REVIEW

The negative impact of antibiotic resistance

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Abstract

Antibacterial therapy is one of the most important medical developments of the twentieth century; however, the spread of resistance in healthcare settings and in the community threatens the enormous gains made by the availability of antibiotic therapy. Infections caused by resistant bacteria lead to up to two-fold higher rates of adverse outcomes compared with similar infections caused by susceptible strains. These adverse outcomes may be clinical or economic and reflect primarily the failure or delay of antibiotic treatment. The magnitude of these adverse outcomes will be more pronounced as disease severity, strain virulence, or host vulnerability increases. The negative impacts of antibacterial resistance can be measured at the patient level by increased morbidity and mortality, at the healthcare level by increased resource utilization, higher costs and reduced hospital activity and at the society level by antibiotic treatment guidelines favouring increasingly broad-spectrum empiric therapy. In this review we will discuss the negative impact of antibiotic resistance on patients, the healthcare system and society.

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

Article published online: 17 December 2015

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Introduction

Antibacterial therapy is one of the most important medical developments of the twentieth century and has become one of the pillars of modern medicine in preventing millions of premature deaths due to bacterial infection. In the pre-antibiotic era, the case fatality rate for pneumonia caused by *Streptococcus pneumoniae* reached as high as 40% [1], the case fatality rate for *Staphylococcus aureus* bacteraemia was 80% [2], and 97% of patients with endocarditis died [3]. Before antibiotics, wound infections were often treated by amputation; indeed, during World War I, 70% of amputations were performed as a result of wound infection [4]. Antibiotics have altered the fate of patients with such infections dramatically, changing the way that we treat and cure diseases such as tuberculosis and syphilis. Moreover, the ability to treat and cure infection has facilitated advances in modern medicine such as increasingly complex surgery, transplantation and chemotherapy. Unfortunately, the spread of resistance in healthcare settings and in the community threatens the enormous gains made by the availability of antibiotic therapy [5].

Microbiological testing for antibiotic resistance is aimed at dichotomizing bacterial strains into treatable and non-treatable categories, and provides guidance to clinicians with respect to the potential use of agents in the treatment of patients. Clinical MIC breakpoints distinguish between infections that are likely or unlikely to respond to antibiotic treatment [6], where organisms classified as 'resistant' imply a high likelihood of treatment failure. However, MIC breakpoints are not precise; there is a grey zone. Resistance does not always lead to inadequate therapy or therapeutic failures and infections caused by fully susceptible organisms may fail therapy. An increase in MIC appears to have an independent effect on the reduced efficacy of various antibacterials regardless of the microbiological susceptibility determination. For example, vancomycin treatment failure is not uncommon, even when methicillin-resistant *S. aureus* (MRSA) strains are reported susceptible to vancomycin but with a high vancomycin MIC (1–2 μg/mL) [7].

http://dx.doi.org/10.1016/j.cmi.2015.12.002

Just as treatment may fail for organisms that are designated 'susceptible' to a given antibiotic, there may also be therapeutic successes among resistant isolates.

For example, β-lactam antibiotics remain appropriate for the treatment of pneumococcal infections that do not involve cerebrospinal fluid, regardless of the *in vitro* susceptibility determined by breakpoints [8].

In this review we will discuss the negative impact of antibiotic resistance on patients, the healthcare system and society.

Historical Perspective

Resistance has long been with us. Bacteria possess a remarkable number of genetic mechanisms for resistance to antibacterials and there is a substantial pool of antibiotic resistance genes in nature that have evolved over millions of years [9]. Analysis of organisms and epidemiological data suggest that the evolution and spread of multidrug-resistant organisms have accelerated dramatically over the past 50 years. This time period coincides with the discovery and increasingly widespread use of antibacterial agents [9].

The history of resistance among *S. aureus* provides an appropriate historical example. Abrams and colleagues described penicillinase before the clinical use of penicillin [10] and while penicillinase production in *S. aureus* was still uncommon. However, it spread rapidly following the introduction of penicillin, and by the late 1940s, approximately 50% of *S. aureus* isolates in the UK were resistant to penicillin. This was closely followed by the accumulation of resistance to tetracycline and macrolides in the 1950s. Methicillin was introduced in 1959 to treat penicillin-resistant *S. aureus* but was followed in 1961 by reports of *S. aureus* isolates with acquired resistance to methicillin (i.e. MRSA). Multidrug-resistant (MDR) MRSA isolates were soon recovered from other European countries and later from Japan, Australia and the USA and have become widespread in hospitals in most parts of the world and are now spreading within 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. Table 1 details the effects 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. aureus* infections [13,14]. 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]. Initial responses to antibacterial therapy (for example, at 72 h) reveal that treatment failure rates for patients infected with ESBL-producing *Klebsiella pneumoniae* are almost twice as high as for those with non-ESBL-producing *K. pneumoniae* infections. Carbapenem-resistant *Enterobacteriaceae* (CRE) are now the emerging contemporary threat. Infections caused by carbapenem-resistant *K. pneumoniae* have approximately a two- 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 45% [20].

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

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 care Need for contact isolation Loss of work
Increased resource utilization and cost	Hospital, intensive-care unit and post-acute care beds Additional nursing care, support services, diagnostic tests and imaging Additional use of isolation rooms and consumables (gloves, gowns) Cost of targeted infection control programmes including 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

associated with more than four times the risk of suppurative complications [21]. Furthermore, in the case of gonorrhoea, there is now a high prevalence of *N. gonorrhoeae* strains with resistance to most antibiotics, leading to treatment failures and subsequent reproductive tract disease, infertility and promotion of the transmission of other sexually transmitted infections, including human immunodeficiency virus [22].

Failures of antibiotic prophylaxis arising from antibiotic resistance have also been observed. 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].

Resistance genes can alter the fitness of a bacterial pathogen but do not necessarily imply increased virulence. However, 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]. Indeed, 'high-risk clones', such as *K. pneumoniae* ST258, *Escherichia coli* ST 131, *Enterococcus faecium* CC17 and *Pseudomonas aeruginosa* ST235, are rapidly spreading, carrying extremely drug-resistant phenotypes and causing difficult-to-treat infections.

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]. For example, in one study, patients with ESBL-producing *K. pneumoniae* and *E. coli* infections were treated with effective antibiotics a median of 72 h after infection was suspected, whereas matched controls infected with non-ESBL-producing strains of *K. pneumoniae* and *E. 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 ESBL-associated bacteraemia [16]. Likewise, patients with carbapenem-resistant *K. pneumoniae* bacteraemia have been shown to experience delays in the administration of antibiotics with *in vitro* activity against carbapenem-resistant *K. pneumoniae* [19,27]. (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 and

TABLE 2. Examples of the consequences of antibiotic resistance

Problem	Example	Consequences	Responses to mitigate the impact of resistance	Problems associated with mitigating responses
Infections caused by MDR bacteria	ESBL *Escherichia coli* bacteraemia treated empirically with ceftriaxone	Inadequate therapy/delay in effective therapy [15–17,26]	Guideline alteration, with carbapenems for empiric therapy Implementing rapid diagnosis and reporting	Overuse of broader spectrum agents for all patients Increased cost, only minimally reducing 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 therapy Toxicity Cost Resource utilization
Colonization with MDR bacteria	Failure of fluoroquinolone prophylaxis to prevent infection by resistant strains of *E. coli* after transrectal ultrasound-guided prostate biopsy [23,24]	Additional infections	Guideline alteration, with fosfomycin, carbapenems or amikacin for prophylaxis Screening of all patients pre-biopsy and targeted prophylaxis	Overuse of broader spectrum agents and use of toxic agents for all patients Increased cost and burden on the healthcare system
Infections caused by non-MDR bacteria	Vancomycin for MSSA [7]	Less efficacious treatment	Antimicrobial stewardship to limit use of vancomycin	Cost Under-treatment of MRSA
	Piperacillin/tazobactam empiric treatment for neutropenic sepsis where the causative organism is MSSA	Excessively broad-spectrum treatment	Antimicrobial stewardship to de-escalate from piperacillin/tazobactam	Under-treatment of MDR organisms
Hospitalization	Spread of epidemic/virulent VRE clones in a unit [40]	Additional infections Lack of access to optimal or lifesaving procedures	VRE targeted infection control measures to prevent transmission	Cost, use of hospital resources such as isolation beds, negative effects on patients related to isolation Limitation of procedures such as transplantation
	Outbreak of carbapenem-resistant *Klebsiella* spp. in a unit [42]	Lack of access to optimal or lifesaving procedures	Need for unit closure	Interruption of hospital activity Limitation of procedures

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

tigecycline 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]. Patel et al. 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 prolonged 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 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 diseases when resistance at the population level reaches a certain threshold [12]. 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. In the case of neutropenic sepsis, broad-spectrum therapy with activity against *Pseudomonas* spp. should be commenced before results of microbiological tests are known [31,32]. 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]. In this way, antibacterial resistance increases the use of antibacterials that may be unnecessary and less efficacious.

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]. In the case of carbapenem-resistant bacteria, polymyxins are suggested 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]. Despite the limited effectiveness of colistin at curing infection, the risk of deteriorating renal function, and the fact that it has little activity against *Serratia* spp., *Providencia* spp. 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].

Some agents used to treat the resistant strain of an organism are less effective than the agents used to treat the susceptible strain of the organism. 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 organism is suspected [7,36] (Table 2).

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. The following paragraphs expand on these concepts.

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 antibiotic resistance would result in 90 infections caused by susceptible strains, and 30 infections caused by resistant strains. The end result is 20 additional infections. The emergence and spread of epidemic clones of both vancomycin-resistant *Enterococcus faecium* [40], and *Acinetobacter* spp. are good examples of additional infections caused by previously harmless commensals of the gastrointestinal tract and the environment, which became important pathogens causing nosocomial infection.

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]. 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 management 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 infection-related mortality of 16% and 64.4%, respectively [42].

Colonization and infection in patients with cystic fibrosis with *Burkholderia* spp. has been associated with accelerated decline in pulmonary function and fatal disease [44], and this colonization has implications for lifesaving lung transplantation. Alexander et al. showed that patients infected with highly resistant *Burkholderia cenocepacia* before transplant were six times more likely to die within 1 year of transplant than those infected with other *Burkholderia* species and eight times more likely to die than non-infected patients [45].

Hospitals spend, on average, an additional US$ 10,000 to 40,000 to treat a patient infected by an MDR organism. The associated impact of lost economic outputs due to increased mortality, prolonged sickness and reduced labour efficiency are likely to double this figure [46]. A recent report estimates that compared with a world without antibiotic resistance, OECD countries may experience cumulative losses of US$ 2.9 trillion (corresponding to about 0.16% of their GDP) by 2050 [46]. 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]. Support services (e.g. food services, laundry, etc.) correspond to about 13% of additional costs, whereas additional diagnostic tests, including laboratory tests and imaging correspond to 12%. 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. Furthermore, elective surgery may need to be cancelled in the setting of outbreaks of antibacterial-resistant bacteria [47]. 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

However, despite all of the aforementioned adverse consequences 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 subconsciously, clinicians mitigate the negative impacts of antibacterial 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 consequences related both to increased costs and to the increase of antibiotic resistance owing to the use of increasingly broad-spectrum therapy (Table 2).

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]. This decline in research and development amplifies the clinical importance of antibiotic resistance.

Conclusion

The selection of resistance in one organism in one part of the world may have long-term and important implications for human health globally. Over the last 50–60 years, resistance and MDR bacteria have spread and the negative impacts of antibiotic resistance have become more apparent. Clinicians are now more frequently faced with the challenge of treating patients with infections caused by MDR bacteria. As the majority of treated infections are not microbiologically diagnosed, the actual magnitude of causative resistant organisms is underestimated, which results in an overall underestimation of the negative impact of resistance. It is in the clinical setting that antibiotic resistance, virulence and endemicity converge within MDR organisms to create the perfect storm for clinicians. This affects their choices of empiric therapy and also the likelihood of therapeutic success. In human health, antibiotic resistance is responsible for the loss of effectiveness of antibacterial agents to the degree that they are not used empirically, worse outcomes from infection, treatment and prophylaxis failures and secondary costly effects on both healthcare delivery and therapeutic options.

Acknowledgements

The research leading to this review has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no. 115618—Driving Re-InVEstment in R&D and responsible AntiBiotic use—DRIVE-AB, resources of which are composed of financial contributions from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution (www.DRIVE-AB.eu).

Transparency Declaration

During the last five years, Yehuda Carmeli, his laboratory, and studies that he has conducted received grants, honoraria, travel support, consulting fees, and other forms of financial support from the following companies: Achaogen Inc, Allecra Therapeutics, AstraZeneca, Biomerieux SA, Cepheid, DaVolterra, Durata Therapeutics, Inc, Intercell AG, Merck & Co. Inc, PPD, Proteologics, Rempex Pharmaceuticals, Syntezza Bioscience LTD, Takeda Pharmaceutical Company Limited.

References

[1] Bartlett JG, Mundy LM. Community-acquired pneumonia. N Engl J Med 1995;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 contribution 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 outcomes 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: correlation 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 Prevention 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 *Staphylococcus 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-analysis. 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 pneumoniae* 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 gonorrhoeae 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 *Klebsiella 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 Chemother 2009;53:1868–73.
[28] Acar JF. Consequences of bacterial resistance to antibiotics in medical practice. 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* bloodstream infections. 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 neutropenic 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. Antimicrob 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 antibiotic. Clin Microbiol Infect 2005;11:115–21.
[36] Falagas ME, Kasiakou SK, Saravolatz LD. Colistin: the revival of polymyxins 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 Staphylococcus aureus 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 pneumoniae* 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. Outbreaks of infectious diseases in stem cell transplant units: a silent cause of 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* complex infection 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×'20 progress—development of new drugs active against gram-negative bacilli: an update from the Infectious Diseases Society of America. Clin Infect Dis 2013. cit152.