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Antibiotic Resistance

Antibiotic Stewardship in Critical and Emergency Care

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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.

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 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 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.

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 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

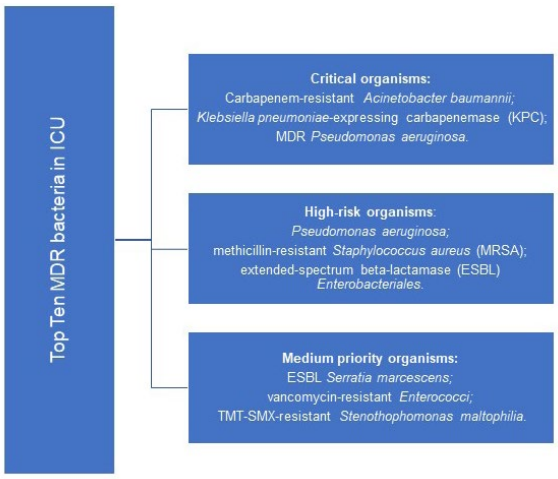

Figure 1. Top Ten MDR bacteria in the ICU. Source: Rello et al. 2019.
MDR: multidrug-resistant; ICU: intensive care unit

shock. Fear of missing causative pathogen or adverse clinical outcomes and aspects 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**).

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

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 regimen (May et al. 2014; Denny et al. 2019). Important details to note when 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 (≤6 days) is as effective as long-term (≥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 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.

	ERS/ESCMID, 2011	ATS/IDSA, 2019
Diagnosis	Recommend the collection of two sets of blood cultures in patients with CAP requiring hospitalisation.	Not routinely recommend Gram stain testing or blood culture for the diagnosis of CAP in healthy outpatients.
	Urinary antigen testing for *S. pneumoniae* and *Legionella pneumophila* should be performed in cases with an indication for hospital treatment.	Not recommend the use of procalcitonin to determine the need for antibacterial therapy.
		Not recommend routine urine testing for pneumococcal antigen or urine testing for *Legionella* antigen.
Treatment		
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 *Pseudomonas aeruginosa*	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

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

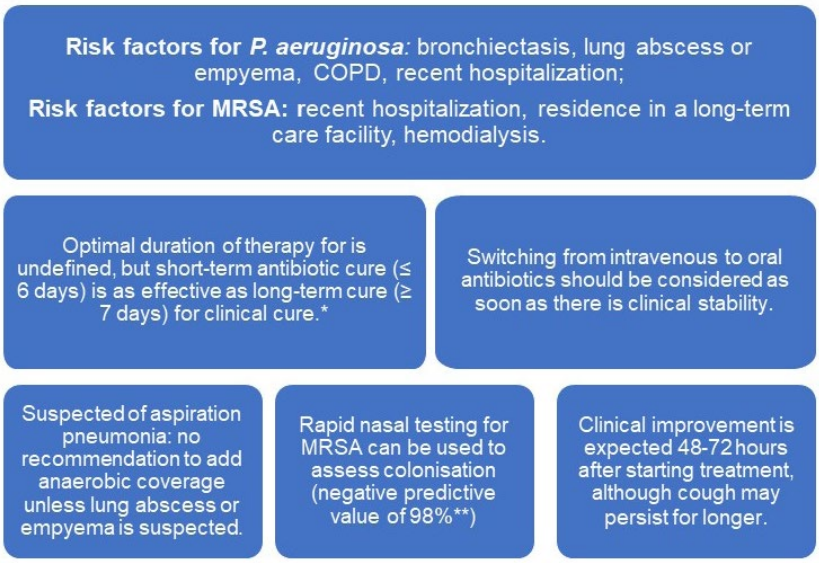

Figure 2. Community-acquired pneumonia - diagnosis and treatment aspects
MRSA: *methicillin-resistant Staphylococcus aureus*; COPD: chronic obstructive pulmonary disease. Sources: Tarsali 2018; Rioux et al. 2017.

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 (PTC)-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), disfavouring 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

For full references, please email editorial@icu-management.org or visit https://iii.hm/1hqd

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