International Journal of Healthcare Sciences ISSN 2348-5728 (Online)
Vol. 11, Issue 1, pp: (202-209), Month: April 2023 - September 2023, Available at: www.researchpublish.com

Review Paper On: The Negative Impact of Antibiotic Resistance

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DOI: https://doi.org/10.5281/zenodo.8246007

Published Date: 14-August-2023

Abstract: **Antimicrobial therapy is one of the most important medical developments of the 20th century; however, the spread of drug resistance in health care settings and in the community threatens the enormous benefits that antibiotic therapy offers. Infections caused by resistant bacteria cause more than two times the rate of adverse events compared with similar infections caused by susceptible strains. These adverse events may be clinical or economic and primarily reflect failure or delay in antibiotic therapy. The magnitude of these side effects becomes more pronounced as disease severity, strain virulence, or host susceptibility increases. The negative effects of antibiotic resistance can be measured at the patient level by increasing morbidity and mortality, at the healthcare level by increasing resource use, higher costs and reduce hospital performance, and at the societal level by broader empiric antibiotic treatment guidelines. treatments. therapy. In this review, we will discuss the negative impact of antibiotic resistance on patients, health care systems, and society.**

Keywords: **Antibiotic, antimicrobial, infection, resistance, selective pressure.**

1. INTRODUCTION

Antibacterial therapy is one of the most important medical breakthroughs of the 20th century and has become one of the pillars of modern medicine in preventing millions of premature deaths from bacterial infections. In the period before the introduction of antibiotics, the mortality rate from pneumonia caused by Streptococcus pneumoniae reached 40% [1], the mortality rate from Staphylococcus aureus bacteremia was 80% [2], and 97% of patients with endocarditis died. [3]. Before antibiotics, wound infections were often treated with amputations; In fact, during World War I, 70% of amputations were performed as a result of wound infection [4]. Antibiotics have radically changed the fate of patients with such infections, changing the way diseases such as tuberculosis and syphilis are treated and cured. In addition, the ability to treat and cure infections has enabled advances in modern medicine, such as increasingly complex surgeries, transplants, and chemotherapy. Unfortunately, the spread of resistance in healthcare settings and communities is jeopardizing the vast improvement in the availability of antibiotic therapies [5]. Microbiological tests for antibiotic resistance are intended to classify bacterial strains into curable and incurable categories and to give physicians an indication of the possible use of drugs to treat patients. Clinical MIC thresholds distinguish between infections that are likely to respond and those that are not likely to respond to antibiotic therapy [6], with organisms classified as "resistant" implying a high probability of treatment failure. However, the MIC limits are not precise; There is a gray area. Resistance does not always result in inadequate therapy or treatment failure, and infections caused by fully susceptible organisms can result in treatment failure. The increase in MIC appears to have an independent effect on the decreased efficacy of various antibacterial drugs, independent of microbiological susceptibility testing. For example, failure of vancomycin treatment is not uncommon, even when methicillin-resistant S. aureus (MRSA) strains are susceptible to vancomycin but have high vancomycin MICs (1–2 μg/mL) [7]. Just as organisms considered "susceptible" to a particular antibiotic may fail, so resistant isolates may respond.

For example, beta-lactam antibiotics remain suitable for the treatment of non-CSF pneumococcal infections regardless of the in vitro susceptibility defined by the thresholds [8]. In this review, we will discuss the negative impact of antimicrobial resistance on patients, the healthcare system and society.

Historical Perspective

The resistance has been with us for a long time. Bacteria have an extraordinary variety of genetic mechanisms for resistance to antibacterial drugs, and there is a large pool of antibiotic resistance genes in nature that have evolved over millions of years [9]. Microorganism analyzes and epidemiological data suggest that the development and spread of multidrug-resistant microorganisms has accelerated dramatically over the past 50 years. This period coincides with the discovery and increasing use of antibacterial agents [9]. history of resistance to S.aureus provides an example from history. Abrams et al. described penicillinase before the clinical use of penicillins [10] and when penicillinase production in S. aureus was still rare. However, following the introduction of penicillin, it spread rapidly and by the late 1940s around 50% of S. aureus isolates in the UK were resistant to penicillin.As a result, resistance to tetracyclines and macrolides increased in the 1950s. Methicillin was introduced in 1959 to treat penicillin-resistant S. aureus, but isolated cases of S. aureus with acquired methicillin resistance emerged in 1961 (ca.MRSA). Multidrug-resistant (MDR) MRSA isolates were quickly isolated from other European countries, then Japan, Australia and the United States and spread to hospitals in most parts of the world and are now spreading in the community [11].

Direct Adverse Outcomes Related to Resistance

Broadly speaking, infections caused by resistant bacterial strains lead to up to two-fold higher rates of adverse outcomes compared with similar infections caused by susceptible strains [12]. These adverse outcomes may be clinical (death or treatment failure) or economic (costs of care, length of stay) and reflect both treatment delays and the failure of antibiotic treatment to cure infections. The magnitude of these adverse outcomes will be more pronounced as disease severity, strain virulence, or host vulnerability increase. It is the cost of these treatment delays and failures to patients and the healthcare system that forms the basis of the negative impact of antibiotic resistance. For example, in the case of bacteraemia and other serious infections due to MRSA, a significantly higher case fatality rate has been clearly demonstrated as compared with methicillin-susceptible S. Extended-spectrum β-lactamase (ESBL) production among Enterobacteriaceae is associated with higher rates of treatment failure and mortality in patients with bacteraemia compared with bacteraemia caused by non-ESBL producers [15–17]. ment failure rates for patients infected with ESBL-producing Klebsiella pneumoniae are almost twice as high as for those with non-ESBL-producing K. Carbapenem-resistant Enterobacteriaceae (CRE) are now the emerging contemporary threat. Infections caused by carbapenem-resistant K. to five-fold higher risk of death than infections caused by carbapenem-susceptible strains [18,19]. Infections caused by CRE are associated with crude in-hospital mortality of 48%–71% [18,19], whereas carbapenem-resistant Acinetobacter baumannii bacteraemia is associated with a 14-day mortality of Although death is the most severe adverse outcome of antibiotic resistance, other adverse outcomes are evident. For example, among adults with bacteraemic pneumococcal pneumonia, infection with penicillin-nonsusceptible pneumococci is associated with more than four times the risk of suppurative complications [21]. gonorrhoeae strains with resistance to most antibiotics, leading to treatment failures and subsequent reproductive tract disease, infertility and promo- Increasing rates of bacteraemia are now well described owing to the failure of fluoroquinolone prophylaxis for transrectal ultrasound-guided prostate biopsy [23,24]. In addition, previous fluoroquinolone use in patients with chronic liver disease as prophylaxis against spontaneous bacterial peritonitis has been significantly associated with community-onset MDR bacterial infections [25].

How Resistance Confers Adverse Outcomes

The reasons for the treatment failures associated with infections caused by resistant bacteria are probably multifactorial, but include bacterial fitness, greater severity of underlying illness [19], delays in initiation of effective therapy and in some cases a lack of effective therapy [12,26]. How- ever, resistant strains seen in the clinical setting are largely those that are able to both survive and effectively spread in high-density antibiotic environments, and are therefore usually fitter than other strains belonging to the same species [12]. Resistance frequently leads to delays in the administration of effective therapy, and a mismatch between empirical therapy and subsequent antibiotic susceptibility test results is the most significant factor in delaying effective therapy [12]. in one study, patients with ESBL-producing K. coli infections were treated with effective antibiotics a median of 72 h after infection was suspected, whereas matched con- trols infected with non-ESBL-producing strains of coli received appropriate antibiotics after a median of 11. 5 h [26]. A meta-analysis corroborated the significantly increased likelihood of delay in effective therapy in pneumoniae bacteraemia have been shown to experience delays in the

administration of antibiotics with in vitro activity against carbapenem-resistant K.(Table 2) illustrates examples of the consequences of antibiotic resistance.) The delayed administration of active agents in the case of resistant infections may be further prolonged by delays in the availability of comprehensive antibiotic susceptibility data. For example, manual testing may be required for polymyxin B andtigecycline susceptibilities, which are not represented in initial testing panels [19]. Patients who do not receive appropriate treatment promptly are at increased risk for a longer disease course or fatal outcome and remain infectious for longer periods, increasing the likelihood of transmission of the resistant microorganisms if infection control measures are not implemented [28].

The poor outcomes observed in patients with infections caused by MDR organisms cannot be explained completely by delays in the initiation of antibacterial therapy with in vitro activity. Patients infected with resistant bacteria have additional risk factors, such as more severe underlying illness requiring longer hospitalization, which contribute to worse outcomes. However, well-designed studies that have controlled for these potential confounders, have found substantially higher mortality among patients infected with resistant bacteria compared with patients infected with susceptible organisms [18,19,29].showed that treatment with one or more antibiotics to which the patient-specific carbapenem-resistant K. pneumoniae isolates were susceptible in vitro was not associated with patient survival, even with early initiation of active therapy [19]. This adds to the evidence that patients with infections due to MDR bacteria have underlying diseases of increased severity. For example, patients with CRE infections are more likely to have received a transplant, require mechanical ventilation, a pro- longed hospitalization, intensive-care unit (ICU) stays, the use of central venous catheters and are more likely to have poor functional status [18,19]. Indeed, underlying conditions and comorbidities are important factors responsible for in-hospital mortality among patients with resistant infections [30]. Finally, patients infected with organisms that are resistant to all available antibacterials may require surgery to remove the nidus of infection, and infections that are not amenable to surgical debridement have high mortality rates [12]. The Negative Impact of Resistance on Patients without Multidrug-resistant Organisms Infections The negative impact of multidrug-resistant organisms is not limited to patients who are infected by them. The negative impact of antibiotic resistance on all patients includes the effect it has on empiric antibiotic regimens, utilizable antibacterial. (Table 1).

TABLE 1. Effects of antibiotic resistance

The effect	Examples
Morbidity and mortality	All-cause
	Attributable to infection Increased length of hospital stay
	Increased length of mechanical ventilation Increased need for intensive care and invasive
	devices Excess surgery
	Functional decline and need for post-acute careNeed for contact isolation
	Loss of work
Increased resource	Hospital, intensive-care unit and post-acuteutilization and cost
	care beds
	Additional nursing care, support services, diagnostictests and imaging
	Additional use of isolation rooms and consumables(gloves, gowns)
	Cost of targeted infection control programmesincluding screening and isolation
Guideline alterations	Loss of narrow-spectrum antibiotic classes
	Altered empiric therapy regimens Use of agents with reduced efficacy Use of agents with increased toxicity
Reduced hospital activity	Unit closures
	Cancellation of surgery

Resistance rates have implications for antibiotic prescribing policies and recommendations, with the loss of the ability to use narrow-spectrum agents to treat common diseases when population-level resistance reaches to a certain threshold of [12]. Empiric therapy guidelines, while based on local susceptibility testing for empiric antibiotic use decisions for common conditions, have been revised frequently over the past decades. to reflect increasing antibiotic resistance. The empiric treatment of a common clinical situation in the hospital such as febrile neutropenia is also influenced by antibiotic resistance. For neutropenic sepsis, broad-spectrum therapy is active against Pseudomonas spp. should be started before microbiological test results are known [31,32].Current guidelines recommend the use of pseudomonal-resistant beta-lactams, such as cefepime, carbapenem, or piperacillin-tazobactam [32]. The end result is an overuse of empiric antibiotic regimens, which may be broader than necessary based on antibiotic sensitivity testing for these clinical situations (Table 2).

TABLE 2. Examples of the consequences of antibiotic resistance

Proble	Example	Consequence	Responses to mitigate the impact of resistance	Problems associated withmitigating
Infections caused by inMDR bacteria	ESBL *Escherichia coli* bacteraemia treated empirically with ceftriaxone	Inadequate therapy/delay effective therapy [15–17,26]	Guideline alteration, with carbapenemsfor empiric therapy Implementing rapid diagnosisand reporting	Overuse of broader spectrum agents for all patients Increased cost, only minimallyreducing the delay
	Carbapenem-resistant *Acinetobacter baumannii* infection [35,36]	Less efficacious or more toxic agents	Treatment with polymixins	Reduced efficacy, increased toxicity
	Infection with colistin-resistant *A. baumannii*	Infection with limited or no therapeutic options	Treatment with combination of agents each likely to be ineffective alone Surgical management	Likely ineffective therapyToxicity Cost Resource utilization
Colonization withMDR	Failure of fluoroquinolone prophylaxis to prevent infectionby resistant strains of *E. coli* after transrectal ultrasound-guided prostatebiopsy [23,24]	Additional infections	Guideline alteration, with fosfomycin, carbapenems or amikacin for prophylaxisScreening of all patients pre-biopsy	Overuse of broader spectrum agents and use of toxic agentsfor all patients Increased cost and burden onthe healthcare system
Infections caused by non-MDR bacteria	Vancomycin for MSSA [7]	Less efficacious	Antimicrobial stewardship to limituse of vancomycin	Cost Under-treatment of MRSA
	Piperacillin/tazobactam empirictreatment for neutropenic sepsis where the causative organism is MSSA	Excessively broad-spectrumtreatment	Antimicrobial stewardship to de-escalatefrom	
Hospitalization	Spread of	Additional infections Lack of access to optimalor lifesaving	VRE targeted infection control measuresto prevent transmission	Cost, use of hospital resources suchas isolation beds, negative effectson patients related to isolation Limitation of procedures such as transplantation
	Outbreak of carbapenem-resistant	Lack of access to optimal orlifesaving procedures	Need for unit	Interruption of hospital

Abbreviations: ESBL, extended-spectrum ß-lactamase; MDR, multidrug-resistant; MSSA, methicillin-susceptible *Staphylococcus aureus*; VRE, vancomycin-resistant

Patients who do not receive appropriate treatment promptly are at increased risk for a longer disease course or fatal outcome and remain infectious for longer periods, increasing the likelihood of transmission of the resistant microorganisms if infection control measures are not implemented [28]. The poor outcomes observed in patients with infections caused by MDR organisms cannot be explained completely by delays in the initiation of antibacterial therapy with in vitro activity. Patients infected with resistant bacteria have additional risk factors, such as more severe underlying illness requiring longer hospitalization, which contribute to worse outcomes. However, well-designed studies that have controlled for these potential confounders, have found substantially higher mortality among patients infected with resistant bacteria compared with patients infected with susceptible organisms [18,19,29]. pneumoniae isolates were susceptible in vitro was not associated with patient This adds to the evidence that patients with infections due to MDR bacteria have underlying diseases of increased severity. Indeed, underlying conditions and comorbidities are important factors responsible for in-hospital mortality among patients with resistant infections [30]. Finally, patients infected with organisms that are resistant to all available antibacterials may require surgery to remove the nidus of infection, and infections that are not amenable to surgical deb

The Negative Impact of Resistance onPatients without Multidrug-resistant Organisms Infections

The negative impact of antibiotic resistance on all patients includes the effect it has on empiric antibiotic regimens, utilizable antibacterial classes and the use of agents that are less efficacious (Table 1). The prevalence of resistance has implications for antibiotic prescribing policies and recommendations, with the loss of use of narrow-spectrum agents for the treatment of common dis- eases when resistance at the population level reaches a certain Guidelines for empiric therapy, although based on local antibiograms to inform empiric antibiotic decisions for common conditions, have been altered regularly over the last several decades to account for the increase in antibiotic resistance. Empiric treatment for a common clinical scenario in hospitals such as neutropenic fever is also impacted by antibiotic resistance. Treatment guidelines now recommend an anti- pseudomonal β-lactam agent, such as cefepime, a carbapenem, or piperacillin-tazobactam [32]. The end result is overuse of empiric antibiotic regimens, which may be broader than is required on the basis of antibiotic susceptibility testing for these clinical scenarios (Table 2). The marked and continued increase of resistance among Streptococcus pneumoniae over several decades has informed guidelines for the empiric treatment of otitis media, meningitis and pneumonia [33]. Furthermore, the emergence of penicillin- resistant and cephalosporin-resistant pneumococcal meningitis, led to recommendations by the American Academy of Pediatrics for the inclusion of vancomycin in empiric therapy regimens for all suspected cases of bacterial meningitis. The result of this has been a substantial increase in vancomycin use and, in some

places, no improvement in outcomes from pneumococcal meningitis [34]. The emergence of MDR Gram-negative bacteria has also led to the revival of older antibiotics that had fallen out of favour because of their reduced efficacy and high toxicity [35]. gested for inclusion in empirical antibiotic regimens in the ICU setting in hospitals where the observed probability that a Gram- negative bacterium is polymyxin-only-susceptible is close to 50% [35,36]. and Proteus mirabilis [36,37], in centres with endemic carbapenem resistance, empiric therapy decisions now may dictate the use of colistin over other agents [36]. When the former are used empirically, patients with susceptible strains are actually receiving treatment with inferior agents. Prime examples are colistin and vancomycin, which are often used empirically instead of a β-lactam agent when a resistant

The Impact of Resistance on Healthcare Systems

The negative impacts of antibiotic resistance on healthcare systems as a whole are substantial, as resistance adds to the number of infections that occur, to expense, to interrupted hospital activity and to limitation of treatment options. Resistant bacterial spread reflects both additional infections caused by resistant strains and replacement of susceptible strains by resistant strains. There is evidence of additional infections caused by resistant strains rather than merely a replacement of susceptible strains [38,39]. In other words, if before the onset of antibiotic resistance there were 100 cases of infection caused by susceptible strains, the onset of anti- biotic resistance would result in 90 infections caused by susceptible strains, and 30 infections caused by resistant strains. Increasing antibiotic resistance potentially threatens the safety and efficacy of surgical procedures and immunosuppressive chemotherapy. It is estimated that between 38$7% and 50$9% of pathogens causing surgical site infections and 26$8% of pathogens causing infections after chemotherapy are resistant to standard prophylactic antibiotics in the USA [41]. Hospitals spend, on average, an additional US$ 10,000 to 40,000 to treat a patient infected by an MDR organism. Antibiotic resistance influences the total disease management costs by increasing ICU and hospital stays and more than half of extra healthcare expenditure caused by multidrug-resistant organisms is to cover additional nursing and medical care [46]. Pharmacy services (including antibacterials) account for <2% of additional costs [46] (Table 1). There is also an enormous impact of antibacterial resistance on day-to-day hospital activity. Total closure of an affected ward or unit is one of the most expensive infection control measures that may be required to contain a nosocomial outbreak. In addition to these costs, are the consumable, microbiology and staff costs associated with the implementation of infection control measures, such as screening and contact isolation, intended to both prevent and eradicate MDR bacteria from healthcare facilities [28].

Factors that Mitigate the Adverse Effects of Antibacterial Resistance

Within the healthcare system, there are cases in which antibiotic resistance may therefore limit available and often lifesaving treatment options. Colonization with multidrug-resistant organisms now has implications for decisions about manage- ment strategies in patients who may require procedures such as bone marrow transplantation [42,43]. CRE colonization documented before or after stem cell transplantation has resulted in an infection in 25.8% of autologous stem cell transplant patients and 39.2% of allograft stem cell transplant patients with Colonization and infection in patients with cystic fibrosis with Burkholderia spp. decline in pulmonary function and fatal disease [44], and this colonization has implications for lifesaving lung transplantation. However, despite all of the aforementioned adverse conse- quences of resistance on hospitalized patients, the community and the healthcare system, there are factors that mitigate these adverse consequences. On a daily basis, and sometimes sub- consciously, clinicians mitigate the negative impacts of antibac- terial resistance. Clinicians regularly broaden empiric antibacterial therapy or use combination therapy, they remove other foci of infection such as invasive devices and they attempt primary source control when faced with a deteriorating patient. Laboratories work to improve the rapidity of microbiological result reporting, and hospitals implement infection control precautions to prevent the adverse consequences of resistance. These responses to either suspected or proven antibiotic resistance may well be lifesaving, but carry with them conse- quences related both to increased Finally, the development of new antibiotic agents with improved spectrum of activity has the potential to mitigate some of the negative effects of antibiotic resistance although their development is alarmingly slow [48]. There has been a marked reduction since the 1980s in both the number of new antibiotics annually approved for marketing in the USA and the number of large multinational pharmaceutical companies actively developing antibacterial drugs [48].

REFERENCES

amplifies the clinical importance of antibiotic resistance.

2. CONCLUSION

Selection for resistance in an organism in one part of the world can have lasting and important implications for human health globally. Over the past 50-60 years, resistance to antibiotics and bacteria MDR has spread and the negative effects of antibiotic resistance have become more apparent. Clinicians are now frequently faced with the challenge of treating patients with MDR bacterial infections. Since the majority of treated infections are not microbiologically diagnosed, the true levels of the resistant organisms responsible are underestimated, leading to an underestimation of the negative impact of resistance. It is in the clinical context that antibiotic resistance, virulence, and endemism converge in MDR organisms to create the perfect storm for clinicians.This affects their empiric therapeutic options and also their likelihood of treatment success. For human health, antibiotic resistance is the cause of the loss of effectiveness of antibacterial agents if they are not used empiric, leading to worse consequences in the case of infections, failure of treatment. and prevention as well as costly side effects to health care delivery and treatment options.

REFERENCES

[1] Bartlett JG, Mundy LM. Community-acquired pneumonia. N Engl J Med1995;333:1618–24.

[2] Karchmer AW. *Staphylococcus aureus* and Vancomycin: the Sequel. Ann Intern Med 1991;115:739–41.

[3] Newman W, Torres JM, Guck JK. Bacterial endocarditis: an analysis of fifty-two cases. Am J Med 1954;16:535–42.

[4] Hirsch EF. The treatment of infected wounds, Alexis Carrel's contri-bution to the care of wounded soldiers during world war I. J Trauma Acute Care Surg 2008;64:S209–10.

[5] Hawkey PM. The growing burden of antimicrobial resistance.J Antimicrob Chemother 2008;62(s1):i1–9.

[6] Mouton JW, Brown DFJ, Apfalter P, Cantón R, Giske CG, Ivanova M, et al. The role of pharmacokinetics/pharmacodynamics in setting clinical MIC breakpoints: the EUCAST approach. Clin Microbiol Infect 2012;18:E37–45.

[7] Holmes NE, Turnidge JD, Munckhof WJ, Robinson JO, Korman TM,O'Sullivan MVN, et al. Antibiotic choice may not explain poorer out- comes in patients with *Staphylococcus aureus* bacteremia and high vancomycin minimum inhibitory concentrations. J Infect Dis 2011;204:340–7.

[8] Yu VL, Chiou CCC, Feldman C, Ortqvist A, Rello J, Morris AJ, et al. An international prospective study of pneumococcal bacteremia: corre- lation with in vitro resistance, antibiotics administered, and clinical outcome. Clin Infect Dis 2003;37:230–7.

[9] Shlaes DM, Gerding DN, John JF, Craig WA, Bornstein DL, Duncan RA, et al. Society for Healthcare Epidemiology of America and Infectious Diseases Society of America Joint Committee on the Pre- vention of Antimicrobial Resistance: guidelines for the prevention of antimicrobial resistance in hospitals. Clin Infect Dis 1997;25:584–99.

[10] Bolhofer WA, Sheehan JC, Abrams ELA. Totally synthetic penicillins. J Am Chem Soc 1960;82:3437–41.

[11] Enright MC, Robinson DA, Randle G, Feil EJ, Grundmann H, Spratt BG. The evolutionary history of methicillin-resistant *Staphylo- coccus aureus* (MRSA). Proc Natl Acad Sci USA 2002;99:7687–92.

[12] Eliopoulos GM, Cosgrove SE, Carmeli Y. The impact of antibacterial resistance on health and economic outcomes. Clin Infect Dis 2003;36: 1433–7.

[13] Cosgrove SE, Sakoulas G, Perencevich EN, Schwaber MJ, Karchmer AW, Carmeli Y. Comparison of mortality associated with methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* bacteremia: a meta-analysis. Clin Infect Dis 2003;36:53–9.

[14] Engemann JJ, Carmeli Y, Cosgrove SE, Fowler VG, Bronstein MZ, Trivette SL, et al. Adverse clinical and economic outcomes attributable to methicillin resistance among patients with *Staphylococcus aureus* surgical site infection. Clin Infect Dis 2003;36:592–8.

[15] Melzer M, Petersen I. Mortality following bacteraemic infection caused by extended spectrum β-lactamase (ESBL) producing *E. coli* compared to non-ESBL producing *E. coli*. J Infect 2007;55:254–9.

[16] Schwaber MJ, Carmeli Y. Mortality and delay in effective therapy associated with extended-spectrum β-lactamase production in Enterobacteriaceae bacteraemia: a systematic review and meta-anal- ysis. J Antimicrob Chemother 2007;60:913–20.

[17] Rottier WC, Ammerlaan HSM, Bonten MJM. Effects of confounders and intermediates on the association of bacteraemia caused by extended- spectrum β-lactamase-producing Enterobacteriaceae and patient outcome: a meta-analysis. J Antimicrob Chemother 2012;67:1311–20.

[18] Borer A, Saidel-Odes L, Riesenberg K, Eskira S, Peled N, Nativ R, et al. Attributable mortality rate for carbapenem-resistant *Klebsiella pneu- moniae* bacteremia. Infect Control Hosp Epidemiol 2009;30:972–6.

[19] Patel G, Huprikar S, Factor SH, Jenkins SG, Calfee DP. Outcomes of carbapenem-resistant *Klebsiella pneumoniae* infection and the impact of antimicrobial and adjunctive therapies. Infect Control Hosp Epidemiol 2008;29:1099–106.

[20] Nutman A, Glick R, Temkin E, Hoshen M, Edgar R, Braun T, et al. A case–control study to identify predictors of 14-day mortality following carbapenem-resistant *Acinetobacter baumannii* bacteraemia. Clin Microbiol Infect 2014;20:O1028–34.

[21] Metlay JP, Hofmann J, Cetron MS, Fine MJ, Farley MM, Whitney C,et al. Impact of penicillin susceptibility on medical outcomes for adult patients with bacteremic pneumococcal pneumonia. Clin Infect Dis 2000;30:520–8.

[22] Unemo M, Shafer WM. Antimicrobial resistance in Neisseria gonor-rhoeae in the 21st century: past, evolution, and future. Clin Microbiol Rev 2014;27:587–613.

[23] Williamson DA, Barrett LK, Rogers BA, Freeman JT, Hadway P, Paterson DL. Infectious complications following transrectal ultrasound-guided prostate biopsy: new challenges in the era of multidrug-resistant *Escherichia coli*. Clin Infect Dis 2013;57:267–74.

[24] Wagenlehner FME, van Oostrum E, Tenke P, Tandogdu Z, Çek M, Grabe M, et al. Infective complications after prostate biopsy: outcome of the Global Prevalence Study of Infections in Urology (GPIU) 2010 and 2011, a prospective multinational multicentre prostate biopsy study. Eur Urol 2013;63:521–7.

[25] Kim J, Kang C-I, Joo E-J, Ha YE, Cho SY, Gwak G-Y, et al. Risk factors of community-onset spontaneous bacterial peritonitis caused by fluoroquinolone-resistant *Escherichia coli* in patients with cirrhosis. Liver Int 2014;34:695–9.

[26] Lautenbach E, Baldus Patel J, Bilker WB, Edelstein PH, Fishman NO. Extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsi- ella pneumoniae*: risk factors for infection and impact of resistance on outcomes. Clin Infect Dis 2001;32:1162–71.

[27] Daikos GL, Petrikkos P, Psichogiou M, Kosmidis C, Vryonis E, Skoutelis A, et al. Prospective observational study of the impact of VIM-1 metallo-β-lactamase on the outcome of patients with *Klebsiella pneumoniae* bloodstream infections. Antimicrob Agents Chemother2009;53:1868–73.

[28] Acar JF. Consequences of bacterial resistance to antibiotics in medicalpractice. Clin Infect Dis 1997;24(S1):S17–8.

[29] Ben-David D, Kordevani R, Keller N, Tal I, Marzel A, Gal-Mor O, et al. Outcome of carbapenem resistant *Klebsiella pneumoniae* bloodstreaminfections. Clin Microbiol Infect 2012;18:54–60.

[30] Bogan C, Kaye KS, Chopra T, Chopra T, Hayakawa K, Pogue JM, et al. Outcomes of carbapenem-resistant Enterobacteriaceae isolation:matched analysis. Am J Infect Control 2014;42:612–20.

[31] Paterson DL. Impact of antibiotic resistance in gram-negative bacilli on empirical and definitive antibiotic therapy. Clin Infect Dis 2008;47. S1: S14–20.

[32] Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, et al. Clinical practice guideline for the use of antibacterial agents in neu- tropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis 2011;52:e56–93.

[33] Doern GV, Heilmann KP, Huynh HK, Rhomberg PR, Coffman SL, Brueggemann AB. Antimicrobial resistance among clinical isolates of *Streptococcus pneumoniae* in the United States during 1999–2000, including a comparison of resistance rates since 1994–1995. Anti-microb Agents Chemother 2001;45:1721–9.

[34] McMaster P, McIntyre P, Gilmour R, Gilbert L, Kakakios A, Mellis C.The emergence of resistant pneumococcal meningitis—implications for empiric therapy. Arch Dis Childhood 2002;87:207–10.

[35] Michalopoulos AS, Tsiodras S, Rellos K, Mentzelopoulos S, Falagas ME. Colistin treatment in patients with ICU-acquired infections caused by multiresistant Gram-negative bacteria: the renaissance of an old anti- biotic. Clin Microbiol Infect 2005;11:115–21.

[36] Falagas ME, Kasiakou SK, Saravolatz LD. Colistin: the revival of poly-myxins for the management of multidrug-resistant Gram-negative bacterial infections. Clin Infect Dis 2005;40:1333–41.

[37] Tzouvelekis LS, Markogiannakis A, Psichogiou M, Tassios PT,Daikos GL. Carbapenemases in *Klebsiella pneumoniae* and other Enterobacteriaceae: an evolving crisis of global dimensions. Clin Microbiol Rev 2012;25:682–707.

[38] Wyllie DH, Crook DW, Peto TE. Mortality after Staphylococcusaureus bacteraemia in two hospitals in Oxfordshire, 1997–2003: cohort study. BMJ 2006;333:281.

[39] Wassenberg MW, De Wit GA, Van Hout BA, Bonten MJ. Quantifying cost-effectiveness of controlling nosocomial spread of antibiotic- resistant bacteria: the case of MRSA. PloS One 2010;5:e11562.

[40] Johnson PDR, Ballard SA, Grabsch EA, Stinear TP, Seemann T,Young HL, et al. A sustained hospital outbreak of vancomycin-resistant*Enterococcus faecium* bacteremia due to emergence of vanB *E. faecium* sequence type 203. J Infect Dis 2010;202:1278–86.

[41] Teillant A, Gandra S, Barter D, Morgan DJ, Laxminarayan R. Potential burden of antibiotic resistance on surgery and cancer chemotherapy antibiotic prophylaxis in the USA: a literature review and modelling study. Lancet Infect Dis 2015. http://dx.doi.org/10.1016/S1473- 3099(15)00270-4.

[42] Girmenia C, Rossolini GM, Piciocchi A, Bertaina A, Pisapia G, Pastore D, et al. Infections by carbapenem-resistant *Klebsiella pneu- moniae* in SCT recipients: a nationwide retrospective survey from Italy.Bone Marrow Transplant 2015;50:282–8.

[43] McCann S, Byrne JL, Rovira M, Shaw P, Ribaud P, Sica S, et al. Out-breaks of infectious diseases in stem cell transplant units: a silent causeof death for patients and transplant programmes. Bone Marrow Transplant 2004;33:519–29.

[44] Courtney JM, Dunbar KE, McDowell A, Moore JE, Warke TJ, Stevenson M, et al. Clinical outcome of *Burkholderia cepacia* complexinfection in cystic fibrosis adults. J Cyst Fibros 2004;3:93–8.

[45] Alexander BD, Petzold EW, Reller LB, Palmer SM, Davis RD, Woods CW, et al. Survival after lung transplantation of cystic fibrosis patients infected with *Burkholderia cepacia* complex. Am J Transplant 2008;8:1025–30.

[46] OECD (2015). Antimicrobial Resistance in G7 countries and beyond: Economic Issues, Policies and Options for Action. 2015. Available at: http://www.oecd.org/els/health-systems/antimicrobial-resistance.htm.

[47] Macrae MB, Shannon KP, Rayner DM, Kaiser AM, Hoffman PN, French GL. A simultaneous outbreak on a neonatal unit of two strains of multiply antibiotic resistant *Klebsiella pneumoniae* controllable only by ward closure. J Hosp Infect 2001;49:183–92.

[48] Boucher HW, Talbot GH, Benjamin DK, Bradley J, Guidos RJ, Jones RN, et al., Infectious Diseases Society of America. 10×'20progress—development of new drugs active against gram-negative bacilli: an update from the Infectious Diseases Society of America.Clin Infect Dis 2013. cit152.