is the respiratory tract infection (McCaig et al. 2006). Thus, we decided to focus on clinical diagnosis and empirical treatment in acute respiratory infections and sepsis in the ED.

### Acute Respiratory Tract Infections

Essentially, acute respiratory tract infections (ARTI) are self-limiting viral diseases that do not require antimicrobial treatment. Distinguishing between viral and bacterial infections is essential but may be difficult in some cases. Bacterial pharyngitis can be confirmed by a rapid antigen detection test, throat culture, or both (Petersen et al. 2007). Acute bacterial rhinosinusitis should be considered when there is persistence of symptoms, for more than 10 days without clinical improvement, or worsening of symptoms after few days of evolution (Woodhead et al. 2011). Acute uncomplicated bronchitis is a self-limited inflammation of the large airways, with inflammation lasting more than six weeks. Occasionally, upper respiratory infections and bronchitis may be complicated with pneumonia, particularly in older people after 65 years (Petersen et al. 2007).

Community-acquired pneumonia (CAP) can be caused by viruses and bacteria, and both pathogens can coexist. For younger immunocompetent adults, bacterial pneumonia is difficult without the presence of clinical signs of systemic inflammatory response syndrome (SIRS) (Harris et al. 2006). The American Thoracic Society and Infectious Diseases Society of America (ATS/IDSA) (Metlay et al. 2019) guideline published in 2019 and The European Respiratory Society and European Society for Clinical Microbiology and Infectious Diseases (ERS/ESCMID) guidelines (Woodhead et al. 2011) have different recommendations for diagnosis and treatment, as described in Table 3. Diagnosis and treatment aspects are described in Figure 2. The optimal duration of therapy for CAP is undefined, but short-term antibiotic ( $\leq 6$  days) is as effective as long-term ( $\geq 7$  days) for clinical cure (Tarsali 2018), and discontinuing treatment on fifth day is safe in the absence of fever or other sign of clinical instability for 48 hours (Uganda et al. 2016).

### Antibiotic Stewardship Programme in the Intensive Care Unit

Sepsis is diagnosed in about 30% of ICU patients. In a one-day prevalence study in European ICUs, 60% of infections were

respiratory tract infections (Vincent et al. 2020). The EU-VAP/CAP study in 27 ICUs in Europe showed that ventilator-associated pneumonia (VAP) is highly

et al. 2015). Automated BC systems can reduce the time needed to detect circulation bacteria, compared to conventional techniques. New molecular diagnostic tests

(Rello and Alonso-Torres 2021). One new technology, the Accelerate PhenoTest BC Kit provides early identification and minimum inhibitory concentration results direct from positive BC, resulting in shorter time to organism identification, shorter time to antimicrobial susceptibility test and to optimal therapy, compared with conventional methods (Bhalodi et al. 2022). This could be a promising technology for the near future. A study comparing conventional bronchoalveolar lavage (BAL) microbiological tests with the rapid diagnostic system by multiplex PCR in suspected VAP found better sensitivity for gram-negative bacteria (90%) than for gram-positive cocci (62%) (Peiffer-Smadja et al. 2020). It is noteworthy that new technologies are expensive, and interpretation and integration of results into patient care require experience in microbiology and knowledge about the limitations of the methods.

### Antibiotic de-escalation

Antibiotic de-escalation (ADE) is the replacement of broad-spectrum antimicrobials with a narrower-spectrum agent or stop components of an antimicrobial combination. The ESICM/ESCMID guide to antibiotic de-escalation (Tabah et al. 2020) recommends ADE within 24 hours of definitive culture and antibiogram results. A meta-analysis about empirical antibiotic de-escalation in patients with sepsis and septic shock, identified no significant difference in mortality between the de-escalation group and the group that maintained broad spectrum coverage, suggesting safety of this ADE strategy (Guo et al. 2016). A study of patients with HAP and VAP, identified that de-escalation was associated with fewer antibiotic days (9 vs 11,  $p < 0.001$ ), fewer episodes of *Clostridioides difficile* infection (2.2% vs 3.8%,  $p = 0.046$ ) and fewer days of hospitalisation (20 vs 22 days,  $p = 0.006$ ); without difference in treatment failure outcome at 30 days (35% ADE vs 33.8% no ADE,  $p = 0.604$ ) (Ilges et al. 2019). However, in clinical practice some aspects disfavour ADE in cases of VAP. Almost 30% of VAP cases have no microorganism identified in respiratory cultures (Rello et al. 2002). Patients with-

	ERS/ESCMID, 2011	ATS/IDSA, 2019
<b>Diagnosis</b>	<p>Recommend the collection of two sets of blood cultures in patients with CAP requiring hospitalisation.</p> <p>Urinary antigen testing for <i>S. pneumoniae</i> and <i>Legionella pneumophila</i> should be performed in cases with an indication for hospital treatment.</p>	<p>Not routinely recommend Gram stain testing or blood culture for the diagnosis of CAP in healthy outpatients.</p> <p>Not recommend the use of procalcitonin to determine the need for antibacterial therapy.</p> <p>Not recommend routine urine testing for pneumococcal antigen or urine testing for <i>Legionella</i> antigen.</p>
<b>Treatment</b>		
Adult outpatients without comorbidities	Monotherapy with amoxicillin or doxycycline or macrolide.	Monotherapy with amoxicillin or doxycycline or macrolide.
Cases of comorbidities such as chronic heart, lung, liver or kidney disease, diabetes mellitus, alcoholism, malignancy or asplenia		Combination therapy: amoxicillin-clavulanate or cefpodoxime or cefuroxime and macrolide or doxycycline; or monotherapy with a respiratory fluoroquinolone (levofloxacin, moxifloxacin, gemifloxacin).
Non-critical inpatients settings without risk factors for MRSA or <i>Pseudomonas aeruginosa</i>	Aminopenicillin and macrolide, or aminopenicillin beta-lactamase inhibitor and macrolide, or non-antipseudomonal cephalosporin, or cefotaxime or ceftriaxone and macrolide, or fluoroquinolone.	Combination therapy with ampicillin-sulbactam or cefotaxime or ceftaroline and macrolide or respiratory fluoroquinolone monotherapy, or combination with doxycycline in case of contraindication to macrolide or fluoroquinolone.

Table 3. ERSE/ESCMID/ATS/IDSA guidelines

prevalent (Koulenti et al. 2017). Considering the importance of sepsis and healthcare-associated infections (Magill et al. 2018), especially hospital-acquired pneumonia (HAP) and VAP, we highlight some useful aspects for antibiotic optimisation in critically ill patients.

### Early aetiological diagnosis

Collection of blood samples for blood cultures and other materials is recommended. Blood cultures (BC) require 12-48 hours of incubation to detect the presence of bacteria, and 40% have negative results (Phua et al. 2013); the sensitivity is influenced by fastidious pathogens and reduced on currently antibiotic therapy (Cohen

provide results in a few hours, informing about the identification of some types of pathogens as well as genotypic antimicrobial resistance markers. These new tests require less blood volume (10mL) than blood cultures (60mL), which may favour false negatives, since low volume bacteraemia is common. False positives can also occur due to contamination during collection or identification of harmless DNA (DNAemia). Although the results of new genotypic techniques can contribute to traditional methods, the variability of resistance patterns within the same bacterial species makes antimicrobial susceptibility testing (phenotypic evaluation) fundamental in the appropriate choice of antibiotic



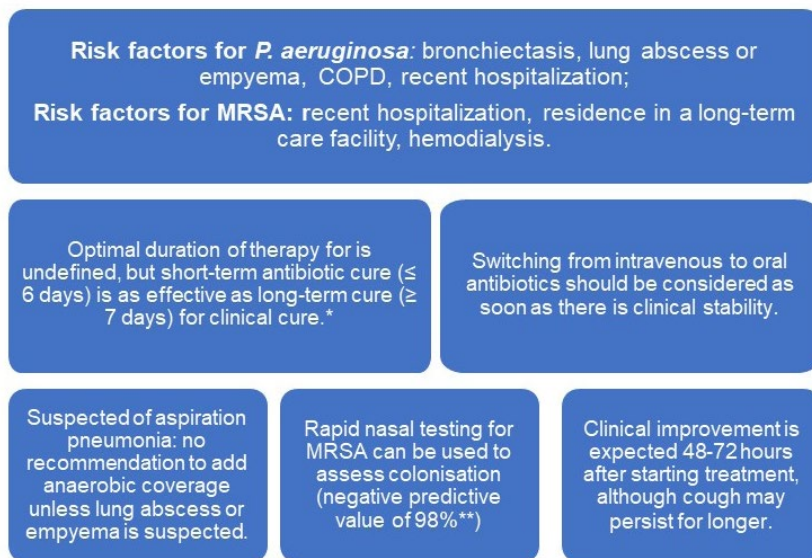


Figure 2. Community-acquired pneumonia - diagnosis and treatment aspects

MRSA: methicillin-resistant *Staphylococcus aureus*; COPD: chronic obstructive pulmonary disease. Sources: Tarsali 2018; Rioux et al. 2017.

out a defined aetiologic agent tend to have higher mortality (Rello et al. 2004). No target makes ADE unlikely; however, there is an opportunity to reassess the indication for antibiotics. In a study with suspected VAP and culture-negative BAL; 66% of cases had alternative aetiology for radiological change (Kollef and Kollef 2005).

### Duration of the antibiotic therapy

The optimal duration is the shortest time needed to control the focus of infection. Individualised assessment of the duration of treatment should include host immune status, profile of the pathogen involved, possible complications of infection, pharmacokinetic and pharmacodynamic profile of the antibiotic and clinical stability with treatment. The studies reviewed in the current version of the Surviving Sepsis Campaign (SSC) found no difference in outcomes when comparing short duration (3-8 days in pneumonia; 5-7 days in bacteraemia) and long duration of treatment (7-15 days in pneumonia; 10-14 days in bacteraemia) (Evans et al. 2021). However, a retrospective study with gram-negative BSI, demonstrated a higher risk of treatment failure in short course (7-10 days) compared with long course ( $>10$

days) treatment (hazard ratio 2.60; 95% CI 1.20-5.53,  $p=0.02$ ) (Nelson et al. 2017). In general, there is a 14-day treatment recommendation for uncomplicated BSI caused by *S. aureus* (Kimmig et al. 2021; Jung 2018).

The use of biomarkers to guide treatment time has been investigated. In studies with procalcitonin (PCT)-guide algorithm for decision making, it is observed that the PCT cut-off points vary widely, as do the parameters of proportional reduction (Rhee 2016), disfavoured the comparison between the results. Additionally, the cost of PCT is high and there is no proof of cost-effectiveness (Kip et al. 2016). It is highlighted that a single PCT dosage is not enough to exclude bacterial infection (De Santis and Corona 2016). Serum C-reactive protein (CRP) is associated with bacterial load and time-course variations of serum CRP between baseline and 96 hours can be appropriate to assess antibiotic therapy in cases of suspected VAP (Lisboa et al. 2008). Treatment CRP-based protocol was associated with more discontinuation of antibiotic therapy on fifth day compared to the control (35.9% vs 10.6%, OR 4.7, 95% CI 1.9-12,  $p=0.001$ ) (Borges et al. 2020). These results suggest that CRP may be

useful in the evaluation of response to treatment and in the reduction of antibiotic time.

A meta-analysis demonstrated that in VAP caused by gram-negative non-fermentative bacilli, short-term therapy (7-8 days) was associated with a higher risk of recurrence (odds ratio [OR] 2.18, 95% CI 1.14-4.16) (Pugh et al. 2015). In contrast, more recently an open-label, randomised, multicentre trial on *Pseudomonas*-caused VAP failed to demonstrate noninferiority of the 8-day compared with 15-day treatment; there was greater recurrence of VAP in the 8-day group, although the difference was not statistically significant (Bougle et al. 2022). Gram positive strain identification and "no growth" in BAL cultures are also factors associated with longer treatment time in VAP (Pouliot et al. 2021). It is important to note that in *Pseudomonas*-positive VAP, persistence of strains in the airway after several days of treatment is frequent, and that lung injury and artificial airways predispose to colonisation (Bodi et al. 2001; Flanagan et al. 2007).

### Conclusion

The interventions addressed in this overview are some key steps to ensure appropriate antibiotic treatment in the fight against the spread of bacterial resistance. As take-home messages we can underline: (I) antibiotic optimisation is a core competency of ICU and ED physicians; (II) antibiotic prescribing skills need to be trained; (III) it is essential to know about the pattern of infections and the antibiotic sensitivity profile in each institution, to favour the adequate choice of empirical antibiotic; (IV) re-evaluation regarding the indication of antibiotic in cases of negative microbiological exams; (V) the main obstacles to ADE and reduction in time of treatment is the assistant team's fear of adverse clinical outcomes; and (VI) education about optimisation of antibiotics may be the most effective measure to fight AMR.

### Conflict of Interest

None. ■

### References

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# Short Acting Beta-Blockers in Critically Ill Patients With Heart Failure

An overview of the clinical evidence demonstrating the effectiveness of landiolol for the treatment of atrial fibrillation or atrial flutter with heart failure and effective heart rate control during arrhythmias.

Supraventricular arrhythmias (SVTs) are common in post-operative and cardiac ICUs. SVTs increase the risk of death as well as the risk of neurological sequelae. Some common risk factors for atrial fibrillation (AF) include age, male sex, history of arrhythmias, hypertension, post-operative atrial pacing, post-operative pneumonia and mechanical ventilation for more than 24 hours. In addition, patients in the ICU often have underlying heart disease. This increases their risk for cardiac arrhythmias (Annane et al. 2008).

Epidemiology data from 26 French ICUs shows that 12% of patients developed arrhythmias. 8% developed supraventricular arrhythmias, and little more than 2% developed ventricular arrhythmias. Among the critically ill patients, 2% also developed conduction abnormalities with low heart rate. Patients with no arrhythmias had a mortality rate of 17%, compared to patients that developed supraventricular tachycardia, who had a mortality of nearly 30%. Patients with ventricular arrhythmias had very high mortality of 73%. The study also reported some hypoxic brain injury in patients with ventricular tachycardia and strokes in patients with supraventricular tachycardia (Annane et al. 2008).

AF and acute heart failure (AHF) often co-exist, leading to increased morbidity and mortality. The development of AF in HF can be due to multiple factors. AF induces electrical and haemodynamic deterioration and causes tachycardia-mediated cardiomyopathy. The presence of AF can increase the likelihood of HF. At the same time, AHF is one of the strongest risk factors for AF.

Studies show that AF is present in approximately 35% of patients with AHF. There are

several clinical scenarios of AF with AHF. In some cases, AF is the only predominant trigger for AHF. In other cases, AF is the consequence of AHF. Sometimes, AF is an innocent bystander in AHF. The goal, in every clinical situation, should be to identify AF and AHF and treat it (Halvorsen et al. 2020).

**Landiolol can treat acute disorders, including supraventricular tachycardia, and is indicated for the rapid control of ventricular rate in patients with atrial fibrillation or atrial flutter in perioperative, postoperative, or other circumstances where short-term control of the ventricular rate with a short acting agent is desirable**

According to the 2020 ESC Guidelines for the diagnosis and management of AF, beta-blockers are the first-line rate-controlling agents based on better acute rate control. Digoxin is not effective in patients with increased sympathetic drive, and studies have associated the use of digoxin with excess mortality in AF patients. Therefore, beta blockers are preferred over digoxin in

acute settings because of their rapid onset of action and effectiveness (Hindricks et al. 2021).

## Landiolol in Acute Decompensated Heart Failure Due to Atrial Fibrillation

AF and atrial flutter (AFL) are especially common in patients with left ventricular (LV) dysfunction. Landiolol is an ultra-short-acting  $\beta$ -blocker that selectively binds to  $\beta_1$  receptors. It is metabolised in the blood and liver and has a short half-life of approximately 4 minutes. The drug has been shown to be useful for treating several acute disorders, including arrhythmias in critical conditions (Nagai et al. 2013).

The J-Land study compared the efficacy and safety of landiolol with digoxin for the control of tachycardia in AF/AFL in patients with LV dysfunction. The study included two hundred patients with atrial fibrillation or atrial flutter. Findings showed that continuous intravenous administration of landiolol effectively controlled rapid heart rate in patients with AF/AFL and LV dysfunction. Landiolol was effective in 48% of the patients, while digoxin was effective in 13.9% of patients. These results show that landiolol was more useful than slow-acting digoxin. Landiolol reaches a steady state rapidly and has a half-life of 4min; therefore, the risk of hypotension is low because its dose can be adjusted according to the patient's condition (Nagai et al. 2013).

Another study evaluated the clinical usefulness of landiolol for rapid AF in patients with acute decompensated heart failure (ADHF) with reduced ejection fraction (HFrEF). Study findings show that landiolol was

safe and effective in decreasing heart rate in these patients. Landiolol has a minimum negative inotropic effect. Treatment with landiolol has been shown to be beneficial in terms of heart rate reduction (Iwahashi et al. 2019).

Furthermore, an AF-CHF landiolol survey also reported the safety and effectiveness of landiolol when it was used for the treatment of AF or atrial flutter with heart failure. No safety concerns were reported, and most patients achieved effective heart rate control after treatment (Yamashita et al. 2019).

In another study, the researchers investigated whether landiolol could effectively control heart rate in septic patients with supraventricular tachyarrhythmias. Findings showed a substantial reduction in heart rate in the landiolol group compared to the control group, and there was no deterioration of haemodynamics. In addition, the conversion to sinus rhythm was observed more frequently in the landiolol group than in the control group (Okajima

et al. 2015).

There is an ongoing trial of landiolol in sepsis patients (LANDI-SEP trial) which recently finished enrollment. Study patients have AF and/or tachycardia in sinus rhythm. Results are expected soon (Unger et al. 2018).

Another study demonstrated the benefit of using a low-dose  $\beta$ 1-blocker in combination with milrinone. The combination rapidly improved the cardiac function of ADHF patients with tachycardia, and the addition of low-dose landiolol eliminated pulsus alternans. Landiolol with milrinone improved cardiac function through the slowing of the heart rate. In addition, the cardioprotective effect of the  $\beta$ -blocker improved haemodynamics. Therefore, the addition of low-dose  $\beta$ -blockers like landiolol may be an effective cardioprotective therapy in patients with ADHF (Kobayashi et al. 2012).

The above clinical evidence demonstrates that landiolol should be the gold standard

for rapidly lowering heart rhythm. It has a better pharmacokinetic and pharmacodynamic profile. It also has a very good safety profile to slow heart rate with no negative inotropic effect. In addition, there is a long range of adjustable dosages. ■

### Key Points

- Ultrashort-acting  $\beta$ -blockers, such as landiolol, can rapidly control heart rate.
- The effectiveness of landiolol has been comprehensively assessed and proven in atrial fibrillation/atrial flutter patients with heart failure.
- The safety of landiolol has been shown to be acceptable without any major concerns.
- Most patients with arrhythmias treated with landiolol achieved effective heart rate control.

### Disclaimer

Point-of-View articles are the sole opinion of the author(s) and they are part of the ICU Management & Practice Corporate Engagement or Educational Community Programme.

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# Multidrug-Resistant Gram-Negative Bacteria in the ICU

Severe infections by antibiotic resistant gram-negative bacteria are frequent in ICU patients. They are associated with high morbidity and mortality.

## Introduction

Bacterial infections in patients hospitalised in the Intensive Care Unit (ICU) are frequent, and they elicit an increase in morbidity and mortality. The emerging development of antibiotic resistance in gram-negative bacteria (GNB) is of concern, since they are the most frequent infectious agents in critically ill patients with comorbidities or prolonged hospital stay, surgical patients and patients with invasive biomedical devices. The most frequent severe infections by GNB are caused by *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Escherichia coli*. These bacteria have developed multiple mechanisms of resistance to various types of antibiotics in the last decades, at a faster rate than the development of new drugs against them. This issue is a matter of concern for the World Health Organization (WHO).

Multidrug-resistant bacteria (MDR) are those which display resistance to three or more groups of antibiotics. Gram-negative bacteria have developed increasing antibiotic resistance; they also possess the capability to find new forms of resistance and are able to transmit them through certain genetic elements such as plasmids and transposons. The Centers for Disease Control and Prevention (CDC) classifies 18 germs into one of three categories: urgent, serious and concerning, according to their development of antimicrobial resistance. The major MDR gram-negative bacteria can be found in the first two groups (CDC 2019; Tacconelli 2014; Tacconelli 2019). According to data from the National Healthcare Safety Network (NHSN), in 2008, 13% of

infections caused by *E. coli* and *Klebsiella*, 17% of those caused by *P. aeruginosa* and 74% of those caused by *A. baumannii* in the ICU were classified as MDR, showing a trend of increasing resistance in the last ten years. Likewise, 22.3% of *K. pneumoniae* positive cultures on invasive biomedical devices were classified as MDR, with an 8% to 15% increase in carbapenem resistance (CDC 2019; Tacconelli 2014; Tacconelli 2019; Hetzler 2022).

In general, MDR-GNB can be classified into four phenotypes: 1) Third-generation cephalosporin-resistant Enterobacteriaceae (3GCephRE) and carbapenem-resistant Enterobacteriaceae (CRE), 2) carbapenem-resistant *P. aeruginosa*, 3) *K. pneumoniae* and 4) carbapenem-resistant *A. baumannii*. These are considered by the WHO as pathogens of critical priority due to their high pathogenic burden and few treatment options (Tacconelli 2014; Tacconelli 2019; Hetzler 2022). Infections caused by MDR gram-negative bacteria (MDR-GNB) in the ICU include ventilator-associated pneumonias (VAP) mainly due to *A. baumannii* and *P. aeruginosa*, catheter-associated urinary tract infections (CAUTI) mostly caused by *Escherichia coli* and *K. pneumoniae*, and surgical site infections (SSI), commonly caused by *P. aeruginosa*, *K. pneumoniae* and *A. baumannii* (Gatti 2021; Tedja 2015) (Figure 1).

## Mechanisms of Antibiotic Resistance

Mechanisms of antibiotic resistance can be classified into four groups (Figure 2). The first mechanism consists of enzymatic

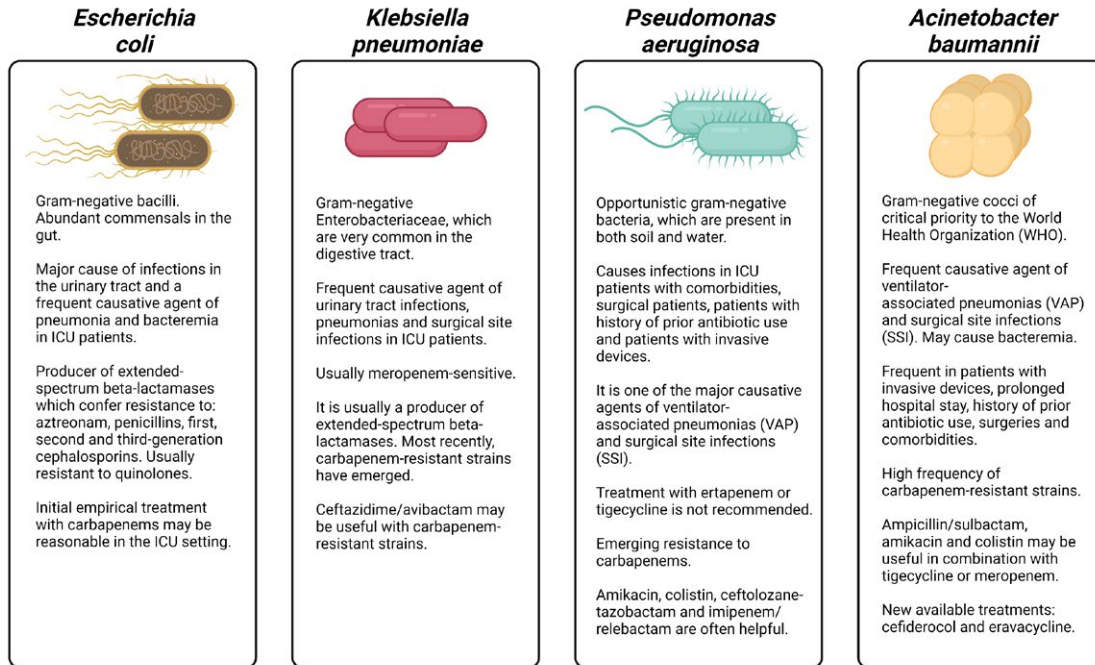


Figure 1. Gram-negative bacteria most frequently associated with severe infections and multidrug resistance in critically ill patients

inactivation through the production of enzymes capable of hydrolysing or inactivating several types of antibiotics, particularly beta-lactams; these are known as producers of beta-lactamases, which are capable of progressively expanding their resistance spectrum. Beta-lactamases are classified as follows: 1) based upon the molecular structure of the active enzyme site and amino acid sequences, 2) based upon the functional profiles of hydrolysis and inhibition, and 3) phenotypically, extended spectrum beta-lactamases (ESBLs), AmpC beta-lactamases, cephalosporinases and carbapenemases. ESBLs inactivate most penicillins and cephalosporins (including third and fourth-generation cephalosporins), as well as aztreonam; nonetheless, they often harbour additional genes or mutations for resistance to other antibiotics and are most frequently produced by *E. coli*, *K. pneumoniae*, *K. oxytoca* and *Proteus mirabilis*, but they are also used by Enterobacteriaceae such as *P. aeruginosa*, *A. baumannii* and *S. maltophilia* (Hetzler 2022; Tamma 2022). Carbapenem-resistant Enterobacteriaceae (CRE) are defined as such when resistance to at least one carbapenem is documented, due to production of carbapenemases and/or amplification of non-carbapenemase

beta-lactamase genes. The most clinically relevant of them are carbapenemase producing *Klebsiella pneumoniae* (KPC-KP), New Delhi metallo-beta-lactamase (NDM)-producing *Escherichia coli* and Verona integron-encoded metallo-beta-lactamases (VIM) produced by Enterobacteriaceae. Other important carbapenemases are imipenem hydrolysing metallo-beta-lactamases (IMPs) and oxacillinases (Hetzler 2022; Tamma 2022).

The second mechanism of resistance is via modification of the antibiotic's target site in the bacterial membrane, by modifying the binding proteins and thus avoiding its effect, or through changes in the polarity of the membrane in order to repel the antibiotic, as is the case with colistin. The third mechanism is generated through the expulsion of active compounds of antibiotics from inside the bacteria through efflux pumps, commonly observed in resistance to aminoglycosides, macrolides and fluoroquinolones by *P. aeruginosa* (Zhanel 2004). The fourth and last described mechanism of resistance consists of mutation of genes that encode porin-type proteins, thereby decreasing permeability to antibiotics (Hetzler 2022; Tamma 2022).

### Important Considerations for Diagnosis and Treatment

When severe infections are suspected, early empirical antibiotic treatment must be prompted. In a patient without hypotension or clinical findings suggestive of tissue hypoperfusion, it is recommended to start antimicrobial therapy within the first three hours, bearing in mind the following considerations: 1) the host's context, risk factors such as comorbidities, immunological and nutritional status, age, sex, antibiotic exposure in the last 30 days, chemotherapy or other relevant treatments, 2) source of infection, organ or biomedical device, 3) local epidemiology and patterns of susceptibility, and antibiotic resistance in the last six months, and 4) clinical guidelines for particular infections (Tamma 2022). In case of septic shock, which is characterised by hypotension and tissue hypoperfusion as evidenced by hyperlactataemia, delayed capillary refill, altered mental status, oliguria/anuria and/or mottled skin, it is recommended to start broad-spectrum antibiotics within the first hour (Surviving Sepsis Campaign Guidelines 2021).

Identification and treatment of the source of infection and the aetiologic agent are the



ICU stay, increasing days on mechanical ventilation and higher mortality. It is recommended to prescribe two anti-*Pseudomonas* antibiotics with different mechanism of action as initial empirical therapy, and once susceptibility tests are available, a single antibiotic may be considered according to sensitivity, except for patients with septic shock or patients with high risk of death, in whom combined therapy is preferred. Aminoglycosides should not be used in single therapy due to low success rates; additionally, the use of inhaled antibiotics is not routinely recommended. For critically ill patients without source control and in whom carbapenem-resistant (though susceptible to beta-lactams) *P. aeruginosa* has been isolated, treatment with either ceftolozane-tazobactam, ceftazidime-avibactam or imipenem-cilastatin-relebactam is suggested (Bassetti 2018; Tamma 2022).

### MDR *Acinetobacter baumannii*

Infections by *A. baumannii* are particularly serious and complicated due to increasing resistance to multiple drugs. In cases of infection by germs susceptible to carbapenems, high-dose meropenem and continuous IV infusion is recommended; nevertheless, its

empirical use is not currently recommended as first-choice single therapy given its high resistance rate. For cases of VAP due to carbapenem-resistant *A. baumannii*, both the guidelines from the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and from the Infectious Diseases Society of America (IDSA) suggest the use of ampicillin/sulbactam according to susceptibility (Gatti 2021; Paul 2022; Anwer 2021; Bartal 2022). Combinations of colistin plus rifampicin, fosfomycin, or ampicillin/sulbactam are associated with higher rates of success compared with colistin alone or ampicillin/sulbactam. Fluoroquinolones and tigecycline are not recommended as single therapy for the treatment of severe infections by *A. baumannii* (Liu 2021). In case of resistance to sulbactam, treatment with cefiderocol (Lawandi 2022) or combined treatment with fosfomycin plus ampicillin/sulbactam may both be considered. Combination therapy with inhaled colistin may also be taken into consideration (Gatti 2021).

### Prevention and Control of Infections

Interventions to prevent and control the

dissemination of MDR-GNB can be grouped into five categories: 1) hand-hygiene, 2) active screening cultures, 3) contact precautions, 4) environmental cleaning and 5) antimicrobial stewardship. Hand-hygiene has shown the greatest impact in reducing cross-contamination. The number of GNB in the skin is very low compared to the high levels of GNB that colonise the gut; however, it has been reported that up to 100% of healthcare workers' hands can be contaminated by GNB (Tacconelli 2014).

### Conclusion

Severe infections by MDR-GNB pose a serious public health threat, mostly affecting hospitalised patients and ICU patients. It is necessary to acknowledge the mechanisms that lead to bacterial resistance in order to implement strategies to decrease its dissemination. It is also necessary to acknowledge the available therapeutic options in order to set the most appropriate treatment in each individual case.

### Conflict of Interest

None. ■

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# Improving Clinical Outcomes With Early Enteral Nutrition

An overview of the benefits of early enteral nutrition, clinical evidence and recommendations, reasons for delayed enteral feeding in critically ill patients and optimal solutions.

Early enteral nutrition is proven to improve clinical outcomes and reduce acute care costs. Nutrition clinicians support the belief that enteral nutrition is preferable to parenteral nutrition (Seres et al. 2013). The hazards of parenteral nutrition are well-established and include immune compromise, increased infections, increased complications and increased mortality (Marek et al. 2001).

Clinical guidelines recommend providing enteral nutrition within 24 to 48 hours of ICU admission. However, studies show that nearly 40% of critically ill patients receive no nutritional support during their ICU stay. Furthermore, approximately 60% of patients who stay in the ICU for at least three days remain unfed for 48 hours or more (Doig et al. 2009).

Despite clinical evidence and recommendation, the optimal time for nutrition support remains unresolved. There are several reasons why early enteral feeding is delayed in critically ill patients. Feeding intolerance is frequent in ICU patients. Nearly 60% of ICU patients exhibit at least one GI symptom for at least one day (Reintam et al. 2009; Reintam et al. 2012). There is also the problem of intolerance to enteral nutrition, which occurs in approximately 40 to 60% of mechanically ventilated patients (Reignier et al. 2013).

Many critically ill patients develop gastroparesis, which reduces their tolerance for gastric feeding. Also, critically ill patients often have diminished or absent bowel movements. There are fears that early enteral feeding would result in aspiration and worsen clinical outcomes for these

patients. There is also the perception that critically ill patients can tolerate five to seven days of starvation without any detrimental effects (Marek et al. 2001).

## Improving Outcomes and Reducing Costs with Early Enteral Nutrition

The benefits of early enteral feeding cannot be overlooked. A meta-analysis of clinical trials shows significant benefits of early vs delayed enteral nutrition. Early enteral nutrition reduces mortality, pneumonia, length of stay in hospital and risk of infection (Marek et al. 2001). In addition, in non-critically ill hospitalised patients for an acute medical condition, early enteral nutrition significantly reduces infectious complications (Doig et al. 2013).

Early enteral nutrition also reduces healthcare resource consumption and total costs. Studies show a reduction of \$14,462 per patient in total acute care costs. Under European distribution, early enteral nutrition saves EUR 5,325 per patient (Doig et al. 2013).

## Jejunal Tube to Manage Intolerance to Gastric Feeding

There is sufficient clinical evidence to show the importance of enteral nutrition in critical care. Numerous studies favour its use over parenteral nutrition. However, intolerance to gastric feeding remains a challenge.

Jejunal feeding might be more appropriate in patients prone to pulmonary aspiration of gastric contents or with duodenal or gastric outlet obstruction (Baskin et al. 1994). A

jejunal feeding tube is recommended for patients who show intolerance to gastric feeding or cannot receive gastric enteral access due to altered autonomy, duodenal obstruction, gastric or duodenal fistula or gastro-oesophageal reflux disease (Itkin et al. 2011). A clinical study with a dual lumen jejunal feeding tube in the ICU showed 100% successful placement and 100% successful gastric decompression. In addition, 89% of patients reached 90% of their caloric goals within 72 hours with the jejunal feeding tube (Baskin et al. 1994).

One such dual-lumen jejunal feeding tube is the Compat StayPut®. It has a dual-port "tube-in-a-tube" design that allows for both jejunal feeding and gastric drainage. This means that only one nasal feeding tube need be inserted to deliver early enteral nutrition and help manage GI symptoms in critically ill patients.

### Key Points

- Early enteral nutrition improves clinical outcomes and reduces acute care costs.
- Clinical guidelines recommend providing enteral nutrition within 24 to 48 hours of ICU admission.
- A jejunal feeding tube is recommended for patients who show intolerance to gastric feeding.
- Compat StayPut® dual-lumen jejunal feeding tube with integrated gastric drainage may facilitate early enteral nutrition in the ICU.

### Disclaimer

Point-of-View articles are the sole opinion of the author(s) and they are part of the ICU Management & Practice Corporate Engagement or Educational Community Programme.

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# Rapid Diagnostics and Antimicrobial Resistance in the ICU

The need to address the problem of antimicrobial resistance, the importance of faster diagnosis of bacterial infections and an overview of rapid diagnostic testing.

Antimicrobial resistance (AMR) is rapidly increasing on a global scale. The discovery of penicillin revolutionised the field of medicine, providing safe harbour from the most pressing threats of the time—infectious diseases. However, the threat of AMR has now escalated to a degree that it has become a major priority for national public health agencies, such as the Centers for Disease Control and Prevention (CDC) in the United States, and the World Health Organization (WHO). Just over one hundred years after the discovery of our first antibiotic, we are quickly running out of treatment options for some organisms. In the battle against bacteria, we are in danger of losing.

How did we get here? The cause of antimicrobial resistance is multifactorial, stemming from microbes' innate ability to develop resistance when exposed to evolutionary pressure. Even when not expressed, microbes carry resistance genes that allow them to modify antibiotics, remove the drugs from their cytosol via efflux pumps, or alter their targets to prevent drug activity (Jian et al. 2021; Hutchings et al. 2019). Constant exposure to antibiotics, such as through injudicious use in healthcare, begets more antimicrobial resistance.

Antimicrobials are commonly prescribed in outpatient, inpatient, and intensive care settings. Numerous studies have now established that timely initiation of anti-

microbials with appropriate activity in serious infections, specifically sepsis and septic shock, leads to marked reductions in mortality. However, the heterogenous presentation of bacterial infections, which often overlap with other causes of non-bacterial sepsis (e.g., viral and fungal infections), and the inevitable delay in obtaining definitive diagnosis can lead to administration of inappropriate and often unnecessary antibiotics. Up to a third of patients treated with broad-spectrum antibiotics for suspected bacterial infections in emergency departments are ultimately diagnosed with non-infectious or viral illnesses (Shappell et al. 2021). These concerns are only magnified in countries where over the counter antibiotic purchasing can lead to unprecedented levels of antibiotic misuse.

How do we become better? Like the cause of antimicrobial resistance, the fix must also be multifactorial. The easiest and most immediately feasible place to start is to become faster in our diagnosis of bacterial infections, as well as recognition of antimicrobial resistance. Traditional culture-based diagnostics are key to the identification of bacterial infection but can require several hours to days to provide actionable data. Other biomarkers, such as procalcitonin, have been studied in the hope of distinguishing between bacterial and viral infection, but these markers have thus far fallen short of their aims and may correlate better with disease severity rather than aetiology (Self et al. 2017).

In order to guide therapy, assays must

be rapid, accurate, and actionable. Recently, rapid molecular tests have shown promise in providing faster and more reliable information to guide clinical decisions. The majority of these assays are based on nucleic acid amplification tests (NAAT) and semi-quantitatively detect bacterial genetic material or protein end-products to identify causes of infection. With some assays, there is the potential to detect genetic determinants of antimicrobial resistance as well. Some of the molecular tests currently available still rely on the growth of bacteria in traditional cultures but can then accelerate the process of identifying the bacteria from 24-72 hours when using culture methods to a matter of hours (Ecker et al. 2010). More novel methods, such as next-generation sequencing (NGS), can bypass the need for culture entirely by identifying cell-free non-human DNA targets within whole blood samples to identify pathogen-derived genetic sequences. Though some of these tests are not yet commercially available for clinical use (or require too much time to be actionable in the ICU), they show promise for future improvements in our ability to rapidly identify and treat infections (Grumaz et al. 2019).

There are a variety of syndromically-based rapid molecular assays available for use in clinical practice, including upper and lower respiratory tract, gastrointestinal, urinary, neurological, and bloodstream infections. Polymerase chain reaction (PCR) assays available for the diagnosis of lower respiratory tract infections may be able to detect pathogens with significantly greater

sensitivity (and speed) when compared with routine culture-based testing, with sensitivities as high as 74% when compared to 44% by cultures (Enne et al. 2022). When testing sputum specimens with higher leukocyte counts on conventional staining, PCR testing has an even greater yield and can detect pathogens at lower leukocyte counts than traditional cultures (Rand et al. 2021).

Another common problem encountered in clinical practice is that of culture-negative pneumonia. Many factors can result in the inability to isolate an organism in a culture, including recent antibiotic exposure or a high inoculum of normal throat flora. Even in this situation, molecular pneumonia panels can identify bacterial targets in 63% more bronchoalveolar lavage samples than traditional cultures (Buchan et al. 2020).

There is a wider variety of rapid molecular tests available in the arena of bloodstream infections. Rapid blood culture identification systems, including the Verigene (Luminex, Austin, Texas, USA) and FilmArray BCID (BioFire Diagnostics, Salt Lake City, Utah, USA) panels, detect key genes to identify bacteria as well as common beta-lactam resistance markers. These tests lack the amplification step of PCR-based tests, and as such require a threshold inoculum in order to identify bacteria, roughly correlating with a positive blood culture; nonetheless, the time to identify both bacterial species and beta-lactam resistance can be reduced by 24-48 hours with these panels (Claeys et al. 2021).

Matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF MS) is an adaptation of

nuclear magnetic resonance testing for the identification of bacteria. Different bacterial molecules have unique mass spectra, which confer to them different times-of-flight when accelerated through a detector. The MALDI-portion of the test confers ionic charge to the molecules to allow for their acceleration. Already in widespread clinical use, MALDI-TOF is currently being actively developed to detect antimicrobial resistance patterns as well (Croxatto et al. 2012).

**▶▶ rapid molecular tests have shown promise in providing faster and more reliable information to guide clinical decisions ▶▶**

Next-generation sequencing (NGS), also known as high-throughput sequencing, can identify billions of DNA sequences simultaneously from clinical samples. NGS can be used to detect non-human cell-free DNA (cfDNA) from whole blood samples and is therefore non-pathogen specific, in comparison to PCR-based tests which are limited in only being able to detect specific, targeted organisms. However, NGS is also limited by its ability to distinguish human genomic material, such as that hosted within circulating leukocytes, versus non-human material. This shortcoming can be bypassed by using targets unique to pathogens, such as the 16S rRNA gene, by comparing a patient's cfDNA with those of healthy controls, or first depleting the

sample of human genetic material (Gu et al. 2019).

In terms of clinical applications, rapid molecular assays can provide clinically actionable information with potential for faster de-escalation of antibiotic therapy. PCR-based pneumonia panels have shown faster test result times and shorter antibiotic therapy times after the implementation of these assays compared to prior (Rogers et al. 2015). These tests, however, require integration with strong antimicrobial stewardship practices. In one series, up to 48% of patients in one study underwent appropriate de-escalation of antibiotics based on test results, but 16% of patients in the same study underwent inappropriate escalation or continuation of therapy despite clear test results. Good stewardship requires better tests but also better implementation (Buchan et al. 2020).

As we work to improve our clinical use of antibiotics in human medicine, we must work as a global health community to improve and reduce the use of antibiotics in veterinary medicine and agriculture. Recognising the strong interconnection between humans, animals, and the environment, CDC and global partners have developed [One Health](#), a project that works to establish mutual goals and projects to combat emerging infectious disease threats, including AMR. Through focused education regarding wise antibiotic use, close monitoring of antibiotic use and waste, and careful surveillance of emerging resistance, we can improve care for all patients.

### Conflict of Interest

None. ■

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## Introduction

Antimicrobial resistance (AMR) is an imminent threat to global health and has been accelerated by the inappropriate use of antimicrobials (Llor and Bjerrum 2014). Antimicrobial stewardship (AMS) is crucial to optimise patient outcomes and minimise drug toxicity and emergence of resistance (Patel and Fang 2018). Diagnostic stewardship (DS) is an essential component of AMS that entails ordering the right tests for the right patient at the right time. It also promotes the use of rapid and novel molecular diagnostic tools to allow for initiation of proper antibiotic therapy

# Diagnostic Stewardship in Five Common Infectious Syndromes

This article defines diagnostic stewardship and discusses how it can be implemented in intensive care units and how it may improve patient outcomes.

while avoiding excessive use of broad-spectrum antibiotics when not needed. Care should be taken in the interpretation of the test results to avoid overdiagnosis, and unnecessary costs (Patel and Fang 2018). Despite promising results, rapid diagnostics are limited by cost, accessibility, and misinterpretation. DS relies on thorough history taking and physical examination, targeted diagnostics, appropriate specimen collection, and proper interpretation of results. Additionally, multidisciplinary teams with highly trained professionals should be involved in the diagnostic pathway. We herein discuss how DS can be implemented in five common infectious syndromes frequently encountered in the intensive care units (ICU).

## 1. Hospital-Acquired and Ventilator-Associated Pneumonia

Ventilator-Associated Pneumonia (VAP) is a leading cause of death in the ICU (Torres et al. 2017; Melsen et al. 2013). However, it may be hard to differentiate colonisation from infection. In addition, given the accessibility of respiratory sampling in intubated patients, clinicians tend to request many respiratory cultures and risk misinterpreting them as infections (Kena et al. 2022; Nussenblatt et al. 2014; Morgan et al. 2017). In fact, up to 50% of patients treated with antibiotics for VAP in the ICU may just be colonised (Swoboda et al. 2006). On the other hand, a delay in initiating antibiotic therapy for VAP is correlated with greater mortality (Fowler et al. 2003). Recent studies suggest that microbiological identification prior to

treatment initiation is desirable in patients who are not septic and may reduce emergence of resistance (Le Terrier et al. 2021). The Infectious Diseases Society of America (IDSA) recommends the use of both clinical and microbiological criteria to diagnose VAP, with re-evaluation occurring no later than 48 hours after starting antimicrobials (IDSA 2005).

Long turnaround times of conventional methods may delay targeted antimicrobial therapy. In a retrospective study conducted in an ICU in France during the COVID-19 pandemic, a rapid microbiological diagnostic test based on the Nested Multiplex Polymerase Chain Reaction (mPCR) method was used on protected telescopic catheter (PTC) specimens. This semi-quantitative test allows detection of 15 bacteria, 3 atypical bacteria, 9 viruses, and 7 antibiotic resistance genes within 1.5 hours of sample collection. This study showed that mPCR performed well on PTC samples with a sensitivity of 93%, a specificity of 99%, and a negative predictive value (NPV) of 100% (Razazi et al. 2022). In another retrospective multicentre study, respiratory samples were simultaneously tested using conventional microbiological methods and the new syndromic rapid multiplex PCR test (rm-PCR). The syndromic rm-PCR detected 83% of episodes of infections compared to 60% in conventional cultures and allowed treatment escalation/de-escalation in 77% of pneumonia cases (Monard et al. 2020). In another study, a multidisciplinary expert panel analysed 95 samples and simulated the changes they would have made had the mPCR been available. It concluded that

mPCR improved empirical therapy, reduced the use of broad-spectrum antimicrobials, and even diagnosed two cases of unexpected severe legionellosis (Peiffer-Smadja et al. 2020).

The INHALE WP1 study is a multicentre study evaluating two mPCR platforms for rapid microbiological screening of critically ill patients with Hospital-Acquired Pneumonia (HAP) in 15 ICUs in the U.K. Both systems were significantly faster and detected more pathogens than regular microbiology tests. Importantly, PCR detects additional organisms and could improve microbiological diagnosis of pneumonia. Bayesian latent class analysis (BLC) showed low sensitivity for routine microbiological analysis, and a higher specificity and PPV of the PCR tests when compared to routine microbiological analysis (Enne et al. 2022). Moreover, although PCR did not provide a complete susceptibility profile, it was a rapid and sensitive predictor of critical resistance that had infection control implications (Enne et al. 2022). Currently, a randomised controlled trial is exploring the potential benefits of mPCR in guiding treatment of HAP/VAP in ICU patients (High et al. 2021).

## 2. Central Nervous System Infections

Central nervous system (CNS) infections are associated with a very high mortality rate (Giovane and Lavender 2018). Clinical presentation cannot often differentiate a bacterial from a viral cause. It is recommended to initiate empiric treatment if microbiological identification is delayed (van de Beek et al. 2016). Additionally, clinical assessment may be inconclusive in critically ill patients (Greenberg 2008). Thus, the use of rapid and precise diagnostic tools may reduce the time to initiate appropriate treatment and avoid unnecessary antimicrobials. Microarray PCR testing of cerebrospinal fluid (CSF) is a promising diagnostic tool. Not only it is capable of detecting organisms that are present in small loads, but it also has an accuracy of 90% and a short turnaround time of one hour (Tansarli and Chapin 2020). Microarray testing of CSF is particularly useful in paediatric patients where CNS infections

can occur in the setting of normal CSF findings (Acuña et al. 2022). Nonetheless, such highly sensitive diagnostic tools may result in overdiagnosis especially if the pre-test probability is low (Moffa et al. 2020). In the absence of guidelines, DS interventions are essential to help clinicians with the proper use of advanced diagnostic tools to reduce overdiagnosis and unnecessary treatment (Goodlet et al. 2021).

Diagnostic algorithms orient clinicians and are successful at reducing excessive microarray PCR testing (Messacar et al. 2022). For instance, Broadhurst et al. (2020) reported that diagnostic algorithms avoided 75% of false-positive results without

▲▲ up to 50%  
of patients treated  
with antibiotics for VAP  
in the ICU may just  
be colonised ▀▀

producing false-negatives. In many cases, the absence of pleocytosis should discourage clinicians from ordering molecular diagnostics. In fact, except in immunocompromised patients and children less than 6 months of age, CSF WBC has a high NPV of 98-100% and rules out CNS infection (Broadhurst et al. 2020). Commonly, management is often influenced by physicians' hesitancy to undertreat, especially in the ICU. This is evidenced by a study where 78% of patients with suspected CNS infection and a negative microarray result were maintained on antimicrobials (Barry et al. 2021; Dack et al. 2019). Used wisely, high-yield diagnostic tests significantly reduce time to adequate treatment and duration of IV antimicrobial therapy (Messacar et al. 2022).

## 3. *Clostridioides difficile* Infection

*Clostridioides difficile* infection (CDI) is very common among ICU patients receiving antimicrobial therapy (Dubberke and Wertheimer 2009). Nonetheless, up to 50% of patients with a positive nucleic acid amplification test (NAAT) are colonised rather than infected (Buckel et al.

2015; Polage et al. 2015). The adoption of highly sensitive NAAT instead of antigen or toxin-based assays increase the risk of over diagnosing CDI (Madden et al. 2018; Bartsch et al. 2015; Leffler and Lamont 2015; Crobach et al. 2016). Additionally, the absence of specific biologic markers for CDI further complicates the diagnosis (McDonald et al. 2018).

"Soft stops" that are integrated into the electronic health system (EHS), such as reminders to check for laxative use, can facilitate decision making for clinicians and improve test appropriateness (Quan et al. 2018; White et al. 2017). Otherwise, strict interventions called "hard stops" where orders are blocked in the absence of prespecified criteria may reduce excessive testing by up to 56% (Quan et al. 2018; Mizusawa et al. 2019; White et al. 2017). Moreover, oral vancomycin prescriptions were reduced in one study, after the implementation of a preauthorisation protocol for CDI testing (Christensen et al. 2019). When collecting samples, stool cultures should be collected in a clean container, kept at room temperature, and transported within two hours. Besides, the microbiology laboratory plays an essential role in promoting DS. For example, rejecting non-loose stools has reduced testing by 43% and CDI events by 60% (Brecher et al. 2013). Sample rejection according to prespecified clinical criteria has also helped reduce unnecessary CDI testing without influencing mortality (Truong et al. 2017). Although negative toxin testing may predict a less severe course of illness, clinicians should be aware that toxin-based testing may not have enough NPV to rule out CDI (Planche et al. 2013).

## 4. Bloodstream Infection

Excessive blood cultures (BC) orders are common in ICU patients with vascular and indwelling catheters who are at high risk for bloodstream infections (BSI) (Hugonnet et al. 2004). BC are often driven by leucocytosis and fever despite limited correlation (Fabre et al. 2020b). In fact, a recent review reported that up to 20% of positive BC may be contaminated (Doern et al. 2019). Contaminated BC

increase antimicrobial exposure, costs, and hospitalisation duration (Bates et al. 1990; Doern et al. 2019). When BC are unlikely to change the management in a patient with a clear site of infection and without sepsis or septic shock, they should not be obtained (Fabre et al. 2020b). However, in the presence of syndromes that are likely to yield positive BC like CNS infections, septic arthritis, and endovascular infections, or when sampling of the primary site of infection is difficult, BC could be of great value (Fabre et al. 2020b). The DISTRIBUTE study aimed to optimise BC practices by implementing an evidence-based algorithm for BC indications and education and feedback to providers about BC rates and appropriateness. It showed that these interventions effectively and safely reduce unnecessary BC (Fabre et al. 2020a). A machine learning model used in a multicentre validation prospective study showed that this model can safely withhold BC analyses in at least 30% of patients presenting to the ED (Schinkel et al. 2022).

BC should be sampled before initiating antibiotics while adhering to strict hygiene measures (Rhodes et al. 2017; Murphy et al. 2014). DS bundles (including an informational video, a standard operating procedure, and ready-to-use paper crates with three culture sets) may also improve outcomes and optimise BC diagnostics (Walker et al. 2022).

Conventional BC have a long turnaround time compared to novel diagnostics and can lead to inappropriate antimicrobial use (MacBrayne et al. 2021). Matrix-assisted laser desorption/ionisation time-of-flight mass systems (MALDI-TOF MS) is used for rapid microbial identification, characterisation, and typing. However, it may better detect gram-negative than gram-positive bacteria. Routine application of this technique, which may also reduce the mortality of bacteraemia, can further advance AMS (Yuan et al. 2020). A randomised controlled trial evaluating outcomes associated with rm-PCR detection of bacteria, fungi, and resistance genes directly from positive BC found a reduction in the use of broad-

spectrum antibiotics but without affecting mortality, length of stay, or cost (Banerjee et al. 2015). Another emerging diagnostic tool is next generation sequencing (NGS), an easy-to-use, culture-free, PCR-based diagnostic method that seems to have promising results (Sabat et al. 2017). Further studies are needed to better understand the cost effectiveness, impact on patient outcome and role in the management of novel diagnostic tools for BSIs.

**▲ ▲ the use of rapid and precise diagnostic tools may reduce the time to initiate appropriate treatment and avoid unnecessary antimicrobials ▀ ▀**

### 5. Urinary Tract Infection

High pre-test probability of urinary tract infection (UTI) should be the main driver for requesting urine culture (UC) orders. However, UC are frequently ordered in the absence of symptoms, or when ambiguous symptoms are present, which may lead to overdiagnosis and inappropriate antibiotic initiation. Additionally, the yield of UC may be compromised by improper sampling, contamination, or misinterpretation. Clinicians should be aware that catheter-associated bacteriuria is common and often indicates colonisation rather than infection (Nicolle et al. 2005). Hence, the IDSA's 2019 clinical practice guidelines strongly recommend against UC screening in patients with indwelling catheters (Nicolle et al. 2019) and only to obtain UC from febrile patients who are at high risk for invasive infections (renal transplant, recent genitourinary surgery, neutropenic patients, or evidence of obstruction).

To reduce unnecessary UC orders, numerous institutions have integrated computerised physician order entry and clinical decision support alerts in the electronic health systems (EHS) which are automatically generated whenever a urinalysis, UC, or

antibiotics commonly prescribed for UTIs are ordered (Keller et al. 2018). These strategies are optimised when combined with educational support on AMS and infectious disease specialist guidance. For example, Shirley et al. (2017) reported 34% fewer UC orders for catheterised patients after including readily accessible guidelines in the EHS and requiring an indication when requesting a UC. Similarly, a neuro-ICU reported a significant reduction in catheter-associated UTI when nurses reviewed UC orders with critical care physicians for patients who did not meet predetermined criteria (Page et al. 2020).

Only allowing UC when urinalysis (UA) meets pre-specified criteria, called reflex UC, has been shown to significantly reduce unnecessary cultures. The presence of pyuria on UA is the most important trigger for reflex UC and has a NPV of more than 90% (Jones et al. 2014; Richards et al. 2019; Fok et al. 2010). Other used indicators can be positive leukocyte esterase, positive nitrite, or >5-10 WBC/HPF (Howard-Anderson et al. 2020). The presence of epithelial cells may indicate that the sample was incorrectly collected and contaminated with skin flora and must prompt physicians to reconsider proceeding with UC (Ling et al. 2020).

Systemic biomarkers such as CRP and procalcitonin were shown to have poor or limited role in DS strategies in UTIs (Covino et al. 2020; Drozdov et al. 2015; Stalenhoef et al. 2019). Other biomarkers such as urinary myeloperoxidase, adenosine-5-triphosphate and urinary xanthine oxidase have too little sensitivity and specificity to be recommended (Gill et al. 2015; Fritzenwanker et al. 2016). Novel diagnostic tools such as flow cytometry (Fritzenwanker et al. 2016), MALDI-TOF-MS and the combination of both (Wang et al. 2013) have also been attempted but are limited by availability and costs.

### Conclusion

Recent advances in AMS strategies aim to guide better patient care and enhance clinical outcomes while reducing unnecessary antimicrobial exposure. DS is essential for better implementation of stewardship

activities. DS include diagnostic strategies for testing based on pre-set algorithms and including novel diagnostic tools in the work-up of patients. Despite some limitations and cost, these novel diagnostic technologies have been shown to contribute to the appropriate use of antimicrobials in various clinical syndromes. Unfortunately,

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novel molecular tests are not available in many middle and low-income countries. A global collaboration between all stakeholders including pharmaceutical companies, governmental, and societal organisations is essential to bring new technology to better use worldwide. In addition, in the hospital setting, a close collaboration between

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infectious disease specialists, critical care physicians and microbiologists is a must to optimise the care of ICU patients and provide evidence-based diagnostics and management.

## Conflict of Interest

None. ■

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Antimicrobial resistance (AMR) has been defined as a major threat to healthcare and to humanity by the World Health Organization (WHO 2015). The level of evidence for the association between AMR and hospital deaths, hospital length of stay and healthcare-associated costs is growing. Cassini et al. (2019) reported an increasing and substantial estimated burden of AMR-related infections compared with other infectious diseases, in children, in the elderly, and in the countries of Southern Europe (Italy and Greece) for 16 pathogen-antibiotic combinations. A systematic analysis showed that the global burden associated with AMR infections in 88 pathogen-antibiotic combinations was estimated to be 4.95 million (95% uncertainty intervals (UI) 3.62–6.57) deaths including 1.27 million (95% UI 0.91–1.71) deaths that were directly attributable to AMR (Murray et al. 2022). Of note, the highest rates of death were located in sub-Saharan Africa and South Asia.

While the AMR burden on hospital length of stay and costs of hospitalisation

# Does Antimicrobial Resistance Affect Clinical Outcomes in the ICU?

An overview of antimicrobial resistance and its impact on clinical outcomes in the ICU.

is not a matter of debate, the relationship between AMR and hospital mortality rates remains controversial, particularly in the intensive care unit (ICU) setting. It is unclear if death should be attributed to the direct effect of AMR bacteria or the patient-related factors. Several studies found that the only independent predictor of hospital mortality was severity of sepsis, irrespective of the AMR status of the causative bacteria (Karvouniaris et al. 2022; Razazi et al. 2017). Lambert et al. (2011) published the largest prospective European ICU study (n=119,699 patients). They defined 20 different exposures according to infection site, pathogen, and resistance status, and then compared outcomes between patients exposed and unexposed. They found a modest, but significant, effect of AMR bacteria on the mortality rate. Risk of death associated with AMR bacteria was 1.2 (1.1–1.4) for pneumonia and 1.2 (0.9–1.5) for bloodstream infections. Interestingly, *Pseudomonas aeruginosa* had the highest burden of healthcare-acquired infections, independently of its resistance profile. Likewise, Paramythiotou et al. (2016) did not conclude a direct association between infections caused by resistant gram-negative bacteria and ICU mortality rates. One limitation is that most studies were conducted in single centres and included a small number of patients. In addition, they were characterised by a high degree of heterogeneity that prevented definitive conclusions from being made (Paramythiotou et al. 2016). Finally, the definitions of resistance are highly variable from one study to another.

A scoping review covering a broad time period from database inception to 2018 showed inconsistencies in AMR detection, AMR definitions and methods for measuring its attributable effect on outcomes (McDonald et al. 2021). On the contrary, three studies suggested that antibiotic resistance led to an increase in crude mortality, even after adjusting for two of them (Razazi et al. 2017; Bottazzi et al. 2018; Barbier et al. 2016). Furthermore, in a retrospective study based on a national database, our team found an association between ICU mortality and the occurrence of an infection due to AMR bacteria in case of ICU-acquired pneumonia (Lakbar et al. 2021). In this study, we assessed the association between pneumonia caused by highly AMR bacteria (including *Staphylococcus aureus*, *Enterobacteriaceae*, *P. aeruginosa*, or *Acinetobacter baumannii*) and ICU mortality on the whole sample and a 1:2 matched sample. We found that 3,081 (16.4%) out of 18,497 patients developed pneumonia due to highly AMR bacteria. The ICU mortality was higher in the patients infected with highly AMR bacteria than in those infected by non-highly AMR bacteria in the whole cohort (odds ratio (OR) 1.57 95% confidence interval (CI) [1.45–1.70],  $P < 0.001$ ) and the matched cohort (OR 1.39 95% CI [1.27–1.52],  $P < 0.001$ ). However, in this study, severity of patients was poorly detailed, which represents a bias for the assessment of outcomes. Indeed, examining the relationship between AMR and outcome is challenging, as it is difficult to discriminate the confounders and determinants of this relationship. Patients



at the highest risk of death are also likely to be those at the highest risk of infection by AMR bacteria (Bottazzi et al. 2018). In addition, the ICU patients infected with AMR bacteria could be those in whom treatments may be limited or withdrawn because considered as futile, increasing per se their mortality rates.

At the bedside, AMR may affect the patient outcomes by three mechanisms. First, inadequate empirical antimicrobial therapy, i.e., giving antibiotics that are not efficient against the bacteria responsible for the current infection, is constantly associated with increased mortality (Retamar et al. 2012; Chen et al. 2013). In real life, the patients infected by AMR bacteria are at high risk to receive inadequate empirical treatment (Rottier et al. 2012). In addition, AMR can be associated with changes in pharmacokinetics, requiring for example higher doses of antibiotics (Mohd Szally et al. 2019). This may also explain failure to treat the patients infected by AMR. Second,

bacterial virulence may be increased in AMR bacteria (Guillard et al. 2016). This hypothesis was tested in a murine model of infection due to *P. aeruginosa* (Roux et al. 2015). Acquisition of AMR resulted in improved fitness of the bacteria, promoting its survival and virulence. However, this hypothesis remains controversial since previous experimental models suggested a loss of virulence in multidrug resistant bacteria (Hraiech et al. 2013; Andersson and Hughes 2010). The third determinant is the patient themselves. The old, frail or immunosuppressed patients often required recurrent hospitalisations to conventional wards before ICU admission, exposure to repeated antibiotic treatments, and invasive procedures. Thus, they are at high risk of colonisation and/or infection by AMR bacteria (Giarratano et al. 2018). These patients are intrinsically at high risk of death, and infection by AMR bacteria could be considered as a symptom of their frailty. Finally, the effects of antibi-

otics themselves could be deleterious, as suggested previously (Jensen et al. 2011). A recent experimental study suggests that antibiotic exposure could result in a decreased immune response (Silva Lajos et al. 2022).

### Antimicrobial Resistance During COVID-19 Pandemic

The COVID-19 pandemic seems to have potentiated the development of AMR bacteria. Reports from Europe and the U.S. suggested increasing AMR infection rates in the ICU during COVID-19 waves, especially due to ESKAPE multidrug resistant infections (Cogliati Dezza et al. 2022; Serapide et al. 2022; CDC 2022). In a systematic review and meta-analysis, Kariyawasam et al. (2022) identified 38 out of 1331 articles and found that prevalence of co-infection with resistant bacteria pathogens was 24% (95% CI 8-40%). Analyses suggested higher rates of AMR bacteria outside Europe and in

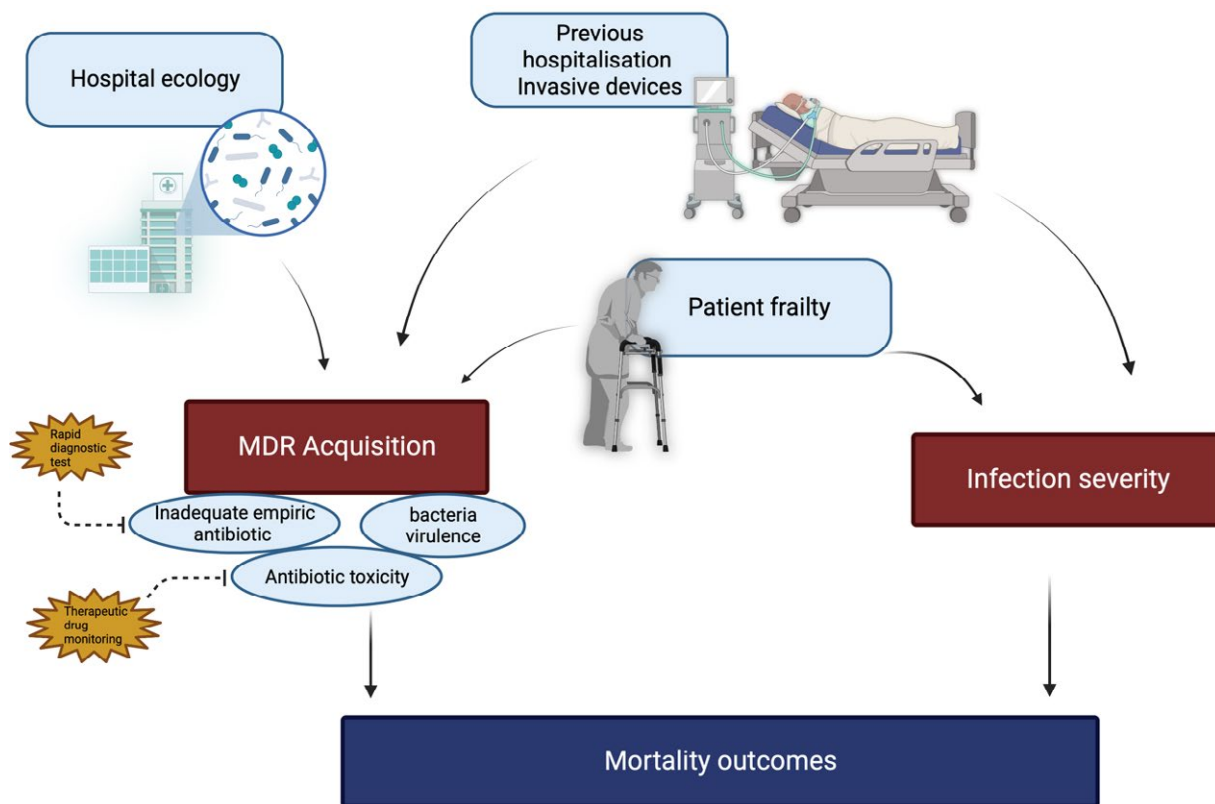


Figure 1. Determinants of mortality outcomes related to MDR infections

ICUs. Among 58 (> 50%) non-survivors, all but six patients were infected with an AMR pathogen.

Of note, during the ICU stay, COVID-19 patients were at high risk of hospital-acquired infections (bloodstream and respiratory tract infections mostly) (Amarsy et al. 2022; Westblade et al. 2021) as they were subject to invasive devices, exposed to multiple antimicrobial treatments and potentially colonised with AMR bacteria. In addition, the inflammatory response they experienced exposed them to a risk of relative immunosuppression (Mehta et al. 2020; Vitte et al. 2020). Furthermore, the early stages of the pandemic were accompanied by the use of large amounts of antibiotics as prophylaxis while immunosuppressive therapy was an integral part of the therapeutic arsenal in COVID-19 patients. This certainly intensified the threat of antimicrobial

resistance (Westblade et al. 2021; Rawson et al. 2020). Thus the surveillance systems should be maintained during pandemics, considering both the numerator and the denominator (Hirabayashi et al. 2021).

## AMR seems associated with increased ICU mortality rate, but the causality of this association remains unclear

In our opinion, one of the lessons of this pandemic is that the principles of antimicrobial stewardship should be carefully studied in all situations. In addition, we need to improve our skills to accurately identify the profile of bacteria responsible for

a bacterial infection, using rapid diagnostic tests to avoid hazardous empirical treatments.

## Conclusion

In conclusion, AMR seems associated with increased ICU mortality rate, but the causality of this association remains unclear (Figure 1). Indeed, to our knowledge, no clinical study provided the required level of details making it impossible to discriminate the factors associated with the bacteria and those associated with the host. Whatever the nature of this association, this underlines the need to provide adequate antimicrobial therapy without delay, promoting the development of rapid diagnostic tests.

## Conflict of Interest

None. ■

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## Introduction

Among healthcare providers, and especially among those working with intensive care unit (ICU) patients, one of the greatest concerns that has emerged in recent decades has been a steady escalation in global resistance against antibiotics among certain strains of bacteria, typically accompanied by elevating rates of mortality (Centers for Disease Control 2019; Weiner-Lastinger et al. 2020a; Weiner-Lastinger et al. 2020b). Where once clinicians largely only had to really contend with hospital-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) (David and Daum 2010), over the past few decades both the number of different pathogens developing resistance to multiple antibiotics and their spread have increased astronomically. Globally, an estimated 700,000 people currently die annually from infections caused by antibiotic-resistant bacteria (Wall 2019), and that number has been projected to increase up to 10 million annually by the year 2050 (O' Neill 2016).

In 2017, the World Health Organization (WHO) published a list of 12 families of bacteria they considered to pose the greatest threat to humans (Mancuso et al. 2021; Mulani et al. 2019). The list categorises bacteria into three categories - critical, high, and medium priority - based upon the urgency of need for effective interventions to be developed and put into clinical use. Designated by the acronym ESKAPE, the six multi-drug resistant pathogens listed as of critical priority are *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter species* (De Oliveira et al. 2020; Mancuso et al. 2021; Mulani et al. 2019). A recent example of one such organism's transition from benign

# Reducing Antibiotic Resistance in the ICU

This article reviews practices currently available to reduce the spread of antimicrobial resistance and novel therapies that are presently being developed.

contaminant to highly-lethal pathogen, concomitant with it developing antibiotic resistance, is *Acinetobacter baumannii* (Visca et al. 2011). As recently as the late 1990s, *A. baumannii* was considered minimally pathogenic and rarely life-threatening (Peleg et al. 2008). Now, however, it has been labelled "an urgent threat" by the U.S. Centers for Disease Control because of rapid increases in its pathogenicity, resistance to antibiotics, and mortality rates, now upwards of 50% (Mohd Szally Lim et al. 2019; Perez et al. 2020; Visca et al. 2011; Weiner-Lastinger et al. 2020b). Mortality rates from nosocomial sepsis with gram negative antibiotic-resistant bacteria have been reported as high as 80-85% (Mathers et al. 2011; Snitkin et al. 2012).

This article examines the management of multidrug resistant pathogens from the perspective of prevention, with prevention further categorised into preventing further development and preventing further spread once encountered, including therapies currently available and those still being tested to prevent further spread.

## Preventing Drug Resistance from Developing

To gain some understanding about how to prevent further drug resistance from happening, one must first appreciate the forces that have been driving its emergence thus far. These forces are multiple and multifaceted. First, bacteria innately change over time in response to their environment – whether their environment is within a human, an animal, or a plant, or on some non-living surface – and this process sometimes results in changes towards antibiotic resistance (Cepas and Soto 2020; Iramiot et al. 2020). Such changes outside of humans may be

accelerated, however; for example, by using antibiotics commercially in food production (Oliver et al. 2011; Tollefson et al. 1997). This said, though antibiotic resistance has been documented in the intestines of beef cattle and other animals, whether and how this adversely affects human health, and to what degree, remains unknown (Oliver et al. 2011; Tollefson et al. 1997).

It is widely believed that the principal driver behind the rapid escalation in the number and severity of infections caused by antibiotic-resistant human pathogens has been the oftentimes non-judicious overuse of broad-spectrum antibiotics, especially among ICU patients (Kollef and Micek 2014; Lindsay et al. 2019; Mulani et al. 2019; Strich and Palmore 2017; Teerawattanapong et al. 2017; Wall 2019; Wunderink et al. 2020). Such use is understandable, since a sizeable percentage of ICU patients either have life-threatening infections upon admission or develop them while they are in the ICU. Antibiotics have unquestionably saved the lives of millions of patients who otherwise would have died. However, their overuse has led to the development of bacterial strains that are resistant to almost all forms of anti-bacterial therapy. Again, *Acinetobacter baumannii* is a prime example of how rapidly antibiotic resistance may develop. In a 2009 study of ICU patients conducted in South Korea (Jang et al. 2009), for example, *Acinetobacter* resistance rates against imipenem and meropenem were both just 4.5%. Yet, five years later, resistance rates to imipenem and meropenem were reported as 45 and 49%, respectively (Viehman et al. 2014); and, in our own recent ICU experience, they now may exceed 90%.

### Antimicrobial stewardship

This alarming rate of elevating resistance among many bacterial strains has led to the concept of antimicrobial stewardship (Medina and Pieper 2016; Strich and Palmore 2017; Wunderink et al. 2020), which calls for optimising the selection and dosing of antibiotic medications and reducing the duration of therapy (Strich and Palmore 2017). Antimicrobial stewardship programmes (ASP) have been examined, both in individual trials and in a recently published meta-analysis, and have been shown both to be feasible to implement and to result in decreased antibiotic use and costs, shorter treatment times, and reduced incidences of antibiotic-resistant infections in the absence of worsening patient outcomes (Karanika et al. 2016; Katsios et al. 2012). In a meta-analysis extracting data from 26 studies with observation periods prior to and after the implementation of an ASP ranging from six months to three years, Karanika et al. (2016) identified pooled reductions in total antimicrobial consumption after ASP implementation of 19.1% (95% confidence interval 7.5–30.1%), with reductions even greater within ICUs (39.5%; 6.4–72.5%). Similarly, the use of broad-spectrum antibiotics declined by a mean 18.5% (5.0–32.0%) for carbapenems and by 14.7% (1.7–27.7%) for glycopeptides, with overall antimicrobial costs also reduced by 33.9% (25.9–42.0%). More pointedly, these reductions were accompanied by reductions in the risk of infection with methicillin-resistant *Staphylococcus aureus*, imipenem-resistant *Pseudomonas aeruginosa*, and extended-spectrum beta-lactamase *Klebsiella* species, as well as shorter hospital stays, and no increase in mortality.

One additional component of ASP is the element of audit and feedback, whereby one or more healthcare workers with specific expertise in antimicrobial stewardship – independent of both the clinical team and any formal infectious disease consultations – provide regular (e.g., multiple times weekly, if not daily), prospective written and/or oral recommendations for antimicrobial use to the ICU clinical team on specific patients (Lindsay et al. 2019). In their meta-analysis of eleven published

case-control studies orchestrated to evaluate the impact on mortality of ASPs that incorporated a prospective, routine-use audit and feedback process and together encompassed a total of 10,545 cases and 9510 controls, Lindsay et al. (2019) identified no increase in the relative risk (RR) of mortality (RR=1.03; 0.93–1.14). However, they also concluded that all 11 studies were at high risk of bias and failed to report any data on the programmes' use of antibiotics or incidence of infections with resistant organisms.

▀▀ the principal driver behind the escalation in the number and severity of infections caused by antibiotic-resistant pathogens has been the non-judicious overuse of broad-spectrum antibiotics ▀▀

### Rapid testing

One major contributor to the overuse of broad-spectrum antibiotics is undoubtedly the time delay that typically occurs between when a presumed septic patient is admitted to the hospital and when culture results return. Conventional methods (i.e., microbial growth-based methods) have the advantage of not only identifying an organism but predicting both its resistance and susceptibility to advantage. An all-too-common disadvantage, however, is that these results typically take from 36–72 hours to return after samples have been sent. Conversely, novel molecular methods that do not rely on microbial growth often yield results within one to a few hours. In a meta-analysis published in 2020, De Angelis et al. (2020) assessed the results of 20 studies involving 1930 isolates, and calculated pooled sensitivity and specificity estimates for two major commercial systems – Verigene® and FilmArray® - which were

85.3 and 99.1% when phenotypic comparators were used and 95.5 and 99.7% when genotypic comparators were used. The meta-analysis did not examine how these results impacted antibiotic use or outcomes, however, and both must be studied to fully establish the clinical utility of these tests. Nonetheless, if rapid testing is proven both accurate and capable of reducing the use of broad-spectrum antibiotics when not needed, without impairing outcomes, it is a reasonable assumption that such tools could become valuable in the fight to reduce both the development and spread of antibiotic resistance.

### Antimicrobial de-escalation

Moving from the initiation to the cessation of antimicrobial therapy, another approach to potentially reducing the development of antimicrobial resistance is to reduce the duration of therapy, a process called antimicrobial de-escalation (ADE), though this approach continues to be considered controversial and lacking sufficient evidence to justify its widespread use (De Bus et al. 2020; De Waele et al. 2020; Lakbar et al. 2020; Tabah et al. 2020; Tabah et al. 2016). As of 2020, the use of ADE was not yet recommended for widespread use by a combined task force of the European Society of Intensive Care Medicine (ESICM) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Critically Ill Patients Study Group (ESGCIP) (Tabah et al. 2020). In a 2016 meta-analysis whose authors included some members of ESGCIP and for which two randomised controlled trials and 12 cohort studies were assessed (Tabah et al. 2016), the investigators identified considerable variability in the definition of ADE; that it was consistently associated with reduced symptom severity scores (with p values ranging from 0.04 to <.001); and that pooled data revealed a reduced relative risk (RR) of mortality (RR=0.68; 0.52–0.88). However, because none of the studies were designed to investigate the effect of de-escalation on antimicrobial resistance, the issue of whether this therapeutic approach should be adopted for the explicit purpose of reducing antimicrobial resistance was

considered unresolved (Tabah et al. 2016).

### Procalcitonin

Procalcitonin is a peptide precursor of the calcium-regulating hormone calcitonin that, over the past two decades, has come into common use as a tool to guide both the initiation and cessation of antibiotic therapy, given the propensity of procalcitonin serum levels to increase in the setting of active infection (Branche et al. 2019; Cleland and Eranki 2022; Kip et al. 2018; Kyriazopoulou et al. 2021; Meier et al. 2019; Schuetz et al. 2017). Its effectiveness, in terms of reducing antibiotic use and enhancing patient outcomes, including mortality and length of hospital stay, has been demonstrated both in randomised clinical trials (Kip et al. 2018; Kyriazopoulou et al. 2021) and in two meta-analyses of individual data. For one, individualised patient data were extracted from 13 clinical trials on 523 patients with positive blood cultures (Meier et al. 2019). In the other, individual patient data were analysed from 26 controlled trials totalling 6708 participants (Schuetz et al. 2017). Both meta-analyses revealed reduced antibiotic use and a decreased rate of mortality, the odds of death decreasing by 17% (OR=0.83; 0.70-0.99,  $p=0.037$ ) in one analysis (Schuetz et al. 2017), while the mortality rate decreased by 7.9% (from 29.8 to 21.8%; 1.8-26.6%) in the other (Kip et al. 2018).

Nonetheless, despite the test's low cost (often roughly \$10 USD), its cost-effectiveness has been called into question (Kip et al. 2018), as have concerns been expressed about its overuse, given its relative lack of specificity, serum procalcitonin levels also increasing with viral infections and a number of other non-infectious states, like certain malignancies and renal failure. Moreover, though its effectiveness decreasing antibiotic use has been documented, its impact upon reducing antibiotic resistance has not yet been adequately studied.

### Emerging supplementary antimicrobial therapies

Since the advent of sulphonamides prior to World War II, antibiotics have progressively been viewed as the cornerstone of

anti-bacterial therapy; and, until the recent surge in antibiotic resistant organisms, there have been few valid reasons to question this. However, this now has changed and the time of merely adding newer antibiotics to pre-existing ones appears to have passed. Among the various supplementary therapies that have been developed to fight infections are bacteriophages (Abedon et al. 2011; Chan et al. 2013; Czaplewski et al. 2016; Górski et al. 2017; Kutter et al. 2010; Lin et al. 2017; Moelling et al. 2018; Sybesma et al. 2018), antimicrobial peptides (Berglund et al. 2015; Du et al. 2017; Mahlapuu et

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al. 2016; Rios et al. 2016), photodynamic light therapy (Cieplik et al. 2018; Hu et al. 2018; Tomb et al. 2018; Wozniak and Grinholc 2018), and silver nanoparticles (Liang et al. 2016; Miller et al. 2010; Munger et al. 2014; Peng et al. 2017; Radulescu et al. 2016; Verbelen et al. 2014). The main rationale behind using such supplementary therapies is two-fold. First, adding them to standard antibiotics may reduce the level of resistance that already-resistant organisms have to antibiotics. Second, their use also may spare clinicians from using broad-spectrum antibiotic cocktails prior to culture and sensitivity results returning. To date, however, data supporting their effectiveness in humans remains limited.

Among these four options listed above, bacteriophage therapy has, by far, the longest history and most published data, actually having antedated the use of antibiotics. Bacteriophages are viruses with the capacity to invade and kill bacterial cells. Among their advantages are their high host specificity for certain bacteria, including

several phages with documented *in vitro* effectiveness against ESKAPE organisms (Abedon et al. 2011; Chan et al. 2013; Górski et al. 2017; Lin et al. 2017; Mulani et al. 2019; Sybesma et al. 2018) and their ability to adapt to bacterial changes, thereby limiting the potential for their bacterial hosts to become resistant to them (Mulani et al. 2019). Their major limitation is the current dearth of any supportive published data beyond *in vitro* studies, anecdotal case reports, and small case series (Mulani et al. 2019).

Moreover, much the same is true for all the other supplementary antimicrobial therapies, clinical trials limited to two randomised clinical trials evaluating silver nanoparticles, both involving their topical use in wound dressings: one demonstrating reduced wound-healing time for leg ulcers (Miller et al. 2010), and the other wound healing in and being well tolerated by burn patients (Verbelen et al. 2014). That said, photodynamic light therapy is already being used widely to treat dental, skin, and soft tissue infections (Mulani et al. 2019).

### Preventing the Spread of Antibiotic-Resistant Organisms

#### Environmental cleaning, decolonisation, and source control

Other strategies have been developed, used, and tested for reducing the incidence of antibiotic resistant infections, including environmental cleaning, decolonisation, and source control. Though each of these three processes involve cleaning, they differ in that environmental cleaning generally entails decontaminating the environment around the patient (e.g., medical equipment, latrines, sinks) (Carling et al. 2008); decolonisation involves decontaminating the patient and any catheters, lines, tubes or other equipment in current direct use on the patient (Decker and Palmore 2013; Huang et al. 2013); and source control entails controlling microbe transmission between patients and caregivers by all means, including cleaning but also ensuring that personal protective equipment – like masks, shields, gloves, and gowns – are used and fit appropriately (Lagunes et al. 2016). One

meta-analysis was recently conducted to assess the use of ASP in conjunction with these three other strategies – of environmental cleaning (EC), decontamination methods (DM), and source control (SC) – to reduce the incidence of antibiotic-resistant infections relative to standard care (Teerawattanapong et al. 2017). This meta-analysis, which assessed 42 studies encompassing 62,068 patients, revealed that combining standard care with ASP, EC, and SC was the most effective approach. Indeed, the CDC has already published guidelines on how to successfully decontaminate the ICU environment, patients, and healthcare personnel and mentions each of these approaches (Sehulster and Chinn 2003). However, research has shown that, while some aspects of decontamination are being applied adequately and appropriately, others – like the decontamination of several objects at high risk of becoming contaminated with nosocomial pathogens, including bedpan cleaners, toilet area handholds, doorknobs and light switches – were not performed as consistently or thoroughly (Carling et al. 2008). This is important, because some common antibiotic-resistant organisms, like *A. baumannii*, thrive on inert surfaces that are commonly overlooked during decontamination efforts, including computers and computer keyboards (Lu et al. 2009), medical charts (Chen et al. 2014), and objects as distant from the patient as elevator buttons, door handles, staircase railings, telephones, and water taps (Bhatta et al. 2018).

### Hand hygiene

Proper hand hygiene would seem a blatantly obvious measure to stop the spread of microbials, especially in an ICU. It is considered one of the overriding goals of infection control by both the CDC and the World Health Organization (WHO). That said, despite considerable research demonstrating this simple concept's efficacy and extensive research efforts to promote its use in hospitals, compliance remains as low as 40-60% and might be even lower in ICUs (Erasmus et al. 2010; Kowitt et al. 2013; Stahmeyer et al. 2017). The most likely explanation for this is the time hand

washing requires; as, in one German study of ICU nurses, mean compliance was 42.6% and the average length of time nurses spent washing their hands per hand washing was just 6.8 seconds, 23.2 seconds less than the 30 seconds recommended in WHO guidelines (Stahmeyer et al. 2017). The investigators further stipulated that, given 218-271 hand-washing opportunities per patient, the average nurse would need to spend an additional 58-70 minutes washing their hands, per patient, over their 12-hour shift, rendering the simple practice of thorough hand hygiene almost impossible to implement without additional changes to ICU nursing care, like additional staff.

▲▲ the effectiveness of any measure designed to reduce antimicrobial resistance and the spread of resistant organisms relies on how, how well, and how consistently they are implemented ▼▼

### Isolation

Another strategy that is simple in concept, but highly dependent on available resources and, hence, sometimes very difficult to implement is isolation (Gasink and Brennan 2009; Landelle et al. 2013; Rosenberger et al. 2011; Strich and Palmore 2017), a practice that is considered one of the core elements of infection control by agencies like the WHO and CDC (Sehulster and Chinn 2003). Isolation is generally used in two clinical settings: to prevent the transmission of micro-organisms from a patient already known to have an antimicrobial-resistant organism, like methicillin-resistant *S. aureus*; and to prevent the potential transmission of micro-organisms from a patient in whom the nature of their infection is not yet known – a process termed empiric isolation. Both these objectives require considerable adjustments to be made, including isolating not only the patient

but their nurse as well, and considerably increased time fulfilling source-control and decontamination protocols like hand hygiene, masking, gloving, gowning, and the decontamination of all equipment. Isolation has been documented to work, however, especially during infection outbreaks (Klein et al. 1989; Palmore et al. 2011; Rosenberger et al. 2011; Snitkin et al. 2012).

### Education

Ultimately, the effectiveness of any measure designed to reduce antimicrobial resistance and the spread of resistant organisms relies on how, how well, and how consistently they are implemented; and all this, in turn, relies on all affected parties being educated both in the process and in the need for such measures. As clearly demonstrated for such a conceptually-simple and easily-justified practice as hand washing (Stahmeyer et al. 2017), proper performance relies on everyone – not just those in direct contact with patients, but also those generating nurse schedules and hospital administrators issuing staffing guidelines – being on board and in full agreement. It also requires that patients and their visitors be educated in required infection control practices and why they are necessary. All this depends on researchers continuing to generate new and improved methods to control infections and empirical evidence to justify their use.

### Conclusion

The exponential increase in antimicrobial resistance in recent decades has created a global health crisis. Generating new, improved antibiotics to replace the old ones is no longer enough. That said, numerous supplementary strategies already exist and have been proven effective at reducing the spread of resistant organisms – including antimicrobial stewardship, rapid testing, antimicrobial de-escalation, employing serum procalcitonin levels to guide antimicrobial initiation and cessation, and various on-site infection-control procedures like environmental cleaning, decontamination, source control, consistent hand washing, and, when necessary, patient isolation.

Several novel avenues of antimicrobial therapy also are presently being developed and tested, including antimicrobial phages and peptides, photodynamic light therapy, and silver nanoparticles. What is needed

now is strict adherence to those practices that have already been documented to be effective, combined with concerted efforts to further develop and test those approaches whose effectiveness hitherto

remains unknown.

## Conflict of Interest

None. ■

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The improvement in mortality outcomes of patients with sepsis is attributable to the early recognition of sepsis, better adherence to guidelines, and a prompt organisation's responsiveness. However, sepsis remains the leading cause of death in the intensive care units and long-term sepsis mortality is still a burden for our healthcare system. In fact, managing infections in a critical area are increasingly complex and today more than ever requires a shared multidisciplinary and structured approach. In order to further improve outcomes, it is vital to highlight the importance of defining uniquely and clearly what is sepsis,

# Sepsis in Critical Care

The importance of clearly defining sepsis, improving early recognition strategy, and increasing the understanding of innate and adaptive immune system derangements that facilitate the development of sepsis.

improving early recognition strategy, and increasing our understanding of innate and adaptive immune system derangements that facilitate the development of sepsis. A deeper understanding of complex interactions between the infectious insult and the host's immune response warrants interesting implications at diagnostic and therapeutic levels, allowing to tailor the treatment to patients' characteristics and to certain phases of the disease.

## The Importance of Definition

Sepsis is a "time dependent" disease, the clinical outcome of which depends on the speed of recognition and the effectiveness of clinical management starting from the first hour. The definition of sepsis has constantly changed over the time. This is due to the importance of defining uniquely and clearly what is sepsis for rapid recognition and treatment, in a standardised way.

In 1991, the initial definition of sepsis and septic shock was proposed during the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference (Bone et al. 1992). Sepsis was defined as a host systemic inflammatory response syndrome (SIRS) to infection. SIRS was defined as a syndrome characterised by at least two of the following parameters: temperature  $>38^{\circ}\text{C}$  or  $<36^{\circ}\text{C}$ , heart rate  $>90$  beats per minute, respiratory rate  $>20$  breaths per minute or  $\text{CO}_2$  partial pressure  $<32\text{mmHg}$ , white blood cell count  $>12,000/\text{ml}$  or  $<4,000/\text{ml}$  or  $>10\%$  immature forms (band). Severe sepsis was sepsis complicated by organ dysfunction and septic shock was defined as sepsis characterised by persistent hypotension despite adequate fluid resuscitation.

In 2001, a task force of 29 participants from Europe and North America gathered during the International Sepsis Definition

Conference with the aim of revisiting sepsis and septic shock definition. Due to the lack of strong evidence, the expert panel concluded not to change the definition of sepsis and septic shock; however, they expanded the list of signs and symptoms of septic panel (Ley et al. 2003). The use of the SIRS concept for the definition of sepsis is burdened by the problem of poor specificity, as multiple non-infectious clinical conditions can be associated with a picture of SIRS. In the emergency room, many patients have criteria compatible with SIRS, but only some have an associated infection, while on the other hand an infection does not always lead to a systemic inflammatory response. Furthermore, the criteria developed for the II definition presented the problem of being difficult to apply in the real world, both due to the complexity deriving from the number of parameters considered, and to the scarce specificity of the criteria.

In an attempt to overcome these problems and to identify more agile tools to be used in clinical practice, in 2016, during the 45th Critical Care Congress, the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) was proposed. Sepsis was defined as "a life-threatening organ dysfunction caused by a dysregulated host response to infection". This new definition revolutionises the previous criteria, overcoming the concept of SIRS and clearly highlighting the importance of the interaction between the host and pathogen with consequent host response (local or systemic). The term "dysregulated" can be conceptualised as an anomalous response of the host that, independently of the infection, might induce organ damage. The immune imbalance resulting from this altered response is characterised by multiple concomitant

proinflammatory and immunosuppressive aberrations involving both the innate and the adaptive immune response systems (Delano and Ward 2016). The loss of the normal homeostasis between the pro and anti-inflammatory system results in uncontrolled activation of the inflammatory response leading to the development of progressive physiologic dysfunction in two or more organs (Chen et al. 2018).

The other fundamental change concerned

useful for early diagnosis. The usual cut-off value for an abnormal lactate level is  $>2$  mmol/L.

In parallel, Surviving Sepsis Campaign (SSC) was launched for the first time by the Society of Critical Care Medicine (SCCM), ESICM, and the International Sepsis Forum during the ESICM annual meeting in Barcelona in 2002. In 2003, representatives of several international societies assembled and started to develop the guidelines for

and their families (Evans et al. 2021). Despite progress in disease definition, there are still opportunities for improvement especially in light of the new understanding of the central role of proinflammatory and immunosuppressive aberrations and possible new diagnostic tools (i.e., immunomonitoring) as described below. An overview of the evolution of sepsis definition and guidelines is provided in Figure 1.

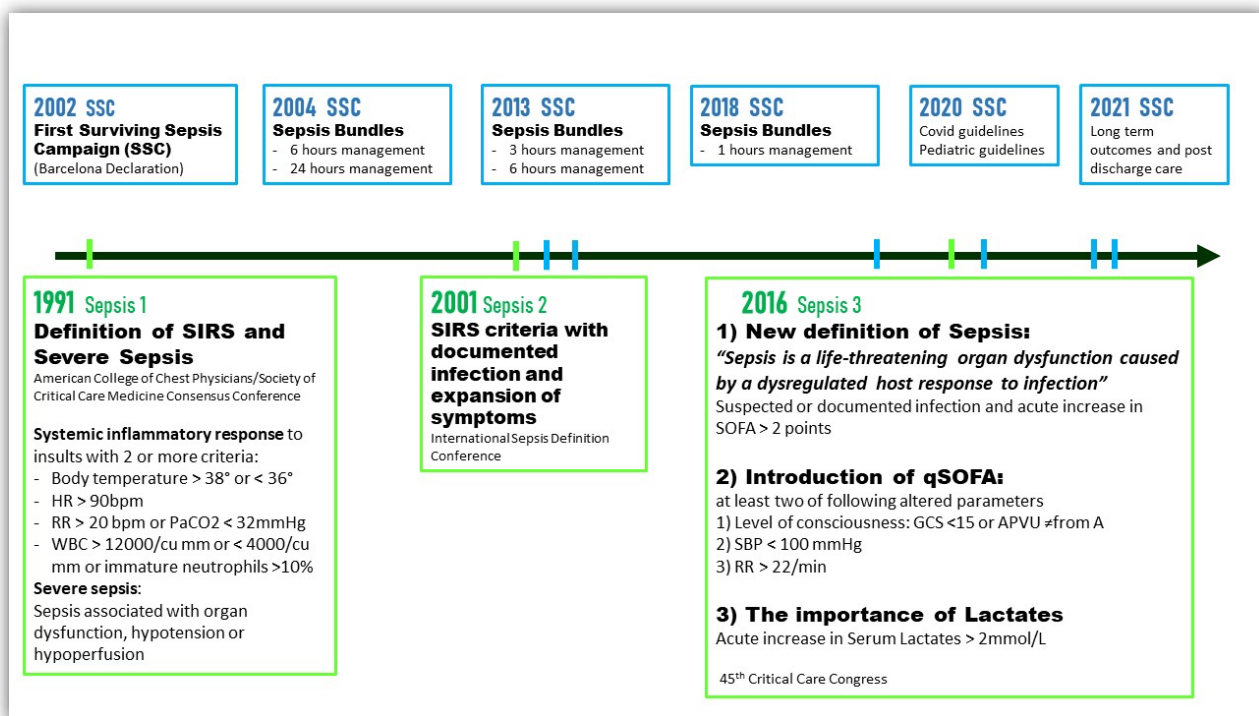


Figure 1. Sepsis - the evolution of definition and guidelines

the introduction of the quick SOFA (qSOFA). The qSOFA is based on the use of three objective parameters: altered level of consciousness (GSC  $<15$  or AVPU  $\neq$  from A), PAS  $<100$  mmHg, FR  $>22$ /min. In the presence of at least two of these parameters altered in the presence of infection, the suspicion of sepsis arises; in these patients the risk of death is high, and it is correct to implement the appropriate management protocols. Another important aspect introduced in 2016 was the concept of the importance of lactate. An increased level of serum lactate is a clear sign of tissue hypoperfusion and septic shock and is

the management of sepsis and septic shock. The first and second edition of the SSC guidelines was published in Critical Care Medicine and Intensive Care Medicine (Dellinger et al. 2004; Dellinger et al. 2008). Guidelines implementation was further realised in 2012 and 2016, along with revised bundles (Dellinger et al. 2013; Rhodes et al. 2017). Finally, in 2021, the Surviving Sepsis Campaign updated the international guideline for management of sepsis and septic shock. The latest version put a special light on the evaluation of post discharge care, long-term outcome, and rehabilitation issues involving patients

### The Importance of Preventing Sepsis and Early Identification of Patients at High Risk

In 2017, a Resolution of the World Health Assembly invited member states to act "for the improvement of the prevention, diagnosis and clinical management of sepsis" (Kilpatrick et al. 2018). The resolution highlighted the need for the prevention of healthcare-related infections, the correct use of antibiotics, and the necessity of training operators on the risk of progression from infection to sepsis. In fact, the response to sepsis can be carried out thanks to an integrated path that expresses the various

functions in relation to the different settings. Managing infections in a critical area are increasingly complex and today more than ever requires a shared multidisciplinary and structured approach (Silal 2021). Preventing sepsis means preventing infection, through the management of risk factors that make it possible to frame the infection in the context (healthcare-related infections and lifestyles) and in the response of the host. It is, therefore, necessary to consider both the risk factors (i.e., frailty, comorbidities) and the patient's clinical history (i.e., recent surgery, immune response).

An important component of the sepsis and septic shock management concerns the identification of infectious risk and choosing the appropriate diagnostic and therapeutic pathways (Leong et al. 2021). The identification of infectious risk situations and the severity of sepsis is based on the use of three types of tools: the risk factors of infection, the severity score and the bioscore.

The identification of risk factors aims to identify the presence of predisposing factors. The reconstruction of the recent medical history (i.e., recent hospitalisation-the risk of colonisation) and the evaluation of the environment in which the patient lives (e.g., family infection cluster, local recent bacteria outbreak) aim to search for all those events that may increase the risk of sepsis and septic shock. The severity scores detect the deterioration of vital signs and are calculated at the time of contact between healthcare professionals and the patient. The severity scores (i.e., NEWS, MEOWS, qSOFA, SOFA) aim to systematically detect and quantify the deterioration of the vital signs of the patient and, therefore, they help the healthcare professional to assess how severe the health status of the patient is compromised (Sricharoen et al. 2022; Latten et al. 2021). The severity scores are intended to frame a state of instability and to trigger the appropriate treatment responses. Finally, the bioscore combines biomarkers (i.e., PCT, lactate), prognostic and infectious risk scores in a multiparametric way (Jekari et al. 2019; Song et al. 2019). This tool intends to

direct the patient to the most appropriate path, based on the processing of all the information collected. The integration of the information collected allow to stratify the risk and to initiate sustainable and consistent diagnostic, antibiotic and sepsis stewardship paths.

The early identification of patients with sepsis and the evaluation of individual risk factors (i.e., immunodepression, long hospitalisation), are also extremely important for the best choice of microbiological test and for evaluating long-term outcome. Being as early as possible in formulating a diagnosis and establishing a rapid and adequate therapy is, undoubtedly, one of the most impacting aspects of the outcome of our patients. It is the clinician's task to identify which patients will benefit the most from new diagnostic methods (i.e., fast microbiology), mainly through multiparametric pathways of clinical reasoning, including, among other things, the advanced use of biomarkers (i.e., procalcitonin) (Mangioni et al. 2020). Fast microbiology allows the evaluation of antibiotic resistance with a faster prescription of the appropriate antibiotic treatment, and prompt de-escalation strategy (Muzzi et al. 2022).

Even more, it is worth remembering the long-term outcome and the rate of hospital readmission in patients who experienced septic shock (Prescott and Costa 2018). After sepsis, patients experience several common persisting complaints such as mental health problems (e.g., anxiety, depression, post-traumatic stress disorder, difficulty in thinking clearly, sleep disorders), muscle weakness, asthenia, difficulty swallowing, greater risk of contracting further infections, heart or kidney failure (Shankar-Hari et al. 2019; Sekino et al. 2022). Subsequent hospitalisation of patients who experienced sepsis is high and it is mainly due to the fact that sepsis is responsible for impairing immune system and accelerating the progression of pre-existing chronic conditions (Schmidt et al. 2020). Consequently, it is extremely important to evaluate the medical history of the patient experiencing sepsis and to individuate fragility patients especially,

at risk of the long-term consequences of sepsis in order to create and support specific post-discharge rehabilitation treatment from hospitalisation for sepsis (e.g., physiotherapy), to identify new physical/cognitive problems and initiate appropriate treatment and to review and adjust long-term drug treatments.

### **The Importance of Understanding the Central Role of Immune Dysfunction**

Given that the centrality of the complex interactions between the infectious insult and the host's immune response is now well established, the investigators' attention cannot help but turn to the mechanisms involved in the dysregulation of the innate and adaptive immune response. Consequently, immune modulation strategies appear as promising adjuvant therapies in septic patients (Evans et al. 2021; Shoji and Opal 2021; Hennessy et al. 2010).

It is not only the pro-inflammatory responses that determine the outcome of an infection, but the final result of the process depends on the homeostasis that is established between pro-inflammatory and anti-inflammatory mechanisms, leading either to the resolution of the infection or to its evolution with organ damage and possible secondary infections. An exaggerated and uncontrolled activation of the inflammatory response, resulting from an alteration of the balance between pro- and anti-inflammatory stimuli that is necessary for proper healing, can result in the inability to confine the flogosis to the site of the primary insult, thus causing diffuse tissue damage and multiple organ failure (MOF). The cellular pathophysiology behind the transition from a circumscribed infection to a systemic syndrome with deep organ derangement still remains largely to be elucidated. It is now clear that the individual genomic profile, through the upregulation or downregulation of genes involved in the inflammatory response, is partly responsible for its inter-individual variability (Sapan et al. 2017). Certain allelic polymorphisms have been shown to be strongly correlated with the develop-

ment of secondary complications and an increased likelihood of MOF (Qiu et al. 2019; Lu et al. 2019). Epigenetic modifications are also able to influence the extent of intercellular crosstalk, contributing to the spread of inflammation (Namath and Patterson 2011).

Among the families of genes that influence the individual response to an insult is that of pattern recognition receptors (PRRs), which are expressed by many cells of the innate immune system rendering them capable of recognising highly conserved motifs recurring in microbe structure, also known as pathogen-associated molecular pattern (PAMPs), and danger-associated molecular pattern molecules (DAMPs), which are molecules released by injured host cells that can start a non-infectious inflammatory response (Rajaei et al. 2018; Mogensen 2009; Grazioli and Pugin 2018). Among the PRRs, toll-like receptors (TLRs) and nucleotide-binding domain leucine-rich repeat containing (NLR) receptors, are the most represented (Ye and Ting 2008). The interaction between PRRs and one of their ligands triggers the activation of a complex transcriptional programme, including the nuclear transcription factor NF- $\kappa$ B, with consequent mediates the expression of genes that code for cytokines, chemokines, nitric oxide and other mediators. A total of ten TLRs are described and differ from each other in their localisation and for their ability to recognise microbial antigens. The possibility for some TLRs to bind different microbial antigens and the presence of multiple antigens on the same germ broaden the range of possible inflammatory cascades that can be activated in response to an infection, further accentuating the interindividual variability (Latz et al. 2004; Wong et al. 2016).

Furthermore, the vascular endothelium is an important effector of the non-specific response, as it is reached by multiple activation signals that cause vasodilation and which are responsible for a series of complex interactions between endothelial cells and immune cells that facilitate the adhesion and migration of the latter through the endothelium to reach the site of interest. The price to pay is endothelial damage

and consequent dysfunction due to the inflammatory response that is triggered by immune cells through the release of mediators such as nitric oxide and reactive oxygen species (ROS). Endothelial dysfunction is one of the cornerstones of the pathophysiology of MOF syndrome, paving the way for further tissue damage and organ failure (Ince et al. 2016). The infection is able to trigger also the complement cascade that in turn contributes to amplify the phenomena described so far (Ward 2010; Markiewski et al. 2008). In addition, endothelial activation with its consequences and the formation of the fibrin plug hinder the ability of germs to disseminate into the tissues through the systemic circulation (Levi and van der Poll 2010). Furthermore, the counter-regulatory pathways that inhibit coagulation are suppressed and fibrinolysis is inhibited

**in the pathophysiology of sepsis not only pro-inflammatory stimuli contribute, but also the anti-inflammatory forces have their own weight in the overall balance**

overall (Levi and van der Poll 2017); the cascade of inflammation and coagulation stimulate and amplify each other, aggravating endothelial dysfunction and thus playing a crucial role in the onset of MOF (Levi 2010).

However, as already mentioned, in the pathophysiology of sepsis not only pro-inflammatory stimuli contribute, but also the anti-inflammatory forces have their own weight in the overall balance. In some patients, for reasons not yet fully understood which certainly depend on multiple factors, anti-inflammatory factors predominate overall, determining a condition of immunoparalysis, equally deleterious even if in different ways (Hamers et al. 2015; Boomer et al. 2011; Nierhaus et al. 2003). In both cases, however, it is evident that the in-depth knowledge of

the complex interactions that govern the immune response could give some explanations on how to possibly intervene to regulate it, conditioning the evolution of sepsis towards its resolution.

### Potential Future Role of Immune Monitoring

The increasing knowledge of the complexity of the pathophysiology of MOF and the growing awareness of the need for targeted therapy based on the individual patient's immune status is leading to a growing interest in immunomonitoring. In fact, the possibility of identifying clinical and laboratory markers that allow portraying the immune status of a patient, defining its degree of activation or suppression, could guide therapeutic choices with a possible impact also on the clinical outcome.

Much attention has been paid to the search for a correlation between the plasma levels of some key cytokines and clinical outcomes (Qiao et al. 2018; Kraft et al. 2015) (i.e., IL10/TNF $\alpha$  ratio). Data from trauma patient studies showed that the IL-6/IL-10 ratio is able to discriminate between more inflammatory response and one that tends toward immunoparalysis, showing in both cases correlation with MOF (Sapan et al. 2017). Finally, in burn patients, high levels of IL-8 correlated with an increased risk of MOF, sepsis, and mortality (Kraft et al. 2015). Nevertheless, none of these are routinely used to stage and monitor septic patients (Bozza et al. 2007). Even more, cytofluorometry allows the measurement of the level of expression of markers on the cell surface, emerging as a method to evaluate immune cell activation and immunophenotypic changes of cells during sepsis (Daix et al. 2018). It is now possible to measure the expression of CD64 on neutrophils, the expression of HLA-DR on monocytes and the percentage of circulating regulatory T lymphocytes. The HLA system molecules are involved in the presentation of antigen to the CD4 + T lymphocytes, leading to their activation and therefore triggering the adaptive immune response (Kessel et al. 2009). It is interesting to note that HLA-DR molecules exhibit a high level of conservation in

those domains that are responsible for the interaction with conserved domains of T lymphocyte receptors, but at the same time show extensive polymorphisms in the domains responsible for binding to antigens and interacting with the variable regions of T-cell receptors (Jin and Wang 2003). This reflects the ability to enormously expand the number of antigens they are able to recognise, always preserving the ability to present them to the cells responsible for carrying out a specific response. Importantly, many studies show that reduced mHLA-DR expression is associated with adverse clinical outcomes, including increased rates of secondary infections and increased mortality, following various types of insults (e.g., trauma, burns, major surgery, and sepsis) (Hotchkiss et al. 2013; Monneret et al. 2006; Venet et al. 2013). Moreover, mHLA-DR levels can be used to assess the status of immunosuppression: patients with reduced levels of mHLA-DR should be considered immunosuppressed and therefore could benefit from targeted immune-enhancing therapies (Boomer et al. 2011; Boomer et al. 2014; Peters et al. 2018).

However, despite the extensive insights from the literature, it should always be kept in mind that measuring the concentration or expression of a single molecule provides only a partial picture of the patient's clinical situation, whereas results are capable of having an impact on the formulation of therapeutic strategies could derive from panels of markers which, unlike the single parameter, could provide greater details about the current immunity profile of the patient.

### Potential Future Role of Immune Modulation Treatment

The possibility of systematically evaluating, in a certain phase of the disease, the state of the immune system of a patient opens up interesting implications also at therapeutic level, allowing to personalise the interventions and to evaluate their accuracy and effectiveness during therapy (Venet et al. 2013).

Despite the large arsenal of potential immune-modulating therapies available

for the septic patient (Figure 2), the only one for which the international guidelines of the Surviving Sepsis Campaign 2021 maintain a recommendation in favour of its use are glucocorticoids (weak recommendation) (Evans et al. 2021). As for

Schmidt et al. 2021; Bermejo-Martin and Giamarellos-Bourboulis 2015). However, the overall balance of the desired and potentially harmful effects remains to be defined, given the non-negligible number of adverse reactions.

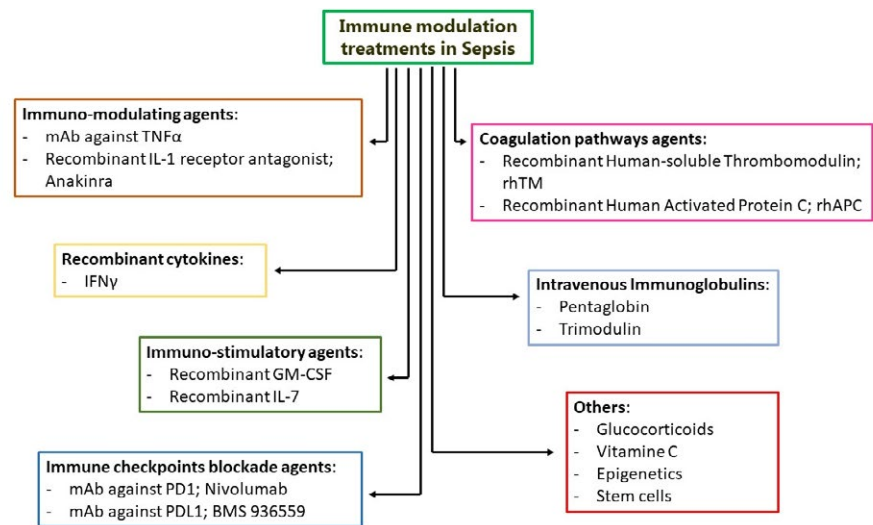


Figure 2 Graphical representation of different types of immunotherapies

vitamin C, no recommendation could be made about its use in the septic patient: in fact, the large trials that have evaluated the effectiveness of administering high-dose vitamin C alone or in combination with thiamine and hydrocortisone did not show significant differences in mortality (Putzu et al. 2019; Fowler et al. 2019; Coloretti et al. 2020; Marik et al. 2017). Similarly, the international guidelines for the management of sepsis maintain the recommendation against the use of IVIGs in this clinical context (Rhodes et al. 2017; Evans et al. 2021). Given that low endogenous immunoglobulin levels in the septic patient correlate with a worse outcome (Venet et al. 2011), the use of immunoglobulins as an adjuvant therapy appeared promising right from the start. It seems that exogenous immunoglobulins not only act as agents capable of enhancing the proinflammatory response, but they act rather as modulators of the immune response as a whole (Lux et al. 2010), proving potentially useful not only in the early stages of sepsis but also in the late ones, characterised by profound immunoparalysis (Lux et al. 2010;

Potential new immune-modulating therapies are constantly increasing with controversial and contrasting results in vitro and vivo studies (Figure 2). Recombinant cytokines, pharmacological analogues of endogenous cytokines and of factors stimulating the growth of colonies, may potentially increase the immune response in the course of immune paralysis induced by sepsis. Studies conducted on animal models have shown that a defect in the production of IFN- $\gamma$  increases secondary infections and mortality (Wang et al. 1994). In humans, IFN- $\gamma$  levels have been found to be reduced in dying septic patients compared to surviving ones (Boomer et al. 2011). However, despite the encouraging data in animal studies, it is still unclear what the role of IFN- $\gamma$  adjuvant treatment in clinical practice may be, as there is a lack of large clinical trials capable of demonstrating its real benefits (Jarvis et al. 2012; Turrel-Davin et al. 2011). Likewise, granulocyte-macrophage colony-stimulating factor (GM-CSF), a myelopoietic growth factor, has attracted great interest due to its immunomodulatory properties active on

the innate system. Despite the promising results of preliminary studies involving the administration of rhGM-CSF, at the moment it is not possible to recommend the use of rhGM-CSF in clinical practice (Mathias et al. 2015; Bernstein et al. 2002; Bo et al. 2011). Given the key role played by some molecules in the cytokine storm during sepsis, interest has grown in monoclonal antibodies capable of selectively targeting them, so as to reduce their levels and somehow mitigate the deleterious inflammatory response. Anakinra represents an interesting example of monoclonal antibody against TNF-alpha and a recombinant antagonist of the IL-1 receptor (Qui et al. 2013; Abraham et al. 2001; Reinhart et al. 2001; Gallagher et al. 2001; Shakoory et al. 2016).

Considering the massive activation of the coagulation cascade during sepsis, interesting therapeutic implications seemed to derive from the use of recombinant human thrombomodulin (rhTM) and recombinant activated protein C (rhAPC), given the involvement of the corresponding endogenous molecules in the modulation of coagulation in an anticoagulant sense. RhTM seems to exert a protective effect on the development of damage to various organs during MOF (Yoshihiro et al. 2019; Yamakawa et al. 2015). RhAPC (drotrecogin alpha), on the other hand, exerts a set of pleiotropic effects by modulating not only the coagulation cascade, but also the inflammatory one, with a protective effect also on the endothelium (Levi and van der Poll 2007; Bernard et al. 2001).

Certain pathways involving immune checkpoints also play a role in sepsis-induced immunosuppression, therefore, the possibility of inhibiting them allows to enhance the immune response (Hotchkiss et al. 2019a). In sepsis-induced immunosuppression, the pathway involving programmed cell death protein-1 (PD-1)

and its programmed cell death-ligand 1 (PD-L1) is upregulated (Hotchkiss et al. 2019b; Chang et al. 2013). The administration of nivolumab, a monoclonal antibody directed against PD-1 already used in the therapy of various tumours, in combination with the antibiotic meropenem can improve the clearance of the pathogen in septic patients compared to the administration of the antibiotic alone (Hotchkiss et al. 2019a; Gillis et al. 2021; Watanabe et al. 2020).

Another possible weapon to be exploited in the treatment of organ damage induced by sepsis derives from the field of regenerative medicine and consists of the use of mesenchymal stem cells. Mesenchymal stem cells not only act through the direct mechanism of replacing and soliciting cells in damaged tissues, but also exert potentially therapeutic effects through mechanisms that involve the release of cellular mediators, capable of modulating the inflammatory state and consequently the damage of organs (Lee et al. 2009; Keane et al. 2017). In particular, the release of microvesicles containing cellular components including mitochondria appears to play a complex role in the dialogue between cells, also allowing the exchange of material (Zhu et al. 2014). Some preclinical studies have produced evidence of the efficacy of MSCs in reducing organ damage induced by sepsis affecting the lung, heart and liver (Wang et al. 2015; Nong et al. 2016); however, the possibility of using MSCs in the therapy of the septic patient remains a very distant prospect (Keane et al. 2017).

Finally, the interaction between pathogen and host can induce important epigenetic changes, capable of influencing both the acute phase of sepsis and having an impact on its long-term sequelae including a prolonged inflammatory or immunoparalysis state (Falcão-Holanda et al. 2021;

Cross et al. 2019); it can also determine a functional reprogramming of the transcriptional pathways of innate immunity cells which takes the name of "trained immunity" (Netea et al. 2020; Saeed et al. 2014; Netea et al. 2016; van der Heijden et al. 2018), thus favouring the memory of the infection (Moorlag et al. 2020). Given the attractive prospects opened by the possibility of regulating epigenetics, preclinical studies are underway which are evaluating various histone deacetylase inhibitors (i.e., HDACi), molecules already in use in cancer patients (i.e., Vorinostat, Givinostat) (Kim and Bae 2011; Mann et al. 2007).

## Conclusions

The management of infection is increasingly complex and requires a common multidisciplinary approach. Central aspects of fighting sepsis are represented by the need for the prevention of healthcare-related infections, the correct use of antibiotics, and the necessity of training operators on the risk of progression from infection to sepsis.

The new definition revolutionises the previous criteria, overcoming the concept of SIRS and clearly highlighting the importance of the interaction between the host and pathogen. Consequently, the new understanding of the central role of proinflammatory and immunosuppressive aberrations opens up interesting diagnostic and therapeutic implications, theoretically leading to a tailored medicine. It is, therefore, necessary to consider both the risk factors and the patient's clinical history and to choose the appropriate diagnostic and therapeutic pathways.

## Conflict of Interest

None. ■

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