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REVIEW

Antibiotic Resistance in the ICU: Clinical and Cost Aspects

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Abstract. *Objective:* **To review the mechanisms and important ICU-related aspects that contribute to the development of infection with antibiotic resistant (AR) pathogens; to describe its incidence; to summarize rates of resistance in the most common pathogens associated with hospital-acquired infections among critically ill patients; to provide an overview of the key principles of microbial surveillance of AR in the ICU, and to detail some cost considerations.** *Summary of findings:* **AR is one of the most pressing problems in healthcare, particularly in the ICU. Several factors unique to the ICU environment make patients in these units five to ten times more likely to develop hospital-acquired infections than patients on a general ward, and approximately half of these infections are caused by AR pathogens. The emergence of AR in the ICU has made treating these infections very difficult and, in some cases, even impossible. In addition to increasing the severity of infections, AR is driving up costs and as such it burdens indirectly the healthcare resources available for developing new antimicrobials.** *Conclusions:* **As the problem of AR is highly complex, a multifaceted approach is needed. A thorough understanding of the underlying grounds and the factors contributing to the further spread of these pathogens in hospitalized patients is of key importance when aiming to reverse, or at least to control this problem. In these times of tight budgets and increased workload, economic aspects of drug therapies should also be taken into account.**

Introduction

Once heralded as a 'miracle drug', penicillin was the first antibiotic in the war against infectious diseases. However, in the early 1940s, shortly after its discovery, Alexander Fleming had already recognized the potential for misuse and warned that this could result in pathogens becoming resistant to the drug [1]. Now, only a few decades later, Fleming's words have been proved true, not just in relation to penicillin, but to each new antimicrobial subsequently developed. In a growing number of cases, pathogens are resistant to multiple drugs, and for some there is now no effective therapy left. Consequently, antibiotic resistance (AR) has become one of the world's most pressing healthcare problems, and particularly in the intensive care unit (ICU) a crisis looms in the near future. According to the Center for Disease Control and Prevention estimates, in the United States (US), on a yearly basis, nearly two million people acquire an infection while in the hospital and about 90,000 of them die. Of the pathogens causing these infections, more than 70% are resistant to at least of one the drugs commonly used to fight them [2]. In addition, besides contributing to unfavourable clinical outcome, both AR and hospital-acquired infections have been recognized to contribute to increased resource utilization [3-6].

The purpose of this review is to highlight important issues of clinical and cost aspects of antibiotic resistance in the ICU, and to discuss the key principles aimed at dealing with and controlling this emerging problem.

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Epidemiology of antibiotic resistance

The onward march of antibiotic resistance

An important factor that is complicating treatment of nosocomial infection is the emergence of AR bacterial pathogens. Over the past decades, the prevalence of nosocomial infection caused by AR pathogens has steadily increased. For instance, in cases of acquired nosocomial infection in the ICUs of National Nosocomial Infection Surveillance (NNIS) system hospitals, the proportion of microbial cultures in which *S. aureus* demonstrated resistance to methicillin, rose from 3% in the early nineteen-eighties to 53% at the beginning of the 21st century; the proportion of *Enterococcus* species demonstrating resistance to vancomycin (VRE) involved in nosocomial infection has followed a comparable tendency. Likewise, Gram-negative pathogens have become increasingly resistant to broad-spectrum antimicrobial drugs. Non-fermenting Gram-negative pathogens such as the *P. aeruginosa* and *Acinetobacter* species that are resistant to almost all beta-lactam antibiotics, fluoroquinolones and aminoglycosides, are commonly isolated from critically ill patients, and resistance related to production of extended-spectrum beta-lactamases (ESBL) is commonly found in Enterobacteriaceae, which are important causes of invasive infection [7]. Moreover, this increasing trend appears to be continuing into the 21st century. In a four-year prospective registration of AR isolates in forty German ICUs, significantly increased incidence densities of ESBL-producing and fluoroquinolone resistant *E. coli*, vancomycin-resistant *Enterococcus faecium*, and ceftazidime-resistant *P. aeruginosa* were observed from 2001 through 2004 [8]. Moreover, from 1997-2002, the Meropenem Yearly Susceptibility Test Information Collection Program revealed no significant increase in resistance to carbapenem antibiotics [9, 10]. Yet the emergence of serine carbapenemases has been identified, which so far has only been a problem of limited scope, but may represent

Table 1. Relative frequency of ten most commonly isolated pathogens associated with ICU-acquired infections in Europe [15]

Pathogen	pneumonia	bloodstream infection
Coagulase-negative staphylococci		29.4
Staphylococcus aureus	19.6	14.1
Pseudomonas aeruginosa	18.8	7.5
Escherichia coli	8.5	6.2
Klebsiella pneumoniae	8.1	4.9
Enterobacter species	7.5	5.2
Serratia species	-	2.1
Haemophilus species	4.3	-
Enterococcus species	3.6	10.8
Other streptococci	3.5	-
Acitenobacter species	3.3	2.0
Candida albicans	-	6.3

Data are expressed as percentages (%).

a significant threat to the efficacy of carbapenem and other beta-lactam antibiotic drugs in the future [11]. Taking this into account, geographical differences also need to be considered. Considerable discrepancies exist between continents, countries, and even local microbial epidemiology [12]. For instance, with regard to methicillin resistant *S. aureus* (MRSA), huge differences in susceptibility patterns have been observed between southern European countries and the Netherlands or the Scandinavian countries, where the incidence of this dreaded pathogen is negligible. [13-15]. Consequently, every country should be aware of the current threats. More details on country-specific aetiology and resistance patterns in ICU-acquired infection have been described elsewhere [14-16].

Mechanisms and risk factors promoting antibiotic resistance

Several factors unique to ICUs contribute to the development and cross-transmission of AR pathogens (Figure 1). The development and spread of AR appears to be driven by the complex interplay of several mechanisms, one of which is the process of natural selection of microbial flora in an environment of antimicrobial pressure [17, 18]. The administration of antibiotic drugs promotes the emergence of resistance in two different ways. First, ecological pressure on a patient's residential flora, or a pathogenic microbial inoculum may selectively advantage the growth of particular bacterial species with pre-existing or intrinsic resistance to the drugs used. Also, by selecting sporadic mutants with diminished susceptibility rather then by inducing expression of gene coding for resistance, initially susceptible bacterial species may become progressively more resistant to the drugs infused during treatment [19]. Examples of this mechanism include the development of resistance to fluoroquinolones,[105] the induction of ESBL enzymes in *Enterobacter* species, and the appearance of resistance mechanisms to almost any antibiotic in *P. aeruginosa* [7, 20]. The transfer of genetic material encoding for AR through plasmids may lead to rapid acquisition of AR (and similar selective advantage under antibiotic pressure) by other microbial strains or even different genera. Biofilms are increasingly being recognized as a 'cradle' for the emergence of AR strains Such biofilms offer protection to the individual pathogens against antimicrobial killing but allow dissipation of some antimicrobial activity exerting selection pressure [21, 22].

A second mechanism through which antibiotics -particularly broad-spectrum antibiotics with anaerobic activity - promote resistance, is by disrupting the host's residential flora. The commensal

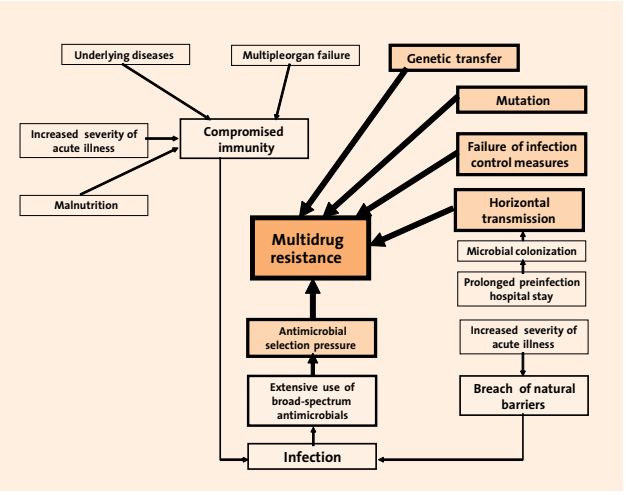

Figure 1. Risk factors contributing in the development and spread of MDR in the ICU

flora prevents colonization by pathogenic organisms by restricting available ecological space; this is also called colonization resistance [19, 23]. Emergence of AR by this second mechanism happens through the transmission of AR pathogens to the 'susceptible' host, for example from other patients through a caregiver's defective hand hygiene or through aerosolization of contaminated droplets. The spread of MRSA or VRE occurs essentially through this second mechanism, and it is also responsible for sporadic clonal outbreaks of infection with AR strains.

Incidence of antibiotic resistance

Several studies have addressed the incidence of AR in the ICU stating that resistance to antimicrobial drugs has increased steadily over time [24-26]. However, a variety of rates of increase have been reported by geographical area and microbial species [27]. A European one-day point prevalence study, undertaken in 1417 ICUs, revealed that 45% of ICU patients had an infection 21% of which were acquired while in the ICU. Of the pathogens causing these infections, *S. aureus* was yielded most frequently (more than half of these were resistant to methicillin), followed by 65% and 73% of isolates yielding *P. aeruginosa* and coagulase-negative staphylococci [28]. The highest infection rates were noted in patients with multiple trauma and burn injuries, in medical patients, and in patients who underwent emergency abdominal surgery whereas in patients who underwent elective surgery, lower infection rates were noted. Archibald and colleagues found that the prevalence of *S. aureus* resistant to methicillin, enterococci resistant to vancomycin, and *P. aeruginosa* resistant to ceftazidime or imipenem, was twice as high in ICU patients than on general wards or outpatient departments [29]. In their study investigating the antimicrobial susceptibility of the most common microbial isolates from ICU patients, Jones and colleagues found that overall *S. aureus* was the most frequently isolated Gram-positive pathogen; whereas *E. coli* and *P. aeruginosa* were the most prevalent among Gram-negative pathogens [25]. Although the predominant pathogens were comparable between the countries under study (i.e. US, Canada, Germany, France, and Italy), susceptibility patterns varied considerably. Data from the National Nosocomial Infections Surveillance system in the US, showed that from 1989 through 1998 the relative risk (RR) of isolating *S. aureus* resistant to methicillin in ICU patients, was 1.09

(95% confidence interval (CI), 1.07-1.16), compared with non-ICU patients [16]. The RR for enterococci resistant to vancomycin was 1.6 (95%CI, 1.13-1.20), and for *Klebsiella pneumoniae*, the risk of being resistant to third generation cephalosporins was found to be 24% higher in ICU patients (RR, 1.24; 95% CI, 1.20-1.30). The ten most common pathogens associated with hospital-acquired infections among ICU patients are depicted in Table 1. Each of the pathogens listed has proven resistance to at least one, and often several, of the antimicrobials commonly used to fight them. Gram-positives are generally associated with intravascular device-related bloodstream or surgical site infection, and Gram-negatives with ventilator-associated pneumonia and catheter-associated urinary tract infection [30]. As resistance rates are all significantly higher in patients cared for in the ICU, these data illustrate the importance of the ICU in terms of AR. Data from only one year later, confirmed these findings by demonstrating an apparent ongoing trend of AR in ICUs in the US [31].

Factors promoting the spread of antibiotic resistance

A pivotal factor promoting resistance is antimicrobial exposure, especially in ICUs, where the antimicrobial selection pressure is higher, and exposure to broad-spectrum antimicrobials is more common [17, 32]. Several studies have demonstrated a relationship between antimicrobial use and AR in hospitals [33-35]. Others have reported that reducing exposure to antimicrobials is effective and safe. In a randomized trial, Fagon and colleagues showed that diagnosing ventilator-associated pneumonia using quantitative cultures of distal airway samples reduces the use of antimicrobials, length of hospitalization and resources [36]. Moreover, the same study group reported that an eight-day course of antimicrobial treatment was as effective as a fifteen-day course, while associated with less development of AR in recurrent infection [37]. Other risk factors promoting AR in the ICU are severe underlying illness, suppressed immune system, malnutrition, history of frequent hospitalization, colonization with AR pathogens, and the widespread use of invasive techniques that breach normal physical barriers [26, 38, 39]. Further, improved emergency and supportive care has resulted in better acute phase survival, but simultaneously has led to a growing number of patients being admitted long-term to the ICU [40]. Furthermore, ICUs are crowded places with a high workload resulting in a suboptimal adherence to aseptic infection control measures. Finally, the transfer of severely ill patients unknowingly colonized or infected with AR pathogens is also an important risk factor for introducing such pathogens from one facility into another. All of the above factors result in a pool of ICU patients more likely to be colonized or infected with AR pathogens.

Surveillance of antibiotic resistance

Several factors, unique to the ICU environment make patients admitted to these units extremely vulnerable to developing hospital-acquired infections [41]. Accordingly, all these factors should be considered when aiming to decrease the emergence of AR. However, most important is the timely control of the endemic spread of AR strains which requires early detection by an efficacious microbial surveillance programme [42-44]. There are three major objectives for microbial surveillance in the ICU; (i) surveillance is a cornerstone in infection control and prevention, (ii) it can be used to control antimicrobial prescription patterns and therefore as a tool to limit the emergence of resistance, and (iii) surveillance cultures can be used to guide empirical therapy [45]. In a study by our group, it was found that in patients with bacteraemia caused by AR Gram-negative bacilli, prediction of the pathogen in surveillance cultures was associated with significantly more appropriate antimicrobial therapy [46]. In a subsequent study, Depuydt and colleagues observed the significant contribution of surveillance cultures to effective early antimicrobial treatment in a specific subgroup of ICU patients at risk for ventilator-associated pneumonia due to AR pathogens [47]. Accordingly, Michel and colleagues found a remarkably high predictive value of tracheal surveillance cultures on the aetiology of subsequent microbiologically-proven, ventilator-associated pneumonia [48]. Finally, Bouza and colleagues predicted catheter colonization and infection by means of surveillance cultures with an accuracy of 71% and 66% respectively [49]. However, the major limitation of a surveillance strategy remains the cost and workload that are imposed, since frequent sampling of cultures from different body sites is mandatory. Also a multitude of cultures are usually necessary to anticipate a minority of infections. The cost-effectiveness of such a policy should be addressed in a randomized controlled study [50]. As surveillance is primarily focused on detection of colonization with resistant pathogens, it is to be expected that the cost-benefit ratio can be most relevant in settings with a high risk of the acquisition of an AR ecology, such as ICUs of university hospitals with a high endemicity of such strains, or alternatively within a subset of patients at the highest risk for AR infection; however, this should be evaluated in future studies.

Clinical impact of antibiotic resistance

Several studies have shown that hospital-acquired infections due to AR pathogens are associated with higher in-hospital morbidity, longer hospital stay, and lower survival rates [3, 51, 52]. Das and colleagues found significantly higher attributable mortality in patients with methicillin-resistant *S. aureus* bacteraemia, but after more fine adjustment for confounding variables, an independent association could not be confirmed [53]. Zahar and colleagues found higher crude mortality rates among patients with AR ventilator-associated pneumonia, however, this difference was not established after controlling for length of ICU stay prior to onset of ventilator-associated pneumonia [54]. However, as there are a number of studies that found a negative impact of AR on patient survival, an equal number of studies could not demonstrated such a relationship [47, 55]. It is uncertain whether infection is the cause or the consequence of adverse outcome in critical illness. Also, it is uncertain whether infections caused by AR pathogens are only a marker of severity of illness resulting in longer hospitalization, and consequently an indicator of longer exposure to risk factor for acquiring infection due to AR strains [56]. For instance, Gonzalez and colleagues failed to demonstrate a difference in mortality when infections caused by methicillin-resistant versus methicillin-susceptible *S. aureus* infections were compared [57]. In a study comparing 96 patients with methicillin-resistant *S. aureus* bacteraemia with 252 patients with bacteraemia caused methicillin-susceptible *S. aureus*, hospital mortality was similar in both groups. This is in contrast with a previous meta-analysis conducted by the same study group, and our own matched cohort study in a subgroup of ICU patients [6, 58].

AR in enterococci has also increased, and prior exposure to antimicrobials has been identified as risk factor number one [59]. Resistance to ampicillin and gentamycin has been associated with a worse clinical outcome; however, early initiation of effective

antimicrobial therapy in this setting is of vital importance [59, 60]. Resistance of enterococci to vancomycin has also emerged significantly over the past decade [61]. According to the National Nosocomial Infection Surveillance system report, an exponential increase of 37.1% for VRE was noted between 1990 and 2002 [27]. Although enterococci are commonly perceived as less virulent pathogens in ICU patients, and in particular in the immunocompromised host, infections caused by these pathogens can have a morbid impact. Importantly, in a recent report by Gonzales and colleagues resistance to linezolid was noted [62]. Further, *P. aeruginosa* is also a common pathogen in hospital and ICU-acquired infections, and frequently isolated from the endotracheal aspirates of mechanically ventilated patients. Prior use of antimicrobials, underlying lung disease, and prolonged mechanical ventilation are the major risk factors for progression to AR, which often develops in patients receiving adequate treatment [61, 63]. Though considered as one of the most dreaded pathogens, several authors were unable to demonstrate excessive mortality in infections caused by AR *P. aeruginosa*, after controlling for inadequate antimicrobial therapy [64, 65]. Lastly, the impact of AR in *Acinetobacter baumannii* infections is difficult to assess due to its intrinsic resistance to multiple antimicrobials, hence the lack of studies comparing this pathogen with an infected control group with susceptible isolates. Blot and colleagues matched ICU patients with *Acinetobacter baumannii* bacteraemia with uninfected controls, but no significant attributable mortality was demonstrated [66]. Yet, in this specific cohort the rate of adequate treatment was high. As such, this study indirectly suggests that the clinical impact of AR in these infections is of minor importance if adequate antimicrobials are infused early in the clinical course.

Cost aspects of antibiotic resistance

Apart from an increased *a priori* probability of dying for the patient affected by a AR infection, resistance boosts the health economic burden of infection through prolonged hospital stay, the prescription of newer, last-line and more expensive antimicrobials, and the urgent need to take costly infection control measures [67-70]. Even when a seemingly simple infection is caused by a pathogen resistant to first-line antimicrobials, the necessarily advanced treatment can double or even triple the cost involved. Also, AR infections can be responsible for the extra loss of working days, physician consultations, laboratory tests, the necessity for extra infection control measures such as source isolation which all account for extra hospital charges. Methicillin-resistance in *S. aureus* remains the biggest concern in hospital-acquired infections [71]. Cosgrove and colleagues found that when comparing patients with methicillin-resistant *S. aureus* with patients with methicillin-susceptible *S. aureus*, the first group had significantly longer hospital stay and higher costs [72]. In another study, Shorr and colleagues observed increased economic cost in patients with hospital-acquired pneumonia and bacteraemia [73]. In a study evaluating hospital costs due to methicillin-resistant *S. aureus*, Abrahamson and colleagues found that the average hospital stay was prolonged by four days if the patient acquired methicillin-susceptible *S. aureus*, compared with twelve days if the patient acquired methicillin-resistant *S. aureus* [74]. The average added cost of the latter infection was $27,083 compared with $9,661 for non-resistant *S. aureus*. A study conducted by Kopp and colleagues evaluating 36 matched pairs of patients with and without methicillin-resistant *S. aureus*, revealed that the first group had a longer hospital stay (16 vs. 11 days), longer duration of antimicrobial therapy (10 vs. 7 days), and higher hospital costs ($16,575 vs. $12,862)[75]. McHugh and colleagues compared the cost of hospitalization of patients with methicillin-resistant *S. aureus* with patients with methicillin-susceptible *S. aureus* bloodstream infection, and showed that costs were significantly higher in the first group ($5,878 vs. $2,073) [76].

Although rational antimicrobial use is out of the scope of this review, optimizing antimicrobial strategies such as de-escalation and surveillance-guided therapy have been shown to reverse AR, and are not necessarily associated with higher expenditure [47, 77-79]. As such, in future research it is increasingly desirable to determine how much of the added cost of AR infection could be prevented by optimizing antimicrobial therapy

Conclusion

Severe hospital-acquired infections as well as AR in ICU patients are associated with a grim prognosis and adverse economic outcome. AR has continued to emerge over the past decades, especially in ICUs. Several considerations must be kept in mind when assessing AR in the ICU context. Many factors, either environmental and/or individual, contribute to the development of AR. Besides improving surveillance of AR, careful and evidence-based prescription of antibiotic agents is considered to be one of the crucial steps in an aim to reverse or at least to control the further spread of AR in the ICU in the near future.

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