Journal of Infection and Public Health (2016) xxx, xxx–xxx

http://www.elsevier.com/locate/jiph

REVIEW

Antibiotic resistance

Marianne Frieri [a,*], **Krishan Kumar** [b,1], **Anthony Boutin** [c,1]

[a] *Division of Allergy Immunology, Department of Medicine, Nassau University Medical Center, 2201 Hempstead Turnpike, East Meadow, NY 11554, United States*
[b] *Division of Pediatric, Department of Emergency Medicine, Nassau University Medical Center, 2201 Hempstead Turnpike, East Meadow, NY 11554, United States*
[c] *Adult Emergency Medicine, Department of Emergency Medicine, Nassau University Medical Center, 2201 Hempstead Turnpike, East Meadow, NY 11554, United States*

Received 21 May 2016; accepted 4 August 2016

KEYWORDS
Antibiotic resistance;
Biofilms;
Infections;
Public health;
Emergency Department

Summary Antimicrobial resistance in bacterial pathogens is a challenge that is associated with high morbidity and mortality. Multidrug resistance patterns in Gram-positive and -negative bacteria are difficult to treat and may even be untreatable with conventional antibiotics. There is currently a shortage of effective therapies, lack of successful prevention measures, and only a few new antibiotics, which require development of novel treatment options and alternative antimicrobial therapies. Biofilms are involved in multidrug resistance and can present challenges for infection control. Virulence, *Staphylococcus aureus*, Clostridium difficile infection, vancomycin-resistant enterococci, and control in the Emergency Department are also discussed.

Contents

* Corresponding author at: Nassau University Medical Center, Department of Medicine, 2201 Hempstead Turnpike, East Meadow, NY 11554, United States. Fax: +1 516 572 5609.
E-mail addresses: mfrieri@numc.edu (M. Frieri), kkumar@numc.edu (K. Kumar), aboutin@numc.edu (A. Boutin).
[1] Fax: +1 516 572 5465.

http://dx.doi.org/10.1016/j.jiph.2016.08.007

Please cite this article in press as: Frieri M, et al. Antibiotic resistance. J Infect Public Health (2016), http://dx.doi.org/10.1016/j.jiph.2016.08.007

Introduction

Antibiotic resistance

This study discusses the impact of antibiotic resistance as a persistent, global health threat and highlights efforts to improve this complex problem [1]. Political agendas, legislation, development of therapies and educational initiatives are essential to mitigate the increasing rate of antibiotic resistance. Prescribers, policymakers and researchers are charged with the complex task of mitigating antibiotic resistance in an era when new treatments for bacterial infections are limited. The authors propose that monitoring, surveillance of practice, policy and new treatments provide solutions to antibiotic resistance in both the human and agricultural sectors. This article emphasizes the complexity of antibiotic resistance and highlights the need for a multifaceted approach to improve health care outcomes [1].

Antimicrobial resistance in bacterial pathogens is a worldwide challenge associated with high morbidity and mortality [2]. Multidrug resistant patterns in Gram-positive and -negative bacteria have resulted in difficult-to-treat or even untreatable infections with conventional antimicrobials. Because the early identification of causative microorganisms and their antimicrobial susceptibility patterns in patients with bacteremia and other serious infections is lacking in many healthcare settings, broad spectrum antibiotics are liberally and mostly unnecessarily used [2]. Dramatic increases in emerging resistance occurs and, when coupled with poor infection control practices, resistant bacteria can easily be disseminated to the other patients and the environment [2]. Availability of updated epidemiological data on antimicrobial resistance in frequently encountered bacterial pathogens will be useful not only for deciding on treatment strategies but also for devising an effective antimicrobial stewardship program in hospitals [2].

Resistance of important bacterial pathogens to common antimicrobial therapies and emergence of multidrug-resistant bacteria are increasing at an alarming rate. There are challenges in the combat of bacterial infections and accompanied diseases and the current shortage of effective drugs, lack of successful prevention measures and only a few new antibiotics in the clinical pipeline will require the development of novel treatment options and alternative antimicrobial therapies [3]. The authors stated that increasing understanding of bacterial virulence strategies and induced molecular pathways of the infectious disease provides novel opportunities to target and interfere with crucial pathogenicity factors or virulence-associated traits of the bacteria while bypassing the evolutionary pressure on the bacterium to develop resistance [3]. The authors took a closer look at the bacterial virulence-related factors and processes that present promising targets for anti-virulence therapies, recently discovered inhibitory substances, their promises and discussed the challenges and problems that need to be faced [3].

Finding strategies against the development of antibiotic resistance is a major global challenge for the life sciences community and for public health. The past decades have seen a dramatic worldwide increase in human-pathogenic bacteria that are resistant to one or multiple antibiotics [4]. More infections caused by resistant microorganisms fail to respond to conventional treatment, and even last-resort antibiotics have lost their power. In addition, industry pipelines for the development of novel antibiotics have run dry over the past few decades. A recent World Health Day by the WHO with the theme ''Combat drug resistance: no action today means no cure tomorrow'' triggered an increase in research activity, and several promising strategies have been developed to restore treatment options against infections by resistant bacterial pathogens [4].

The emergence and spread of antibiotic resistance among pathogenic bacteria has been a growing problem for public health in recent decades. It is becoming increasingly recognized that not only antibiotic resistance genes (ARGs) encountered in clinical pathogens are of relevance, but rather, all pathogenic, commensal as

Please cite this article in press as: Frieri M, et al. Antibiotic resistance. J Infect Public Health (2016), http://dx.doi.org/10.1016/j.jiph.2016.08.007

well as environmental bacteria, mobile genetic elements and bacteriophages, form a reservoir of ARGs (the resistome) from which pathogenic bacteria can acquire resistance via horizontal gene transfer (HGT) [5]. HGT has caused antibiotic resistance to spread from commensal and environmental species to pathogenic ones, as has been shown for some clinically important ARGs. While transformation and transduction are deemed less important, recent discoveries suggest their role may be larger than previously thought. Understanding the extent of the resistome and how its mobilization to pathogenic bacteria takes place is essential for efforts to control the dissemination of these genes. The authors discussed the concept of the resistome, providing examples of HGT of clinically relevant ARGs and an overview of the current knowledge of the contributions the various HGT mechanisms make to the spread of antibiotic resistance [5].

Multidrug-resistant bacteria have increased at an alarming rate over recent decades and cause serious problems [6]. The emergence of resistant infections caused by these bacteria has led to mortality and morbidity and there is an urgent need to find solutions to combat bacterial resistance [6]. In this paper, the authors discuss some mechanisms of antibiotic resistance such as changing the antibacterial agent's uptake and biofilm formation as well as a wide range of approaches such as developing new generations of antibiotics, combination therapy, natural antibacterial substances and applying nanoparticulate systems [6].

In this study, the authors assessed the propensity of biocide exposure in the development of bacterial antimicrobial resistance [7]. Their protocol was based on reporting changes in established antimicrobial susceptibility profiles in biocides and antibiotics during and after exposure to a product. Their results showed that exposure to triclosan (0.0004%) was associated with a high risk of developing resistance and cross-resistance in *Staphylococcus aureus* and *Escherichia coli* but was not observed with exposure to chlorhexidine (0.00005%) or a hydrogen peroxide-based biocidal product (in during use conditions) [7]. Exposure to a low concentration of hydrogen peroxide (0.001%) carried a risk of emerging resistance to antibiotics if the presence of the oxidizing agent was maintained. They observed a number of unstable clinical resistances to antibiotics after exposure to the cationic biocide and oxidizing agent, notably to tobramycin and ticarcillin-clavulanic acid. Using a decision tree based on the change in antimicrobial susceptibility test results, they were able to provide information on the effect of biocide exposure on the development of bacterial resistance to antimicrobials [7]. Thus, such information should address the call from the U.S. FDA and European Union Biocidal Products Regulation for manufacturers to provide information on antimicrobial resistance and cross-resistance in bacteria after the use of their product [7].

Biofilms

Pathogenic microbial biofilm is considered a worldwide challenge due to the inherent antibiotic resistance conferred by its lifestyle [8]. By living in a community in a clinical situation, microbial organisms are responsible for severe and dangerous cases of infection. Combating this organization of cells usually requires high antibiotic doses for a prolonged time, and these approaches often fail, contributing to infection persistence [8]. In addition to therapeutic limitations, biofilms can be a source of infections when they grow in medical devices. The challenge imposed by biofilms has mobilized researchers in the entire world to propose or develop alternatives to control biofilms. The authors in this review summarized the new frontiers that could be used in clinical circumstances to prevent or eliminate pathogenic biofilms [8].

The treatment of biofilm infections with antibiotics remains a puzzle although progress on biofilm research has been made. Past pharmacokinetic (PK) and pharmacodynamic (PD) profiles of an antimicrobial agent provide important information helping to establish an efficient dosing regimen and to minimize the development of antimicrobial tolerance and resistance in biofilm infections [9]. Most previous PK/PD studies of antibiotics have been performed on planktonic cells, and extrapolation of the results on biofilms is problematic as bacterial biofilms differ from planktonic grown cells in terms of growth rate, gene expression, and metabolism. These authors set up several protocols for the studies of PK/PD of antibiotics in biofilm infections of *Pseudomonas aeruginosa* in vitro and in vivo. It should be underscored that none of the protocols in biofilms have yet been certificated for clinical use or proved useful for guidance of antibiotic therapy [9].

The increase in multi-drug resistant *P. aeruginosa* infections is a worldwide dilemma. At the heart of the problem is the inability to treat established *P. aeruginosa* biofilms with standard antibiotic therapy, including fluoroquinolones [10]. These authors addressed a previously unstudied question regarding the effect of the commonly prescribed

Please cite this article in press as: Frieri M, et al. Antibiotic resistance. J Infect Public Health (2016), http://dx.doi.org/10.1016/j.jiph.2016.08.007

calcium channel blocker (CCB) diltiazem on biofilm growth. Real-time monitoring of the overall growth and killing of *P. aeruginosa* biofilm during fluoroquinolone therapy in the presence and absence of diltiazem was performed. The authors found that for *P. aeruginosa* biofilms, resistance to first-line fluoroquinolones may be induced by the commonly prescribed calcium channel blocker diltiazem [10].

The conventional in vitro models simulate pharmacodynamics of antibiotics in the treatment of planktonic *P. aeruginosa*. In this study, the authors proposed a novel pharmacodynamic model of ofloxacin activity in the treatment of *P. aeruginosa* biofilm [11].

Samples from the coupons and the central compartment bioreactor (CCB) were assessed for viability of the biofilm and shedding planktonic cells over 24 h. Ofloxacin concentrations were assessed in each sample withdrawn for the CCB using a bioassay method [11].

The microbiological outcomes on *P. aeruginosa* biofilm and the shedding planktonic cells in response to different ofloxacin dosing regimens were not parallel and this may explain the non-coincidence of microbiological and clinical outcomes with biofilm-associated infections [11].

The current study introduced an unprecedented novel dynamic model for the assessment of the microbiological outcome on both biofilm and shedding planktonic cells of *P. aeruginosa* in response to different dosing regimens of ofloxacin, which, in turn, can simulate the clinical outcomes in biofilm-associated infections of *P. aeruginosa*, e.g., cystic fibrosis. Different scenarios of antibiotic dosing regimens against biofilm-related infections can be mimicked using such a model [11].

Biofilms also occur in chronic rhinosinusitis (CRS), which is a highly prevalent disease in the adult and pediatric population; it causes a significant burden and the management is considered one of the most costly public health expenditures [12]. Comorbidities include asthma, aspirin sensitivity, and nasal polyposis. *S. aureus* biofilms and exotoxins that act as super-antigens have been implicated to play an important pathological role in the incidence, maintenance, and ongoing burden of CRS. A better understanding of the interplay between bacterial factors, host factors, and the environment will facilitate better management of this disease. This literature review focused on these factors and highlighted current research in this field [12].

In recent years, the number of multidrug-resistant bacteria has increased rapidly and several epidemics were identified in different regions of the world. Faced with this situation that presents a major global public health concern, the development and the use of new and rapid technologies is critical [13]. The use of the next-generation sequencing platforms by microbiologists and infectious disease specialists has allowed great progress in the medical field. These authors reviewed the usefulness of whole-genome sequencing for the detection of virulence and antibiotic resistance-associated genes [13].

The importance of bacterial biofilms in chronic wound pathogenesis is well established. Different treatment modalities, including topical dressings, have yet to show consistent efficacy against wound biofilms. This study evaluated the impact of a novel, antimicrobial test dressing on *P. aeruginosa* biofilm-infected wounds. Six-mm dermal punch wounds in rabbit ears were inoculated with 10(6) colony-forming units of *P. aeruginosa* [14]. Biofilm was established in vivo using our published model. Dressing changes were performed every other day with either active control or test dressings. Treated and untreated wounds were harvested for several quantitative endpoints. Confirmatory studies were performed to measure treatment impact on in vitro *P. aeruginosa* and in vivo polybacterial wounds containing *P. aeruginosa* and *S. aureus*. The test dressing consistently decreased *P. aeruginosa* bacterial counts and improved wound healing compared to inactive vehicle and active control wounds ($p < 0.05$). In vitro bacterial counts were also significantly reduced following test dressing therapy ($p < 0.05$). Similarly, improvements in bacterial burden and wound healing were also achieved in polybacterial wounds ($p < 0.05$). This study represented the first quantifiable and consistent in vivo evidence of a topical antimicrobial dressing's impact against established wound biofilm. The development of clinically applicable therapies against biofilm such as this is critical to improving chronic wound care [14].

Bacteria survive in nature by forming biofilms on surfaces and probably most, if not all, bacteria (and fungi) are capable of forming biofilms. A biofilm is a structured consortium of bacteria embedded in a self-produced polymer matrix consisting of polysaccharide, protein and extracellular DNA. Bacterial biofilms are resistant to antibiotics, disinfectant chemicals and to phagocytosis and other components of the innate and adaptive inflammatory defense system of the body [15]. It is known, for example, that the persistence of staphylococcal infections related to foreign bodies is due to biofilm formation. Chronic *P. aeruginosa* lung infections in cystic fibrosis patients are caused by biofilm-growing mucoid strains. Gradients of nutrients and oxygen exist from the top to the bottom of biofilms and the bacterial cells located

Please cite this article in press as: Frieri M, et al. Antibiotic resistance. J Infect Public Health (2016), http://dx.doi.org/10.1016/j.jiph.2016.08.007

in nutrient poor areas have decreased metabolic activity and increased doubling times. These more or less dormant cells are therefore responsible for some of the tolerance to antibiotics. Biofilm growth is associated with an increased level of mutations. Bacteria in biofilms communicate by means of molecules, which activates certain genes responsible for production of virulence factors and, to some extent, biofilm structure [15]. This phenomenon is called quorum sensing and depends upon the concentration of the quorum-sensing molecules in a certain niche, which depends on the number of the bacteria. Biofilms can be prevented by antibiotic prophylaxis or early aggressive antibiotic therapy and they can be treated by chronic suppressive antibiotic therapy. Promising strategies may include the use of compounds that can dissolve the biofilm matrix and quorum-sensing inhibitors, which increases biofilm susceptibility to antibiotics and phagocytosis [15].

Acinetobacter baumannii, a Gram-negative, opportunistic pathogen can form biofilm and increasing resistance to antibiotic agents presents challenges for infection control [16]. A better understanding of the influence of biofilm formation and antibiotic resistance on environmental persistence of *A. baumannii* in hospital settings is needed for more effective infection control [16]. These authors studied high biofilm forming, clinical, multidrug-resistant-(MDR)-positive strains. Environmental, MDR-positive, low biofilm forming strains had a 2.7 times increase in risk of cell death due to desiccation compared with their MDR-negative counterparts. MDR-negative, high biofilm-forming environmental strains had a 60% decrease in risk compared with their low biofilm-forming counterparts. The MDR-positive phenotype was deleterious for environmental strains and the high biofilm phenotype was critical for survival. This study provided evidence of the trade-off between antibiotic resistance and desiccation tolerance, driven by condition-dependent adaptation, and establishes rationale for research into the genetic basis of the variation in fitness cost between clinical and environmental isolates [16].

In this study, an interdisciplinary team implemented a screening program targeting patients with a history of methicillin-resistant *S. aureus* (MRSA) to reduce unnecessary contact isolation [17]. After converting from a 2-step culture-based protocol to single polymerase chain reaction (PCR) testing, the authors increased the efficiency of the screening program from 77% to 100%. Despite the higher cost of PCR-based testing, this program remained cost-saving [17].

Virulence and *S. aureus*

S. aureus is an opportunistic pathogen and the leading cause of a wide range of severe clinical infections. The range of diseases reflects the diversity of virulence factors produced by this pathogen [18]. To establish an infection in the host, *S. aureus* expresses an inclusive set of virulence factors such as toxins, enzymes, adhesins, and other surface proteins that allow the pathogen to survive under extreme conditions and are essential for the bacteria's ability to spread through tissues. Expression and secretion of this array of toxins and enzymes are tightly controlled by a number of regulatory systems. *S. aureus* is also notorious for its ability to resist the arsenal of currently available antibiotics and dissemination of various multidrug-resistant *S. aureus* clones limits therapeutic options for a *S. aureus* infection. The development of anti-virulence therapeutics that neutralize *S. aureus* toxins or block the pathways that regulate toxin production has shown potential in thwarting the bacteria's acquisition of antibiotic resistance. In this review, these authors provided insights into the regulation of *S. aureus* toxin production and potential anti-virulence strategies that target *S. aureus* toxins [18].

Successful methicillin-resistant *S. aureus* (MRSA) clones have evolved to adapt to healthcare and environments such as the community and in livestock. The authors reviewed recent studies on clone adaptation and the importance of genes acquired during horizontal gene transfer to survival in specific environments [19]. The review also discussed the role of global regulators controlling virulence gene expression and resistance to antibiotics, such as the *agr* and *vraRS* systems. The authors stated that understanding these processes in successful clones could reveal novel targets for therapeutic agents, which are urgently required to reduce the infection burden and improve treatment options [19]. The effect of decolonization on the control of methicillin-resistant *S. aureus* (MRSA) may differ depending on intensive care unit (ICU) settings and the prevalence of antiseptic resistance in MRSA.

Community-associated methicillin-resistant *S. aureus* (CA-MRSA) is a prevalent cause of skin and soft tissue infections (SSTI), but the association between CA-MRSA colonization and infection remains uncertain. These authors studied the carriage frequency at several body sites and the diversity of *S. aureus* strains from patients with and without SSTI [20]. Specimens from the nares, throat, rectum, and groin of case subjects with a closed skin abscess (i.e., without drainage) and matched control subjects without a skin infection

Please cite this article in press as: Frieri M, et al. Antibiotic resistance. J Infect Public Health (2016), http://dx.doi.org/10.1016/j.jiph.2016.08.007

presenting to 10 U.S. Emergency Departments were cultured using broth enrichment; wound specimens were cultured from abscess cases. Methicillin resistance testing and spa typing were performed for all *S. aureus* isolates. *S. aureus* was found in 57.8% of abscesses; 49 isolates were MRSA, and 36 were methicillin-susceptible *S. aureus* (MSSA) [20]. *S. aureus*-infected subjects were usually (75/85) colonized with the infecting strain; among MRSA-infected subjects, colonization was most common in the groin. The CC8 lineage accounted for most of both infecting and colonizing isolates, although more than 16 distinct strains were identified. Nearly all MRSA infections were inferred to be USA300. There was more diversity among colonizing than infecting isolates and among those isolated from controls versus cases. Detection of *S. aureus* colonization, and especially MRSA, may be enhanced by extranasal site culture [20].

This study was conducted in a 14-bed surgical ICU over a 40-month period. The baseline period featured active surveillance for MRSA and the institution of contact precautions. MRSA decolonization via chlorhexidine baths and intranasal mupirocin was implemented during a subsequent 20-month intervention period [21]. Both pre-post and interrupted time series analyses were used to evaluate changes in the clinical incidence of hospital-acquired MRSA colonization or infection. MRSA isolates were tested for the presence of qacA/B genes and mupirocin resistance.

In pre—post analysis, the clinical incidence of MRSA significantly decreased by 61.6% after implementation of decolonization ($p < 0.001$) [21]. Interrupted time series analysis showed decreases in both the level and trend of clinical MRSA incidence. Of 169 MRSA isolates, 64 carried the qacA/B genes, and 22 showed a high level of resistance to mupirocin. Low-level mupirocin resistance significantly increased from 0—19.4% during the study period. These authors felt that although decolonization using antiseptic agents was helpful in decreasing hospital-acquired MRSA rates, the emergence of antiseptic resistance should be monitored [21].

Current approaches to antibiotic susceptibility testing of cultured pathogens have several limitations ranging from long run times to dependence on prior knowledge of genetic mechanisms of resistance. These authors developed a rapid antimicrobial susceptibility assay for *S. aureus* based on bacterial cytological profiling, which uses quantitative fluorescence microscopy to measure antibiotic-induced changes in cellular architecture [22]. Thus, bacterial cytological profiling provides a rapid and flexible alternative to gene-based susceptibility testing methods for *S. aureus*, and should be readily adaptable to different antibiotics and bacterial species as new mechanisms of resistance or multidrug-resistant pathogens evolve and appear in clinical practice [22].

Healthcare workers may acquire methicillin-resistant *S. aureus* (MRSA) from patients, both hospital and home environments, other healthcare workers, family and public acquaintances, and pets [23]. There is a consensus of case reports and series that now strongly support the role for MRSA-carrying healthcare personnel to serve as a reservoir and as a vehicle of spread within healthcare settings. Carriage may occur at a number of body sites and for short, intermediate, and long terms. A number of approaches have been taken to interrupt the linkage of staff-patient spread, but most emphasis has been placed on handwashing and the treatment of staff MRSA carriers [23]. The importance of healthcare workers in transmission has been viewed with varying degrees of interest, and several logistical problems have arisen when healthcare worker screening is brought to the forefront. There is now considerable support for the screening and treatment of healthcare workers, but it is suggested that the intensity of any such approach must consider available resources, the nature of the outbreak, and the strength of the epidemiological associations. The task of assessing healthcare personnel carriage in any context should be shaped with due regard to national and international guidelines, should be honed and practiced according to local needs and experience, and must be patient-oriented [23].

S. aureus is an important human pathogen, responsible for infections in the community and healthcare settings. Although much of the attention is focused on the methicillin-resistant ''variant'' MRSA, its methicillin-susceptible counterpart (MSSA) remains a prime species in infections [24]. *S. aureus* epidemiology, especially that of MRSA, has evolved rapidly in recent years. First representing a typical nosocomial multidrug-resistant pathogen, MRSA has recently emerged in the community and among farmed animals due to its ability to evolve and adapt to different settings. Global surveillance has shown that MRSA represents a problem in all continents and countries, with an increase in mortality and the need for expensive last-resource antibiotics. *S. aureus* can easily acquire resistance to antibiotics and MRSA is characteristically multidrug resistant [24]. Newer anti-staphylococcal drugs have been developed, but because their clinical use has been very limited so far, little is known about the emergence of resistance. Molecular typing techniques have allowed

Please cite this article in press as: Frieri M, et al. Antibiotic resistance. J Infect Public Health (2016), http://dx.doi.org/10.1016/j.jiph.2016.08.007

identification of the major successful clones and lineages of MSSA and MRSA, including high-risk clones, and tracing their diffusion [24]. In this earlier review, the authors depicted the most common clones circulating in different geographical areas and in different present settings. The authors stated that because the evolution of *S. aureus* will continue, it is important to maintain the attention on the epidemiology of *S. aureus* in the future with a global view [24].

Emergency Department

Hand hygiene is essential in preventing nosocomial infections. The Emergency Department is an open portal of entry for pathogens into the hospital system, hence the important sentinel function of Emergency Department personnel [25]. The main objective of this study was to assess the effect of a multimodal improvement strategy on hand hygiene compliance in the Emergency Department [25]. This was a prospective before-and-after study to determine the effect of a multimodal improvement strategy on the compliance of hand hygiene in the Emergency Department according to the ''My 5 Moments'' of hand hygiene defined by the WHO Interventions as education, reminders, and regular feedback on hand hygiene performance and role models were planned during the 3 intervention weeks [25]. A total of 57 Emergency Department nurses and Emergency Department physicians were observed in this study; approximately 1000 opportunities for handrubs were evaluated during the 3 intervention periods. Hand hygiene compliance increased significantly from baseline from 18% to 41% after the first intervention and stabilized to 50% and 46% after the second and third interventions, respectively. Thus, implementing a multimodal hand hygiene improvement program significantly improved the compliance of Emergency Department personnel [25].

Clostridium difficile infection

Health care-acquired Clostridium difficile infection is associated with adverse outcomes at both the organization and patient levels. Factors that increase the risk for the development of health care-acquired Clostridium difficile infection have been identified [26]. The objectives of this study were to develop a predictive screening tool to identify patients at risk for health care-acquired Clostridium difficile infection I and implement a bundle of mitigation interventions [26].

A predictive screening tool was developed based on risk factors identified in the literature and validated by retrospective analysis of all cases occurring in critically ill patients during 2013. The tool was used to screen all patients admitted to an intensive care unit. Evidence-based interventions were implemented for patients identified as being at high risk for health care-acquired Clostridium difficile infection [26]. Effectiveness of the model was measured by the reduction in the health care-acquired Clostridium difficile infection rate during the intervention period compared with the pre-intervention period. During the 12-month intervention period, 217 high-risk patients were identified as infected with Clostridium difficile. Sixty-two of these met the exclusion criteria, resulting in a study population of 157 patients. During the pre-intervention phase, 10 cases occurred. During the 12-month study period, 2 cases were identified; the reduction was statistically significant. Thus a strategy for identifying patients at increased risk and the implementation of multidisciplinary risk-mitigation strategies is effective in reducing the incidence of health care-acquired Clostridium difficile infection [26].

Residents of long-term care facilities are at increased risk for colonization and development of infections with multidrug-resistant organisms. This study was undertaken to determine the prevalence of asymptomatic rectal colonization with Clostridium difficile (and proportion of 027/NAP1/BI ribotype) or carbapenem-resistant Enterobacteriaceae in the long-term care facilities population [27].

Active surveillance was performed for C. difficile and carbapenem-resistant Enterobacteriaceae rectal colonization of 301 residents in a 320-bed (80-bed ventilator unit), hospital-affiliated long-term care facility with retrospective chart review for patient demographics and potential risk factors [27]. Over 40% of patients had airway ventilation and received enteral feeding. One-third of these patients had prior C. difficile-associated infection. Asymptomatic rectal colonization with C. difficile occurred in 58 patients (19.3%, one-half with NAP1+), carbapenem-resistant Enterobacteriaceae occurred in 57 patients (18.9%), and both occurred in 17 patients. Recent carbapenem-resistant Enterobacteriaceae was significantly associated with an increased risk of C. difficile ± carbapenem-resistant Enterobacteriaceae colonization. Multivariate logistic regression analysis revealed the presence of tracheostomy collar to be significant for C. difficile colonization, mechanical ventilation to be significant for carbapenem-resistant Enterobacteriaceae colonization, and prior Clostridium difficile infection to be significant

Please cite this article in press as: Frieri M, et al. Antibiotic resistance. J Infect Public Health (2016), http://dx.doi.org/10.1016/j.jiph.2016.08.007

for both C. difficile and carbapenem-resistant Enterobacteriaceae colonization [27].

Thus, the strong association of C. difficile or carbapenem-resistant Enterobacteriaceae colonization with disruption of normal flora by mechanical ventilation, enteral feeds, and prior Clostridium difficile infection carries important implications for infection control intervention in this population [27].

Vancomycin-resistant enterococci

Between 2013 and 2014, a vancomycin-resistant enterococci (VRE) outbreak occurred in a teaching hospital in France. The outbreak was possibly due to the lack of implementation of recommended control measures. The aim of this study was to identify the effect of the lack of adherence to control measures for prevention of VRE acquisition in contact patients taking into account individual risk factors [28]. Contact patients with VRE acquisition were compared to patients without VRE acquisition in terms of institutional characteristics and risk factors. Between December 2013 and February 2014, 282 contact patients were included in the study. The prevalence of VRE acquisition was 6.4% and significant risk factors for VRE acquisition according to logistic regression analysis included lack of isolation, hospitalization in the same hospital unit as a VRE carrier patient and lack of isolation, hospitalization in a specific unit, age, hemodialysis, central venous catheter and surgery [28] Antibiotic use was a significant risk factor for VRE acquisition using univariate analysis. The findings of these authors confirmed that the factors focused on by the study (lack of isolation and dedicated unit) had a significant effect on VRE acquisition as patient-associated factors. It highlighted the importance of observance of the guidelines [28].

Infections attributable to VRE have become increasingly prevalent over the past decade. Prompt identification of colonized patients combined with effective multifaceted infection control practices can reduce transmission of VRE and aid in preventing hospital-acquired infections [29]. The clinical microbiology laboratory is being asked to support infection control efforts through early identification of potential patient or environmental reservoirs. This review discussed the factors that contribute to the increase in VRE as an important healthcare-associated pathogen, the utility of laboratory screening and various infection control strategies and the available laboratory methods to identify VRE in clinical specimens [29].

VRE infections are a public health threat associated with increased patient mortality and healthcare costs. Antibiotic usage, particularly of cephalosporins, has been associated with VRE colonization and VRE bloodstream infections. These authors examined the relationship between antimicrobial usage and incident VRE colonization at the individual patient level [30]. Prospective weekly surveillance was undertaken for incident VRE colonization was defined by negative admission but positive surveillance swab in a medical intensive care unit over a 17-month period [30]. Ninety-six percent of admitted patients were swabbed within 24 h of intensive care unit arrival; of the 380 patients in the ICU long enough for weekly surveillance, 22% developed incident VRE colonization. Incident colonization was associated with male gender, more previous hospital admissions, longer previous hospital stay, and the use of cefepime/ceftazidime, fluconazole, azithromycin, and metronidazole [30]. After controlling for demographic and clinical covariates, metronidazole was the only antibiotic independently associated with incident VRE colonization. Their findings suggest that risk of incident VRE colonization differs between individual antibiotic agents and support the possibility that antimicrobial stewardship may impact VRE colonization and infection [30].

These authors reported an outbreak of vancomycin variable vanA$^+$ enterococci (VVE) able to escape phenotypic detection by current guidelines, and demonstrate the molecular mechanisms for in vivo switching into vancomycin resistance and horizontal spread of the vanA cluster [31]. Forty-eight vanA$^+$ Enterococcus faecium and one *Enterococcus faecalis* isolates were analyzed for clonality with PFGE and their vanA gene cluster composition assessed by PCR and whole genome sequencing of six isolates. The VVE had insertion of IS1542 between orf2 and vanR that attenuated the expression of the vanHAX activator coded by vanRS. Growth of susceptible VVE occurred after 24—72 h of exposure to vancomycin due to excision of the ISL3-family element [31]. The vanA gene cluster was located on a transferable broad host-range plasmid also detected in outbreak isolates with different pulsotypes as well as one *E. faecalis*. Horizontally transferable silenced vanA able to escape detection and revert into resistance during vancomycin therapy represents a new challenge in the clinic. Genotypic testing of invasive VSE by vanA-PCR is advised [31].

Control in the Emergency Department

A prospective observational study was conducted at a university-affiliated urban teaching hospital and level-1 trauma and burn center. All adult patients

Please cite this article in press as: Frieri M, et al. Antibiotic resistance. J Infect Public Health (2016), http://dx.doi.org/10.1016/j.jiph.2016.08.007

who triggered a Code Sepsis in the Emergency Department between January 2010 and December 2011 were included [32]. Hospital mortality and hospital loss of stay of sepsis are similar to those reported in other observational studies. This study confirmed a decline in the mortality of sepsis predicted by earlier longitudinal studies and should prompt a resurgence in epidemiological research of sepsis syndromes in the United States [32].

How closely physicians follow Infectious Disease Society of America guidelines is unknown, particularly in the Emergency Department observation unit where increasing numbers of patients are treated for these infections. The objectives of this paper were to describe (1) the antibiotic treatment patterns in the Emergency Department observation unit; (2) physicians' adherence to the Infectious Disease Society of America guidelines; and (3) factors that influence physicians' prescribing practices [33]. This paper showed that physician antibiotic prescribing practices demonstrated poor adherence to Infectious Disease Society of America guidelines and were influenced by the patient's age and sex. Standardized antibiotic protocols for the treatment of skin and soft tissue infections to Infectious Disease Society of America guidelines is unknown, particularly in the Emergency Department observation unit, which would minimize physician bias [33].

The increase in antibiotic-resistant pathogens is believed to have influenced the Emergency Department epidemiology and management of infectious diseases since 2000 [34].

Data from the National Hospital Ambulatory Medical Care Survey from 2000 to 2010 were used to examine temporal trends in the incidence of infectious diseases presenting to the Emergency Department. Outcome measures included national visit rates, visit proportions, and antimicrobial prescriptions for all infectious disease primary diagnoses, as well as for specific organ systems of interest such as the respiratory tract, skin/soft tissue, and urinary tract [34].

An infectious disease-related primary diagnosis was given in 18.3% of all Emergency Department visits during the study period. Management of skin and soft tissue infections shifted from predominant use of cephalosporins to sulfonamides. For UTIs, quinolones were most commonly prescribed, with an increasing use of third-generation cephalosporins [34]. Antibiotics were more frequently prescribed to patients who were white. Thus, the changing epidemiology of infectious diseases diagnosed in US Emergency Departments reflects national trends in emerging pathogens and drug resistance. Broad-spectrum antibiotics are being prescribed at increasing rates. There are significant demographic disparities in nationwide antibiotic prescription practices [34].

Conclusion

Antimicrobial resistance in bacterial pathogens is a significant challenge that has a high morbidity and mortality. Multidrug resistant patterns in Gram-positive and -negative bacteria are difficult to treat and may even be untreatable with conventional antibiotics. Challenges associated with bacterial infection and associated diseases are due to the current shortage of effective therapies, lack of successful prevention measures, and lack of new antibiotics, which require development of novel treatment options and alternative antimicrobial therapies. Biofilms are involved in multidrug resistance and can present challenges for infection control. Virulence, *S. aureus*, Clostridium difficile infection vancomycin-resistant enterococci, and control in the Emergency Department were discussed.

Funding

No funding sources.

Competing interests

None declared.

Ethical approval

Not required.

References

[1] Velez R, Sloand E. Combating antibiotic resistance, mitigating future threats and ongoing initiatives. J Clin Nurs 2016;(March).
[2] Akova M. Epidemiology of antimicrobial resistance in bloodstream infections. Virulence 2016;(March).
[3] Mühlen S, Dersch P. Anti-virulence strategies to target bacterial infections. Curr Top Microbiol Immunol 2016;(March).
[4] Chellat MF, Raguž L, Riedl R. Targeting antibiotic resistance. Angew Chem Int Ed Engl 2016;(March).
[5] von Wintersdorff CJ, Penders J, van Niekerk JM, Mills ND, Majumder S, van Alphen LB, et al. Dissemination of antimicrobial resistance in microbial ecosystems through horizontal gene transfer. Front Microbiol 2016;7(February):173.

[6] Khameneh B, Diab R, Ghazvini K, Bazzaz BSF. Breakthroughs in bacterial resistance mechanisms and the potential ways to combat them. Microb Pathog 2016;95(February):32—42.
[7] Wesgate R, Grasha P, Maillard JY. Use of a predictive protocol to measure the antimicrobial resistance risks associated with biocidal product usage. Am J Infect Control 2016;44(April (4)):458—64.
[8] Ribeiro SM, Felício MR, Boas EV, Gonçalves S, Costa FF, Samy RP, et al. New frontiers for anti-biofilm drug development. Pharmacol Ther 2016;160(April):133—44.
[9] Hengzhuang W, Høiby N, Ciofu O. Pharmacokinetics and pharmacodynamics of antibiotics in biofilm infections of *Pseudomonas aeruginosa* in vitro and in vivo. Methods Mol Biol 2014;1147:239—54.
[10] Elkhatib WF, Haynes VL, Noreddin AM. Unexpected induction of resistant *Pseudomonas aeruginosa* biofilm to fluoroquinolones by diltiazem: a new perspective of microbiological drug-drug interaction. J Infect Public Health 2008;1(2):105—12.
[11] Noreddin AM, Elkhatib WF. Novel in vitro pharmacodynamic model simulating ofloxacin pharmacokinetics in the treatment of *Pseudomonas aeruginosa* biofilm-associated infections. J Infect Public Health 2009;2(3):120—8.
[12] Madeo J, Frieri M. Bacterial biofilms and chronic rhinosinusitis. Allergy Asthma Proc 2013;34(July—August (4)):335—41.
[13] Bakour S, Sankar SA, Rathored J, Biagini P, Raoult D, Fournier PE. Identification of virulence factors and antibiotic resistance markers using bacterial genomics. Future Microbiol 2016;11(March):455.
[14] Seth AK, Zhong A, Nguyen KT, Hong SJ, Leung KP, Galiano RD, et al. Impact of a novel, antimicrobial dressing on in vivo, *Pseudomonas aeruginosa* wound biofilm: quantitative comparative analysis using a rabbit ear model. Wound Repair Regen 2014;22(November—December (6)):712—9.
[15] Hoiby N, Ciofu O, Johansen HK, Song ZJ, Moser C, Jensen PØ, et al. The clinical impact of bacterial biofilms. Int J Oral Sci 2011;3(April (2)):55—65.
[16] Greene C, Vadlamudi G, Newton D, Foxman B, Xi C. The influence of biofilm formation and multidrug resistance on environmental survival of clinical and environmental isolates of *Acinetbacter baumannii*. Am J Infect Control 2016;44(May (5)):e65—71.
[17] Goldsack JC, DeRitter C, Power M, Spencer A, Taylor CL, Manta CJ, et al. Increasing the efficiency of a targeted methicillin-resistant *Staphylococcus aureus* screening program. Am J Infect Control 2016;44(January (1)):117—9.
[18] Kong C, Neoh HM, Nathan S. Targeting *Staphylococcus aureus* toxins: a potential form of anti-virulence therapy. Toxins (Basel) 2016;8(March (3)).
[19] Purrello SM, Daum RS, Edwards GFS, Lina G, Lindsay J, Peters G, et al. Meticillin-resistant *Staphylococcus aureus* (MRSA) update: new insights into bacterial adaptation and therapeutic targets. J Glob Antimicrob Resist 2014;2(June (2)):61—9.
[20] Albrecht VS, Limbago BM, Moran GJ, Krishnadasan A, Gorwitz RJ, McDougal LK, et al. *Staphylococcus aureus* colonization and strain type at various body sites among patients with a closed abscess and uninfected controls at U.S. Emergency Departments. J Clin Microbiol 2015;53(November (11)):3478—84.
[21] Cho OH, Baek EH, Bak MH, Suh YS, Park KH, Kim S, et al. The effect of targeted decolonization on methicillin-resistant *Staphylococcus aureus* colonization or infection in a surgical intensive care unit. Am J Infect Control 2016;44(May (5)):533—817.
[22] Quach DT, Sakoulas G, Nizet V. Bacterial Cytological Profiling (BCP) as a rapid and accurate antimicrobial susceptibility testing method for *Staphylococcus aureus*. EBioMedicine 2016;4(January):95—103.
[23] Cimolai N. The role of healthcare personnel in the maintenance and spread of methicillin-resistant *Staphylococcus aureus*. J Infect Public Health 2008;1(2):78—100.
[24] Monaco M, Pimentel de Araujo F, Cruciani M, Coccia EM, Pantosti A. Worldwide epidemiology and antibiotic resistance of *Staphylococcus aureus*. Curr Top Microbiol Immunol 2016;(March).
[25] Arntz PR, Hopman J, Nillesen M, Yalcin E, Bleeker-Rovers CP, Voss A, et al. Effectiveness of a multimodal hand hygiene improvement strategy in the emergency department. Am J Infect Control 2016;(May).
[26] Cruz-Betancourt A, Cooper CD, Sposato K, Milton H, Louzon P, Pepe J, et al. Effects of a predictive preventive model for prevention of Clostridium difficile infection in patients in intensive care units. Am J Infect Control 2016;44(April (4)):421—4.
[27] Prasad N, Labaze G, Kopacz J, Chwa S, Platis D, Pan CX, et al. Asymptomatic rectal colonization with carbapenem-resistant Enterobacteriaceae and Clostridium difficile among residents of a long-term care facility in New York City. Am J Infect Control 2016;44(May (5)):525—32.
[28] Djembi LF, Hodille E, Chomat-Jaboulay S, Coudrais S, De Santis N, Gardes S, et al. Factors associated with Vancomycin-resistant Enterococcus acquisition during a large outbreak. Factors associated with Vancomycin-resistant Enterococcus acquisition during a large outbreak. J Infect Public Health 2016;(April).
[29] Faron ML, Ledeboer NA, Buchan BW. Resistance mechanisms, epidemiology, and approaches to screening for Vancomycin Resistant Enterococcus (VRE) in the health care setting. J Clin Microbiol 2016;(May).
[30] McKinnell JA, Kunz DF, Moser SA, Vangala S, Tseng CH, Shapiro M, et al. Patient-level analysis of incident vancomycin-resistant enterococci colonization and antibiotic days of therapy. Epidemiol Infect 2016;144(June (8)):1748—55.
[31] Sivertsen A, Pedersen T, Larssen KW, Bergh K, Rønning TG, Radtke A, et al. Silenced vanA gene cluster on a transferable plasmid cause outbreak of vancomycin variable enterococci. Antimicrob Agents Chemother 2016;(May).
[32] Tulloch LG, Chan JD, Carlbom DJ, Kelly MJ, Dellit TH, Lynch JB. Epidemiology and microbiology of sepsis syndromes in a university-affiliated urban teaching hospital and level-1 trauma and burn center. J Intensive Care Med 2015;(June).
[33] Haran JP, Wu G, Bucci V, Fischer A, Boyer EW, Hibberd PL. Treatment of bacterial skin infections in ED observation units: factors influencing prescribing practice. Am J Emerg Med 2015;33(December (12)). A1—A12, 1721—1896.
[34] Mohareb AM, Dugas AF, Hsieh YH. Changing epidemiology and management of infectious diseases in US EDs. Am J Emerg Med 2016;(March) [colonization with carbapenem-resistant].

Please cite this article in press as: Frieri M, et al. Antibiotic resistance. J Infect Public Health (2016), http://dx.doi.org/10.1016/j.jiph.2016.08.007