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 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. 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.

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. 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.

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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 trends. 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 the 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 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 infections, respectively, of Enterococcus species 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 [30]. 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
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 the ICU [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 [30, 31]. As surveillance is primarily focused on detection of colonization with resistant pathogens, it is to be expected that the cost-benefit ratio can be more 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 bacteremia, 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 demonstrate 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 bacteremia with 252 patients with bacteremia 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
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 bacteremia [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 $9,861 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 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.
References


