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REVIEW

Association between infections caused by multidrug-resistant gram-negative bacteria and mortality in critically ill patients

Elisabeth Paramythiotou, Christina Routsi

Elisabeth Paramythiotou, Second Department of Critical Care, Medical School, University of Athens, Attikon University Hospital, 12462 Athens, Greece

Christina Routsi, First Department of Critical Care, Medical School, University of Athens, Evangelismos Hospital, 10676 Athens, Greece

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Correspondence to: Elisabeth Paramythiotou, MD, PhD, Second Department of Critical Care, Medical School, University of Athens, Attikon University Hospital, Rimini Stree, 12462 Athens, Greece. lparamyth61@hotmail.com
Telephone: +30-210-6003766
Fax: +30-210-5326414

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Abstract

The incidence of gram-negative multidrug-resistant (MDR) bacterial pathogens is increasing in hospitals and particularly in the intensive care unit (ICU) setting. The clinical consequences of infections caused by MDR pathogens remain controversial. The purpose of this review is to summarize the available data concerning the impact of these infections on mortality in ICU patients. Twenty-four studies, conducted exclusively in ICU patients, were identified through PubMed search over the years 2000-2015. Bloodstream infection was the only infection examined in eight studies, respiratory infections in four and variable infections in others. Comparative data on the appropriateness of empirical antibiotic treatment were provided by only seven studies. In ten studies the presence of antimicrobial resistance was not associated with increased mortality; on the contrary, in other studies a significant impact of antibiotic resistance on mortality was found, though, sometimes, mediated by inappropriate antimicrobial treatment. Therefore, a direct association between infections due to gram-negative MDR bacteria and mortality in ICU patients cannot be confirmed. Sample size, presence of multiple confounders and other methodological issues may influence the results. These data support the need for further studies to elucidate the real impact of infections caused by resistant bacteria in ICU patients.

Key words: Critically ill patients; Infections; Multidrug resistance; Gram-negative pathogens; Mortality

Core tip: The incidence of gram-negative multidrug-

resistant (MDR) bacterial pathogens is increasing in hospitals and particularly in the intensive care unit (ICU) setting. The clinical consequences of infections caused by MDR pathogens remain controversial. Until the present time a direct association between infections due to gram-negative MDR bacteria and mortality in ICU patients cannot be confirmed by the studies available. Further studies are needed to elucidate the real impact of infections caused by resistant bacteria in ICU patients.

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INTRODUCTION

Nosocomial-acquired infections are a frequently encountered problem in critically ill patients posing a severe burden on the morbidity and mortality noticed in the intensive care unit (ICU) setting. In the Extended Prevalence of Infection in Intensive Care (EPIC Ⅱ) study carried out in May 2007[1] recruiting 1265 ICUs in 75 countries, 51% of patients were considered infected, a prevalence rate considerably higher than the 20% of the previous EPIC Ⅰ study[2]. Furthermore, ICU and hospital mortality rates of infected patients were more than twice than those of non-infected. Notably, 62% of the isolates were gram-negative bacteria.

An important factor further contributing to the untoward effects of infection is the ever growing resistance of pathogens. Although resistance trends vary among hospitals, there is significant evidence that the prevalence of multidrug-resistance (MDR) is increasing. Particularly in the ICU setting several specific factors contribute to higher percentages of antimicrobial resistance in this particular environment[3,4]. Overuse of antibiotics, prolonged ICU stay, use of indwelling devices, presence of comorbidities, lack of isolation practices, easy spread of resistant pathogens among countries as a result of international travels significantly increase the burden of resistance in the critically ill.

Since 2008 the acronym "ESKAPE" has been given to a group of pathogens [*Enterococus faecium, Staphylococcus aureus, Klebsiella pneumoniae* (*K. pneumoniae*), *Acinetobacter baumannii, Pseudomonas aeruginosa* (*P. aeruginosa*) and *Enterobacter* species] that pose a high threat to patients' safety emphasizing the need for new and effective antibiotics[5]. In the critically ill patient the importance of gram-negatives as pathogens in the ICU has been featured by several epidemiologic studies both in Europe[1] and in the United States[6]. In addition, the Centers for Disease Control and Prevention (CDC) identified the increase in antibiotic resistance as one of the most important threats to human health worldwide[7].

Apart from the clinical, the economic consequences of antimicrobial resistance are also a matter of concern[8]. It is almost generally accepted that acquisition of MDR strains is often associated with higher utilization costs, compared to susceptible ones[9,10]. On the contrary, the clinical consequences of infections caused by MDR pathogens have been a matter of debate. Although there is a general agreement about the association of MDR with prolonged hospital stay, the possible association between antimicrobial resistance and mortality remains controversial. In some studies a positive association has been found whereas in other studies no significant excess of mortality has been detected.

Earlier studies regarding the resistance and ICU outcomes have addressed gram-positive organisms, such as methicillin-resistant *Staphylococcus aureus* (MRSA) or *Vancomycin-resistant enterococcus*[11-13]. Furthermore, though numerous studies have examined the impact of resistant gram-negative bacilli in hospitalized patients in general, a limited number of them have focused exclusively on ICU patients. The purpose of this review is to summarize the available data concerning the impact of infections caused by MDR gram-negative pathogens upon clinical outcome, laying particular emphasis on mortality of the critically ill. A brief description of the epidemiology and characteristics of the main gram-negative pathogens will precede.

EPIDEMIOLOGY AND MECHANISMS OF RESISTANCE

In the critically ill patients gram-negative pathogens with the greatest burden are the non-fermenting bacteria *Acinetobacter baumannii* and *P. aeruginosa* for which few therapeutic options are available and *Enterobacteriacae* mainly *Kebsiella pneumoniae* equipped with a significant number of resistance mechanisms. The Antimicrobial Availability Task Force formed by the Infectious Diseases Society of America has identified these three gram-negative pathogens as a source of particular importance for difficult to treat infections[5].

K. pneumoniae

K. pneumoniae is an established nosocomial pathogen capable of collecting plasmids which confer resistance to many antimicrobials. An illustrating example of their capacity are plasmids encoding extended-spectrum beta-lactamases rendering them resistant against newer cephalosporins. Later, another main mechanism of resistance for *K. pneumoniae* was added, the acquisition of carbapenemases. The carbapenemases commonly encountered are the *K. pneumoniae* carbapenemase (KPC) variants and the zinc-dependent metallo-beta-lactamases (Mbls).

KPCs are beta-lactamases capable of hydrolyzing penicillins, all cephalosporins, mono-bactams, carbapen-

ems and even β-lactamase inhibitors. They were firstly isolated in 1996 in Northern Carolina, United States, then in New York city hospitals and then in many states[14]. Since then, KPC-producing bacteria have been isolated in most places around the world, including South America, Europe and Asia. In many countries such as Greece, Israel, Poland and Italy[15-17], KPCs have become endemic but in other cases they remain a rare infection cause. Infections caused by KPCs include life-threatening infections such as bacteremia and pneumonia in critically ill patients.

The three families of metallo-beta lactamases (VIM, IMP and NDM) have spread inter-nationally but with significant local differences. VIM-producing *K. pneumoniae* are isolated mainly in Europe where they are epidemic in some countries of Southern Europe. On the contrary, IMPs are isolated in countries of Asia and also in Australia[18,19]. New Delhi metallo-beta-lactamase is the most recently isolated type of metallo-beta-lactamase. Although the epidemic started in India, it has spread to several parts of the world[20].

P. aeruginosa

P. aeruginosa is a common cause of nosocomial infections, often associated with higher mortality when compared to other bacterial pathogens[21,22]. Especially in the ICU setting severe infections are caused by this aerobic gram-negative bacilli, namely bloodstream infections, whether related or not to the use of a central venous catheter and ventilator-associated pneumonia. *P. aeruginosa* is the cause of a high percentage of nosocomial infections in critically ill patients. In the EPIC Ⅱ study *Pseudomonas* species caused 19.9% of infections in the ICU[1] while another multicenter study concerning bloodstream infections coming from 9 countries, showed that *P. aeruginosa* was the cause of bacteremia in 5.3% of cases[23]. Several mechanisms are implicated in the development of resistance in *P. aeruginosa* strains. One of the main mechanisms is the resistance to carbapenems, one of the most important drugs for the treatment of *P. aeruginosa*-associated infections. Resistance is often caused by carbapenemases, mainly Ambler class B metallo-b-lactamases and more recently KPC serine carbapenemases. A combination of resistance mechanisms is usually present[24]. In a recent study Castanheira *et al*[25] examined 529 carbapenem non-susceptible *P. aeruginosa* isolates from 14 European and Mediterranean countries. They noticed an increased prevalence of Mbls and increased resistance to imipenem and meropenem while a percentage of 99.3 of isolates was susceptible to colistin.

Acinetobacter baumannii

Acinetobacters are gram-negative, catalase-positive, oxidase-negative, non-motile, non-fermenting coccobacilli. They have concentrated a wide array of antimicrobial resistance mechanisms which include enzymatic degradation by beta-lactamases (including TEM, SHV, CTX-M, OXA, VIM, IMP and others). Furthermore, several non-enzymatic mechanisms contribute to the emergence of resistance to a variety of antimicrobials including quinolones, aminoglycosides, tetracyclines, glycylcyclines and polymyxins[19]. One of the most important mechanisms is the emergence of resistance to carbapenems, which is encountered in larger percentages than in other gram-negatives[26]. In such cases polymyxins are the only therapeutic solution. Unfortunately, the isolation of colistin-resistant carbapenem-resistant *A. baumannii* is on the rise[27]. A large spectrum of nosocomial infections are caused by *A. baumannii* including bloodstream infections, pneumonia, catheter-associated infections, *etc. A. baumannii* belongs to the group of ESKAPE pathogens and in the EPIC Ⅱ study infections caused by this pathogen covered a percentage of 8.9%[1].

DEFINITIONS

Antimicrobial resistance

A general definition of antimicrobial resistance is the ability of an organism to resist the action of an antimicrobial agent to which it was previously susceptible. One of the major difficulties in the evaluation of relevant studies was the lack of a standard definition for the MDR, extra-drug resistant (XDR) and the pan-drug resistant (PDR) pathogens due to the lack of classification criteria and specific definitions. Various authors have used different methods to characterize organisms as "resistant" based on *in vitro* antimicrobial susceptibility test results. As a result, microbiology data could not be reliably compared across different healthcare settings. The diversity of definitions of MDR and PDR for *A. baumannii* and *P. aeruginosa* has been reviewed by Falagas *et al*[28]. In this paper, an impressive diversity of resistance definitions became apparent highlighting the need for a consensus on that important matter.

In 2012 Magiorakos *et al*[29] international experts established a standardized international terminology through a joint initiative by the European Centre for Disease Prevention and Control and the CDC. In this definition an "antimicrobial category" was constructed for each isolate. Accordingly, MDR was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories; XDR was defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories and PDR was defined as non-susceptibility to all agents in all antimicrobial categories. Applying the suggested definitions could make data from relevant studies comparable allowing therefore, the extraction of reliable conclusions.

In the present review, since we included studies between 2000 and 2015, the definitions used by different authors of the included studies vary. Some of them define the resistance as resistance only to carbapenems while others to several classes of antimicrobial agents.

Twenty four studies were identified during the predefined period according to the search criteria[9,30-56]. A synopsis of the studies' characteristics such as design, sample size, type of infection, resistance definition, pathogen (s) and clinical outcome data are presented in Table 1. Nine out of the twenty three studies had a retrospective study design, ten were prospective and in two studies the type was not reported. Two studies were part of secondary analysis of large prospective studies.

Several differences regarding definitions, design, control group selection and the sample size were observed. Two studies were conducted in surgical ICUs while others in mixed ICUs. The causative pathogen was only one in thirteen studies (*P. aeruginosa* in 5, *A. baumannii* in 5, and *K. pneumoniae* in 3 studies) whereas two studies dealt with two resistant pathogens. The remaining studies examined the impact of all three important gram-negative pathogens, some of them involving also other *Enterobacteriacae* (such as *E. coli*) or gram-positive bacteria such as *S. aureus*. Four studies have focused exclusively on carbapenem-resistant compared to carbapenem-susceptible strains of *P. aeruginosa* or *A. baumannii*.

The site of infection differed among studies. Eight studies examined bloodstream infections; four studies examined respiratory infections related to mechanical ventilation, one study enrolled patients with pneumonia or bloodstream infection and nine studies enrolled patients affected by infections of any origin. Finally, in two studies colonization with or without infection was examined. One of them is the recent large, two-center prospective cohort study, which quantified the effects of carbapanemase-producing *Enterobacteriaceae* carriage on patient outcome in the ICU (MOSAR study)[30]. Although this study did not explore any association with infection, being focused on colonization, it was included because colonization precedes infection in most instances and, therefore, it represents an indirect marker of a patient being at risk of a possible poorer outcome.

Concerning the control group selection, in nine studies both cases and controls came from the pool of patients presenting an infection due to a MDR pathogen and survivors were compared to non-survivors. In eight studies patients infected with a MDR strain were compared to those with a susceptible one or to those without any infection. Comparative data on the appropriateness of empirical antibiotic treatment were provided by only seven[48,50,51,52,54,55] out of twenty-four studies.

As for the main target of this review, *i.e.,* resistance-associated mortality, a negative association was documented in ten studies. In the remaining studies a positive result was noted, though with different endpoints. Among the latter, the hospital-associated mortality was affected in two studies while in another study both ICU and hospital mortality were influenced. In the large sample size study by Lambert *et al*[47] the results showed that the presence of antimicrobial resistance had a low additional effect (20%) on mortality. In two other studies, the increased mortality was considered as the indirect consequence of the inappropriate therapy. Finally, in the study by Dautzenberg *et al*[30] patients colonized with carbapenemase-producing Enterobacteriaceae had a 1.79 times higher hazard of dying in ICU than no colonized patients, primarily because of an increased length of stay.

Additionally, 3 review articles summarizing the published data on this issue were identified[31-33] as well as another one presenting the clinical consequences of specific MDR pathogen, namely *P. aeruginosa*[34]. In the review by Shorr[33], studies mostly conducted on general hospitalized population were included providing that among the studied patients a more than 39% of cases was hospitalized in the ICU. The collective findings of these studies suggested that gram-negative bacterial resistance increases the burden in the ICU in terms of mortality, length of stay and charges. Of note, associations between gram-negative resistance and mortality or prolonged length of stay sometimes disappeared in multivariate analyses after adjusting for confounding factors.

GENERAL COMMENTS

The clinical consequences of the common MDR gram-negative bacilli on the critically ill patients have been the subject of examination in a number of studies presented in this review. Several studies found a significant impact of antibiotic resistance on mortality whereas others did not show such impact. However, as shown in Table 1, there was a considerable heterogeneity of published studies with respect to study design, definitions and outcomes measured. As a result, some confusion with regard to the actual antibiotic resistance impact on mortality from gram-negative infections is unavoidable.

Assessing the contribution of infections caused by antimicrobial resistant pathogens to an adverse clinical outcome in ICU patients is difficult, given the confounding created by crucial factors such as the illness severity, co-morbidities, infection site, treatment strategy and others[9,57]. Large, well-conducted epidemiological studies, focusing on the association between gram-negative bacterial resistance to antimicrobial agents and mortality in the ICU setting are limited in the currently available literature.

Most of the studies identified suffer from a number of limitations. Firstly, nine studies were retrospective and, therefore, prone to several forms of potential biases. Secondly, diverse definitions of the term "multi-drug resistance" have been used based on different thresholds over the past years in different institutions[28], particularly before the standardized international terminology was available[29]. As a result, according to *in vitro* susceptibilities some patients would have been classified into the opposite category (or vice versa).

Table 1 Studies describing mortality in intensive care unit patients with infections caused by multi-drug resistant bacteria *vs* susceptible

Ref.	Study design	No. of cases	Type of infection	Isolates/resistance definition	Results/comments
Blot *et al*[35]	Retrospective, cohort study	328	BSI	Variable/ceftazidime-resistance	Antibiotic resistance does not affect the outcome
Peres-Bota *et al*[36]	Prospective	186	Variable infections	Variable[2]/at least to ceftazidime, animoglycosides, carbapenems or quinolones	No difference in mortality
Ortega *et al*[37]	Single center prospective study	53	Colonization and infection	*P. aeruginosa*/resistant at least to two classes of antibiotics	No difference in mortality
Combes *et al*[38]	Secondary analysis of a large prospective cohort study	115	VAP	*P. aeruginosa*/resistance to piperacillin	28-d mortality not associated with piperacillin resistance
Kwa *et al*[39]	Retrospective cohort study	129	VAP	Variable MDR bacteria/resistance to all available systemic antibiotics	MDR was associated with a higher likelihood of infection-attributed mortality
Playford *et al*[9]	Retrospective case-control study	197	Variable (including colonization)	*A. baumannii*/susceptible only to amikacin and colisin	Positive association with increased hospital mortality
Daniels *et al*[40]	Retrospective, propensity-matched cohort study	84	Variable infections	*A. baumannii*/resistance to 3 or more classes of antibiotics	No difference in 28-d mortality
Parker *et al*[41]	Secondary analysis of a randomized trial	739	VAP	*P. aeruginosa* or variable MDR bacteria[2]/resistance to 2 or more classes of antibiotics	Higher 28-d ICU and hospital mortality
Pinheiro *et al*[42]	Retrospective case–control study	131	Variable infections	*P. aeruginosa*/multi- or pandrug resistant	No association with mortality
Katsaragakis *et al*[43]	Prospective observational study in a surgical ICU	60	Variable infections	*A. baumannii*/susceptibility only to colistin	Multi- resistance not associated with mortality
Routsi *et al*[44]	Prospective observational study	96	BSI	*A. baumannii*/carbapenem resistance	No association with mortality
Mouloudi *et al*[45]	Double case -control study	59	BSI	*K. pneumoniae*/carbapenem resistance	Positive association between KPC producing *K. pneumoniae* and mortality
Michalopoulos *et al*[46]	Retrospective case-control study	84	Primary BSIs (78% ICU-acquired, 22% ward-acquired)	*K. pneumoniae*, *A. baumanni*, *P. aeruginosa*/resistance to at least 4 out of 7 antibiotic classes	Higher hospital mortality, compared to controls
Lambert *et al*[47]	Multicenter prospective cohort study	119699	Pneumonia,	*E.coli*, *A. baumannii*, *P. aeruginosa*, *S. aureus*/resistance to 3rd generation cephalosporins, ceftazidime, and oxacillin, respectively	The additional effect of the most common antimicrobial resistance patterns on mortality is comparatively low
Tabah *et al*[48]	Prospective multicentre cohort study	1156	BSI BSI	Multiple isolates[2]/according to the ESCMID	Resistance is associated with increased 28-d mortality
Patel *et al*[49]	Prospective cohort matched case-control	298	Variable infections	*A. baumannii*, *K. pneumoniae*, *P. aeruginosa*/susceptible to ≤ 1 antimicrobial agent	Resistance not associated with mortality
Zilberberg *et al*[50]	Single center retrospective cohort study	1076	BSI	Variable gram-negative/*Paeruginosa* resistant to at least 3 antimicrobials, ESBL, CPE	Impact of MDR on inappropriate therapy/indirect effect on increased hospital mortality
Shorr *et al*[51]	Retrospective cohort study	131	BSI	*A. baumannii*/carbapenem resistance	Impact of carbapenem resistance on inappropriate therapy/indirect effect on mortality
Papadimitriou–Olivgeris *et al*[52]	Single center study	273	Variable infections	*K. pneumoniae*/resistance to gentamicin, colistin and/or tigecycline	Positive association with mortality
Dabar *et al*[53]	3-center, prospective cohort study	120	Variable infections	Variable pathogens/MDR *P. aeruginosa*: Resistance to at least 3 of the following: *Pseudomonas* acting beta-lactams, carbapenems, aminoglycosides, and quinolones	MDR *P. aeruginosa* infection was independent risk factor for mortality

Dautzenberg *et al*[30]1	2-center prospective cohort study	132	Colonization	*CPE*	Higher hazard of dying (primarily because of an increased LOS)
Bass *et al*[54]	Prospective case-control study	168	BSI	Gram-negative bacteria/carbapenem resistance	Increased mortality/combination therapy was associated with improve survival rate
Vardakas *et al*[55]	Retrospective Cohort study	140	Variable infections	*K. pneumonia*/carbapenem resistance	No difference in mortality
Martin-Loeches *et al*[56]	Prospective observetional study		VAP and HAP	Variable/according to CDC/ECDC	Patients with MDR bacteria had a higher mortality than those with no-MDR

[1]Colonization only; [2]Gram-positive included. BSI: Blood stream infection; VAP: Ventilator associated pneumonia; MDR: Multidrug-resistant; ESCMID: European Society of Clinical Microbiology and Infectious Diseases; CPE: Carbapenem – producing enterobactaeriacae; ESBL: Extended spectrum beta lactamases; HAP: Hospital acquired pneumonia; ECDC: European Centre for Disease Prevention and Control; CDC: Centers for Disease Control and Prevention.

Thirdly, different outcome definitions could have also influenced the results. For example, some studies assess the overall ICU mortality, while others the in-hospital or the attributable mortality[57]. Of note, whether the deaths in critically ill patients are directly attributable to antibiotic resistant infections cannot be easily evaluated since it is often subjected to the physicians' clinical assessment. Finally, the small sample size of cases in some studies was a restricting factor for the detection of any significant difference.

SPECIFIC METHODOLOGIC ISSUES

Important methodologic issues addressing the choice of reference group might influence the conduct and the results of studies evaluating the relationship between acquisition of antimicrobial-resistant organisms and outcome, as discussed in detail elsewhere[57-59]. Briefly, instead of the standard case-control method, a case-case-control study design has been proposed with two separate case-control analyses to overcome limitations of the conventional studies assessing the effect of hospital or ICU-acquired infections by a particular pathogen. A complete analysis might include two groups of case patients; those infected with resistant pathogens and those with susceptible ones, compared with the control group, *i.e.,* uninfected patients. To our knowledge, only few studies have included double-case patients in similar efforts and none of the studies that have been included in the present review.

SITES OF INFECTION

In several studies all patients infected with antimicrobial resistant gram-negative pathogens are analyzed together. This is due, in part, to the small size of studies; insufficient numbers of the patients included do not allow stratification. However, certain types of infection as pneumonia or peritonitis may carry greater mortality than other infection types[35,60,61]. Indeed, among bacteremic patients, high-risk source of bacteremia (including the lung, abdominal or unknown sources) were more prevalent among nonsurvivors[35,60].

ROLE OF VIRULENCE

Whether the association of antimicrobial resistance with an increased risk of death, found in some studies, is exclusively related to the risk of receiving inappropriate initial empirical antimicrobial treatment, or it is also related to a higher virulence of pathogens exhibiting higher MICs to certain antimicrobials is not clear[62]. Probably, this question cannot be answered by such type of clinical studies where different gram-negative bacteria of nonsimilar virulence are usually examined together[60]. For example, *P. aeruginosa* isolates are known to be extremely virulent; however, as it has been shown, MDR *P. aeruginosa* strains have impaired virulence when compared to susceptible ones[63].

Theoretically, an increased intrinsic virulence of resistant gram-negative strains could explain, at least in part, an adverse clinical outcome. However, to date, no studies have demonstrated such an association; thus, in general, antibiotic resistance is not believed to be itself a virulence factor as compared to similar susceptible species[57]. Nevertheless, in certain situations the antimicrobial resistance may be considered a "virulence like" factor in specific ecological niches which MDR bacteria are able to colonize. This is especially true in the ICU environment where MDR pathogens can cause disease more readily[64].

ROLE OF INITIAL APPROPRIATE ANTIMICROBIAL TREATMENT

Treatment factors may contribute to adverse outcomes in patients infected with a resistant pathogen[57].The importance of an early and appropriate antimicrobial treatment and its favorable impact on the clinical outcome is well known[60,65]. Inappropriate empirical antimicrobial therapy is one of the major confounders in studies aiming to assess the impact of MDR to mortality[32].

This issue was not assessed in sixteen out of the twenty-three studies included in the present review. In most studies which addressed this issue, the presence of MDR pathogens was an important factor for receiving

inappropriate empiric treatment. For example, in a recent study[51], the presence of carbapenem-resistant *A.baumannii* as the infectious pathogen more than doubled the risk of receiving non-initially appropriate antimicrobial treatment, compared to having a carbapenem-susceptible isolate.

Failure to receive appropriate therapy further increases the risk of hospital mortality. In the EUROBACT study[48], even after controlling for adequacy of antimicrobial treatment, antimicrobial resistance, along with the timing to adequate treatment, was an independent predictor of 28-d mortality. However, XDR or PDR resistance levels were not associated with higher 28-d mortality when compared with MDR levels.

To our knowledge, this is the first review that focuses exclusively on studies conducted in the critical care setting. Studies examining the impact of antimicrobial resistance on the outcome of hospitalized patients in general (either in the ICU or in the hospital wards) have also shown diverse results[66]. As a case in point, a prospective observational study, evaluating the impact of VIM production on the outcome of patients with *K. pneumoniae* bloodstream infections, showed that VIM production had no effect on mortality whereas in the subgroup of patients infected with VIM - producing *K. pneumoniae*, carbapenem resistance, advanced age and severity of underlying disease were independent predictors of adverse outcome. However, after adjustment for inappropriate therapy, the effect of carbapenem resistance on outcome was nonsignificant. Therefore, the higher mortality was probably mediated by the failure to provide effective antimicrobial therapy[67].

Finally, it should be noted that there is little data assessing whether being admitted to an ICU with high levels of antimicrobial resistance is associated with a worse outcome than being admitted to an ICU with low rates of resistance. A recent publication using data from the large, international EPIC Ⅱ study on infections in ICUs[1] showed that being hospitalized in an ICU in a region with high levels of antimicrobial resistance is not associated *per se* with a worse outcome[68]. In this study the selection of countries with high levels of antimicrobial resistance rates was made using reported MRSA rates. According to the authors this could be considered as a selection bias because general resistance rates may have been different.

CONCLUSION

Although mortality associated with gram-negative infections is high, data from the available literature do not confirm that there is a direct association between antimicrobial resistance and mortality in ICU patients. Appropriate antimicrobial administration remains of paramount importance. Due to papers' limitations including the sample size and multiple confounders due to individual patient's characteristics and different healthcare systems any conclusion should be carefully considered. These data support the need of further studies to elucidate the real impact of infections caused by resistant bacteria in ICU patients.

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