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Multidrug-Resistant Gram-Negative Pneumonia and Infection in Intensive Care Unit

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Additional information is available at the end of the chapter

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Abstract

Multidrug-resistant (MDR) pneumonia can be problematic and challenging to treat in an era of increasing resistance and limited treatment armamentarium. Multidrug-resistant pathogens are associated with increased morbidity and mortality, thus early empiric appropriate antibiotics are critical for survival. Many factors play a role in the selection, optimization, and duration of therapy that should be made on an individual basis. New technologies such as “rapid diagnostics” may provide the clinician with early phenotypic or genotypic result, thus improving early appropriate therapy. The increasing antibiotic resistance is a global threat to patients worldwide and is an economic burden. In the United States, drug-resistant bacteria cause approximately 2 million cases of illnesses and contribute to 23,000 deaths each year. The inappropriate use of antibiotics has contributed to the healthcare burden that ranges from \$27 to \$42 billion annually. As a result, several governmental agencies have placed forth regulatory mandates to enforce antimicrobial stewardship programs in acute care hospitals. Education will be vital across all healthcare disciplines to ultimately ensure optimal prescribing and reduce the emergence of resistance.

Keywords: multidrug-resistant infections, intensive care unit, pneumonia, healthcare-associated infections, critically ill patients, antibiotic stewardship

1. Introduction

In this chapter, we will focus on the critically ill patients with Gram-negative **pneumonia**, the prevalence of multidrug resistance, factors associated with patients developing these resistance infections. Surveillance, infection control, and early detection by means of utilizing rapid diagnostics and other methodologies are important for early prevention of disease. The reader will be able to understand how and why the administration of early appropriate empiric antibiotics is

key for survival in the critically ill. We will emphasize on the importance of robust antimicrobial stewardship programs, which are in accordance with Centers for Disease Control and Prevention (CDC) core elements. New regulatory mandates from the Joint Commission (TJC) on antimicrobial stewardship programs will require hospitals to be compliant for accreditation. Finally, we will end the chapter with an outlook on future antibiotics in Phase III development to aid in the combat against multidrug-resistant (MDR) organisms.

2. Global resistance and global economic impact

The preantibiotic era is a reality for many parts around the world, especially among the developed countries, driven in part by antibiotic overuse and misuse. Increasing antibiotic resistance is a global threat to patients worldwide and an economic burden. According to the U.S. Centers for Disease Control and Prevention (CDC), each year in the United States, drug-resistant bacteria cause approximately 2 million cases of illnesses and contribute to 23,000 deaths. A key driver has been the inappropriate use of antibiotics, which as an avoidable cost and burden to healthcare dollars, ranges from \$27 billion to 42 billion annually [1, 2]. The Infectious Diseases Society of America (IDSA) white paper entitled “Bad Bugs, No Drugs” commented on the declining research investments in antimicrobial development, as did an update on this article from clinical infectious disease (CID) in 2009 [3]. These papers identified certain Gram-negative bacteria that are particularly problematic pathogens, which tend to “escape” the activity of many antibiotics. These problematic pathogens are known as, the “ESKAPE” pathogens, which include: *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterobacter species* and *Clostridium difficile* is also include to the list. In addition to the “ESKAPE” pathogens, the prevalence of *C. difficile* infection (CDI) has risen dramatically in just the last 2 decades. Since 2001, surveillance data has shown a dramatic increase. The number of CDI cases (any diagnosis) per 10,000 hospital discharges increased from 25.0 to 40.0, a 60% increase. However, over the next 4 years (2001–2005), a 92% increase was observed (from 40.0 to 76.9) [3–5]. The CDC has placed these resistant pathogens into three categories: urgent, serious, and concerning threat levels. Several recent efforts have attempted to raise awareness and focus attention on antibiotic overuse in healthcare including: the World Health Organization, the CDC, and White House. The White House issued executive order 13,676: combating antibiotic-resistant bacteria, which is a roadmap to guide the nation that was issued by President Obama on September 18, 2014. This executive order will implement the *National Action Plan for Combating Antibiotic-Resistant Bacteria*, a plan that intends to have major reductions in the occurrence of urgent and serious threatening pathogens, including methicillin-resistant *S. aureus* (MRSA), carbapenem-resistant *Enterobacteriaceae* (CRE), and *C. difficile* [6]. Recent studies have demonstrated that critically ill patients colonized with multidrug-resistant pathogens also have a high prevalence of being infected with that particular organism. In such, antimicrobial resistance (AMR) as an independent risk factor also increases morbidity and mortality [7, 8].

3. Prevalence of MDROs and risk factors in the critically ill

The CDC in 2013 published *Antibiotic Resistance Threats in the United States*. Regarding the level of concern, CDC has, for the first time, prioritized bacteria in this report into one of three categories: urgent, serious, and concerning (Table 1).

The CDC has placed carbapenem-resistant *Enterobacteriaceae* (CRE) as an urgent threat level. CRE confers resistance to last-line antibiotics such as carbapenems, by producing a β -lactamase enzyme called KPC (*K. pneumoniae* carbapenemase-producing). The CDC reports their laboratories have confirmed CRE in 44 states within healthcare facilities across the United States. CRE causes more than 9000 healthcare-associated infections (HAI) annually, among these the two most common types are carbapenem-resistant *Klebsiella* and carbapenem-resistant *E. coli*. The percentages of the United States CRE healthcare-associated infections for *Klebsiella* spp. and carbapenem-resistant *Escherichia coli* are 11 and 2%, respectively. These serious infections contribute to roughly 600 deaths each year [5].

Urgent threats
<i>Clostridium difficile</i>
Carbapenem-resistant <i>Enterobacteriaceae</i> (CRE)
Drug-resistant <i>Neisseria gonorrhoeae</i>
Serious threats
Multidrug-resistant <i>Acinetobacter</i> *
Drug-resistant <i>Campylobacter</i>
Fluconazole-resistant <i>Candida</i> (a fungus)
Extended spectrum β -lactamase producing <i>Enterobacteriaceae</i> (ESBLs)*
Vancomycin-resistant <i>Enterococcus</i> (VRE)
Multidrug-resistant <i>Pseudomonas aeruginosa</i> *
Drug-resistant nontyphoidal <i>Salmonella</i>
Drug-resistant <i>Salmonella</i> Typhi
Drug-resistant <i>Shigella</i>
Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA)*
Drug-resistant <i>Streptococcus pneumoniae</i> *
Drug-resistant tuberculosis*
Concerning threats
Vancomycin-resistant <i>Staphylococcus aureus</i> (VRSA)
Erythromycin-resistant Group A <i>Streptococcus</i>
Clindamycin-resistant Group B <i>Streptococcus</i>

Notes: *MDROs associated with pneumonia. Reproduced from CDC. Antibiotic resistance threats in the United States, 2013 [5].

Table 1. CDC antibiotic resistance threats in the United States, 2013.

The first case of *K. pneumoniae* carbapenemase-producing CRE was reported in North Carolina in 2001. Since then, cases have been reported in almost every state. Carbapenemase-producing CRE carries antimicrobial resistance genes on mobile plasmids that can move between organisms, thus potentially facilitating a wider and more rapid spread. A clone known as *K. pneumoniae* sequence type 258 was responsible for this global dissemination, particularly in the United States. Knowing the genotype level aids in tracking the epidemiology worldwide [9]. Guh et al. conducted a 2-year surveillance period, which included 599 incident CRE cases that were reported across 7 Emerging Infections Program (EIP) sites (Georgia, Minnesota, Oregon, Colorado, Maryland, New Mexico, and New York). They concluded that the overall crude incidence CRE was 2.93 per 100,000 populations [10]. The overall CRE incidence may be underreported as many hospital laboratories may not perform confirmatory testing [11].

CRE is encountered in patients with extensive healthcare exposure. Patients can be hospitalized in an acute short stay hospital, residents of LTCFs (long-term care facilities), LTACHs (long-term acute care hospitals), or outpatients with recent healthcare exposure. These patients also frequently have multiple comorbidities, poor functional status, recent intravenous antibiotic exposure (within 90 days), and indwelling devices (urinary catheter, mechanical ventilation, indwelling lines). Patients that recover from their acute hospitalization are frequently discharged to LTCFs or LTACHs, thus contributing to a viscous cycle [10, 12]. LTACHs play an important role in the regional epidemiology of CRE. In a recent study, 30% of LTACH residents were colonized with *K. pneumoniae* carbapenemase-producing CRE. This represented a ninefold higher prevalence in LTACHs compared to intensive care unit (ICU) patients in acute short-stay hospitals in the same area. Various efforts to reduce the burden of CRE in LTACHs have had only a slight impact [13].

Common sites of infection include respiratory, bloodstream, -wounds, and urinary tract. Urine is the most common site for infection and colonization. Outcomes associated with CRE infections are poor with high mortality rates as high as 50% in some studies. Outcomes vary by the site of infection with blood stream infections carrying the highest mortality and urinary tract infection the lowest [10, 13].

According to the CDC, *Acinetobacter* in the United States causes approximately 12,000 health-care-associated infections annually. Approximately 7000 of these infections are considered to be multidrug-resistant *Acinetobacter* at a staggering 63%, meaning at least three different classes of antibiotics no longer cures these infections, which contributes to 500 deaths per year. The CDC 2013 publication does not estimate long-term care hospitals or long-term care facilities in the prevalence statistics [10]. Others [14] have estimated that there may be as many as approximately 46,000 cases of *Acinetobacter*-related infections per year in the U.S. and approximately 1 million cases per year globally. In the United States, a 2006–2007 report of 463 hospitals participating in the National Healthcare Safety Network (NHSN) indicated that infections due to *Acinetobacter baumannii* accounted for 3% of all health-care-associated infections (HAI). Focusing on the ICU, approximately 7% of all HAIs were associated with critically ill patients on mechanical ventilation in the United States, which were caused by *Acinetobacter* [11].

A further concern is that the prevalence of resistance among *Acinetobacter* infections is increasing. Between 2000 and 2009, the percentage of imipenem-resistant *A. baumannii*

increased from ~5% to an approaching 40%, an increase that has been observed across most of U.S. states [15]. *Acinetobacter* is uniquely able to survive in hospital environments and to develop resistance to antibiotics. When combined these attributes result in both a high potential for endemicity and epidemicity, resulting in both hospital outbreaks and persistent colonization [16]. Studies have indicated that key sources of *Acinetobacter* transmission within hospital units include the following: hands of hospital personnel, contamination of environmental surfaces and medical equipment, environmental shedding by colonized patients, procedures that result in a spray of contaminated fluids, and airborne particles are believed to play a role in transmission [17].

In critically ill patients, *A. baumannii* can invade through breaches in skin integrity or airway protection. This pathogen is associated with high mortality [18]. Debilitated patients in ICUs are especially prone to *Acinetobacter* infections [15]. High-risk patients include:

- a) Severe underlying illness or comorbidities such as diabetes mellitus and chronic lung disease.
- b) Circumstances of hospitalization, such as length of stay, high workload, and admission to units in the acute care center with high a density of infected.
- c) Infection or colonization of specific sites, respiratory, urinary, gastrointestinal tracts, burns, or surgical wounds.
- d) Exposure to prolonged antimicrobial therapy with broad-spectrum antibiotics, which include carbapenems, fluoroquinolones, aminoglycosides, third generation cephalosporins.
- e) Administration of blood product transfusions, enteral feeding and contaminated parenteral solutions.

Common sites of infection include respiratory, bloodstream, skin and soft tissue and urine. Mortality associated with *A. baumannii* infections ranges from 7.8 to 23% in general hospital patients and from 10 to 43% in ICU patients. Bacteremia has the highest mortality, and in hematopoietic stem cell transplantation (HSCT) recipients, mortality rates associated with *Acinetobacter* bacteremia may reach up to 70% [19].

Extended spectrum β -lactamase (ESBLs) producing *Enterobacteriaceae* produce a hydrolytic β -lactamase enzyme that confers resistance to various penicillins, which also include extended spectrum cephalosporins. Given the resistance, clinicians' remaining treatment option is a carbapenem antibiotic. Carbapenems are last-line antibiotics, and their use in ESBL infections has also contributing to additional resistance [20, 21]. In the United States, the CDC reports an estimated 140,000 healthcare-associated *Enterobacteriaceae* infections occur each year. The CDC also reports that approximately 26,000 of these infections are caused by ESBL-containing *Enterobacteriaceae* bloodstream infections, which contribute to 1700 deaths. The total excess hospital charges per episode of ESBL-bacteraemia are roughly \$40,000 per occurrence. ESBL-producing *Klebsiella* spp. and ESBL-producing *E. coli* are the most common and percentage resistant to extended spectrum cephalosporins are 23 and 14%, respectively [5].

Sequence type 131 (ST131) is a pathogenic clone of *E. coli* and it also frequently expresses a hydrolytic β -lactamase enzyme called CTX-M-type and has rapidly disseminated worldwide. *E. coli* expressing CTX-M-type enzymes containing ESBLs have been increasingly seen in the community [12, 22–26]. Residency of a long-term care facility has been recognized as a prominent risk factor for acquisition of ESBL infections in the community. Various studies have also identified ESBL bacteremia as an independent risk factor from exposure to fluoroquinolones, first-generation cephalosporins, and finally, a previously known colonization history with an ESBL [25, 27]. Patients are 57% more likely to die from bloodstream infections associated with ESBL-producing *Enterobacteriaceae* than those with bloodstream infections caused by a non ESBL-producing strain [26].

In a study by Ha et al. [28], they concluded that significant risk factors associated with ESBL-producing *E. coli* bacteremia were prior treatment with fluoroquinolones and cephalosporins, as previous studies have also demonstrated. Moreover, recent surgery, liver disease, and immunosuppressant use were also deemed as significant risk factors. The study resulted in an overall 30-day mortality rate of 14.9%. As described previously, the mortality rate was higher in patients with ESBL-producing *E. coli* than in those without ESBL bacteremia (22.1 vs. 12.2%; $P = 0.02$). A multivariate analysis in this study demonstrated an independent risk factor for mortality (odds ratio = 3.01, 95% confidence interval 1.45–6.28; $P = 0.003$) for ESBL bacteremia [26, 28].

P. aeruginosa is a common cause of healthcare-associated infections including pneumonia, bloodstream infections, urinary tract infections, and surgical site infections. *P. aeruginosa* can easily adapt to the environment it inhabits, this ability can lead to colonization, and ultimately invade the human host defenses and cause serious infections. According to the CDC, approximately 7.1% of all healthcare-associated infections in the United States are caused by *P. aeruginosa*. This organism was the second most common cause of pneumonia in the hospital setting, and the third most common cause of Gram-negative bloodstream infections [5]. Kollef et al. recently conducted a global prospective epidemiological study on the prevalence of *P. aeruginosa* causing Ventilator-associated pneumonia (VAP). They concluded that global incidence was 4.1%, and did not differ among countries significantly [29].

In 2013, the CDC's National Healthcare Safety Network (NSHN) reported that 8% of all healthcare-associated infections are caused by *P. aeruginosa*. Among these 8% reported to the NSHN, approximately 13% were considered severe healthcare-associated infections caused by MDR *P. aeruginosa*. By definition, MDR is resistance to at least three different antibiotics classes (mainly antipseudomonal penicillins, aminoglycosides, cephalosporins, and carbapenems). Each year, approximately 51,000 healthcare-associated *P. aeruginosa* infections occur in the United States (according to the CDC). Of these infections, more than 13% are classified as multidrug-resistant (MDR) *P. aeruginosa* and contribute roughly to 400 deaths per year [5].

The true prevalence of multidrug-resistant *P. aeruginosa* is not well established, mainly because there are considerable different definitions used in the literature. Upon reviewing many studies, they tend to report on both MDR and "pan-drug resistant" *P. aeruginosa* infections. In 2011, a new standardized definition was proposed, which classified *Pseudomonas* as MDR, XDR, or pan drug-resistant (PDR) bacteria. MDR as described above is resistant to at least one antibiotic

in three or more classes. Extensively drug-resistant (XDR), resistance to all FDA-approved, systemically active agents except for those known to be substantially more toxic than or inferior in efficacy to alternative agents when used to treat susceptible organisms [30]. Finally, PDR, defined, is resistant to all commercially available antibiotics in all classes. MDR *P. aeruginosa* should not be synonymous with carbapenem resistance, as multiple mechanisms of can contribute to resistance. Risk factors for multidrug-resistant (MDR) infections include the following: length of hospital stay, prior use of IV antibiotics, history of *P. aeruginosa* infection, or colonization within the previous year, bedridden in the intensive care unit, mechanical ventilation, history of chronic obstructive pulmonary disease, and malignant disease. Nseir et al. concluded that a new patient admission into a previously occupied ICU room with a patient that had either MDR *P. aeruginosa* or *A. baumannii* was at an independent risk factor for acquisition of those pathogenic organisms. Many studies have examined multidrug-resistant infections as an independent risk factor for mortality, especially when combined with inappropriate antimicrobial therapy [31, 32].

4. Infection control

Environmental reservoirs may be unrecognized as the culprit for outbreaks or ongoing sporadic transmission. Recent studies suggest that the risk of acquiring multidrug-resistant pathogens such as *Acinetobacter* spp., *Pseudomonas* spp., vancomycin-resistant Enterococcus (VRE), MRSA, or *C. difficile* is increased if a new patient admission is placed in a room previously occupied by a colonized or infected patient with one of the above pathogens [33–38]. “Terminal cleans” have been utilized for multidrug-resistant Gram-negative organisms and may be integrated with infection control measures, along with surveillance to limit the horizontal transmission of multidrug-resistant organisms.

Environmental survival times of infectious pathogens [39]:

- a) MRSA survival time ranges from 7 days to >7 months
- b) *Acinetobacter* survival time ranges from 3 days to >5 months
- c) *C. difficile* survival is >5 months
- d) *Vancomycin-resistant Enterococcus* ranges from 5 days to >4 months
- e) *E. coli* from 2 h to 16 months
- f) *Klebsiella* from 2 h to >30 months.

Environmental surfaces are routinely disinfected in hospitals based on infection control policies and procedures. Several factors dictate the type and frequency for these cleanings such as surface characteristics, intensity of people traffic, clinical risk, and patient turnover. Following a patient discharge that was known to be colonized or infected with a multidrug-resistant pathogen, a terminal or deep cleaning may be performed. The cleaning regimen

is usually tailored with a disinfectant and strength of choice for that particular pathogen. This process usually includes initial removal of all detachable objects from the room, such as bedding and curtains. The terminal clean also includes wiping down any ventilation components on the ceiling or lighting. Finally, all other surfaces and sites are cleaned downward toward the floor level, and all equipment and items that were removed from the room are wiped over with disinfectant before returning to the room. Automated technologies have been recently introduced and may offer enhanced decontamination. Although these technologies are automated they do not replace routine daily cleaning [39].

In the following study, terminal cleaning, combined with standard infection control policies resulted in 70–40% reduction in patients colonized with MDR *Enterobacteriaceae*. These results were attributed to the overall combined intervention. Universal decolonization has been conducted in many ICUs; particularly, after the results of a landmark trial called REDUCE MRSA [33]. Huang et al. concluded that routine ICU practice and universal decolonization was more effective than targeted decolonization or screening [40]. The universal decolonization was effective at reducing rates of MRSA and bloodstream infection from any pathogen. In the treatment group, the number needed to treat (to prevent one) bloodstream infection was per 99 patients. Other technologies have been explored such automated decontamination devices which include peroxide and UV light. As mentioned earlier, these automated technologies could possibly offer some improvement, but they should not replace routine daily cleaning. Common pitfalls for these techniques include additional training of staff, management and personnel oversight, logistical complexities, and costs of equipment. Future studies are warranted to evaluate overall costs versus benefits [39].

The Affordable Care Act in 2015 mandated that the hospital-acquired condition (HAC) reduction program reduce hospital payments by 1% for hospitals performing at the lowest ranked 25% with regard to hospital-acquired conditions. These conditions include Catheter Associated Urinary Tract Infections (CAUTI) and Central Line Associated Bloodstream Infections (CLABSI). As of 2017, CMS has also added both CDI and MRSA to the program. Given that hospitals are now accountable for these conditions, it is imperative that they have robust infection control policies and procedures and have also successfully implemented antimicrobial stewardship programs as defined by the Joint Commission Medication Management (MM) Standard MM.09.01.01 [41–43].

5. Surveillance

Surveillance systems allow the evaluation of the local and regional healthcare associated infections (HAI) and antimicrobial resistance (AMR) patterns. Surveillance systems contribute to the early detection of HAI and new patterns of AMR, including identifying new clusters or outbreaks. Surveillance is a key component on a local, regional, national, and even on a global scale (WHO) for determining these patterns [44]. Knowing and identifying resistance patterns can help provide guidance to practitioners by means of antibiograms. Antibiograms give the clinician the most appropriate empiric antibiotic information choice while awaiting further confirmation by either phenotypic or genotypic means. The CDC will soon require hospitals

to report their antimicrobial use and resistance patterns into the National Healthcare Safety Network (NHSN). This tracking system is the nation's most widely used for healthcare-associated infection. This process will enable the CDC to benchmark hospitals and assess antimicrobial use by measuring the Standardized Antimicrobial Administration Ratio (SAAR). The measurement is a ratio of observed-to-expected (O-to-E). Ratio values greater than 0, and a value of 1.0 suggests equivalency between the observed and predicted antimicrobial use. Values above 1.0 may indicate statistically significant excessive antimicrobial use [44]. In addition to the CDC, many hospital regulatory agencies such as the Joint Commission and CMS will be enforcing this element as part of complying with antimicrobial stewardship program mandates [42, 43].

6. Mechanisms of resistance

Microorganisms are tenacious at survival, they have been on the Earth for billions of years, and their sole existence is based on their ability to adapt to the environment. This ability for survival despite the introduction of antibiotics is best described antimicrobial resistance. The mechanisms of antimicrobial resistance are as follows: (a) enzymatic degradation of antibiotics via hydrolytic enzymes, (b) alteration of bacterial proteins or target sites, and (c) changes in membrane permeability to antibiotics either by penetration or by expulsion of the actual antibiotic from within the bacteria. Antibiotic resistance can be either plasmid or chromosomal mediated. One of the most important mechanisms of resistance to beta-lactams is enzymatic hydrolysis of the ring structure resulting in inactivity [45]. The chromosomal β -lactamases expression can either be depressed or induced or by the exposure to β -lactam antibiotics. Overcoming resistance to β -lactam antibiotics includes the coadministration of inhibitors to protect the ring structure, and the development of new antibiotics that are stable against enzymatic degradation. By adding a β -lactamase inhibitor to a β -lactam antibiotic, this allows the β -lactam to avoid enzymatic hydrolysis and perform its bactericidal effects. The following are examples of resistance [45]:

- a) Efflux pumps (especially overexpression), which pump the drug out of the cell.
- b) Changes in porin protein channels in outer membrane (decreased number or channel charge alteration), which decreases drug uptake.
- c) Circumvent metabolic pathways.
- d) Enzymatic hydrolysis, i.e., beta-lactamases in Enterobacteriaceae, and nonfermentative Gram-negatives (Acinetobacter).
- e) Change in binding affinity of antibiotic for target, i.e., penicillin-binding proteins, DNA topoisomerases, and ribosomal targets.

Bacterial resistance to β -lactam antibiotics as mentioned earlier is mediated via β -lactamases; this mode is the primary mechanism of resistance. Ambler molecular classification is used to classify β -lactamases and is based on the amino acid sequence and divides the class into four

(A, B, C, and D). A, C, and D enzymes utilize serine for β -lactam hydrolysis and class B metalloenzymes require zinc bivalent metal ion, usually Zn^{2+} ions for substrate hydrolysis [46–48].

Example enzymes are as follows:

- a) Class A enzymes TEM, SHV, ESBL, CTX-M, KPC, PC1, SME, IMI/NMC, GES/IBC.
- b) Class B enzymes MP, VIM, SIM, GIM, SPM, NDM-1.
- c) Class C enzymes AmpC, CMY.
- d) Class D OXA superfamily (OXA-23, OXA-40 in US outbreaks).

Multidrug efflux mechanisms in bacteria contribute significantly to intrinsic and acquired resistance to many antibiotics. Whole genome sequencing has confirmed the broad distribution of these systems in Gram-negative as well as in Gram-positive bacteria. Multidrug efflux systems have given rise to high-level resistance to Gram-negatives, particularly when multiple mechanisms or resistances are simultaneously produced by a single isolate. The efflux system is mediated by transport proteins, which confer resistance antimicrobial agents. The tripartite efflux system in Gram-negative bacteria is necessary to expel the antibiotic to the outer medium. The system consists of (a) protein localized in the cytoplasmic membrane, (b) protein located in the periplasmic space, and (c) a third protein located in the outer membrane. These active transport proteins are grouped in families, which are based on their amino acid sequences and mechanisms. The most identified and studied multidrug efflux systems among Gram-negative bacteria are *P. aeruginosa* and *E. coli* [49].

7. Early detection

The surviving sepsis guidelines now recommend IV antibiotics to be started within 1 h of sepsis recognition and should include combination therapy (at least two classes of antibiotics to cover a known or suspected pathogen) for patients with septic shock. Combination therapy should not routinely be used for patients without shock. Many studies have demonstrated improved survival in early appropriate administration of antibiotics at the first presence of septic shock [50]. Kumar et al. concluded for each hour of delay of appropriate antimicrobials resulted in a mean increase in mortality by 7.6%, with a range 3.6–9.9% [51]. Ferrer et al. published the results of a large population, which concluded that a delay in first antibiotic administration was associated with increased in-hospital mortality in patients with severe sepsis and septic shock [45]. It was also noted that there was a linear risk increase in mortality for every hour delay in antibiotic administration. Another study by Vazquez-Guillamet concluded that improved targeting in multidrug-resistant bacteria would have the greatest impact on reducing overall mortality. In their study, they calculated the number of patients needed to treat and found for every four patients treated with appropriate antimicrobial therapy in severe sepsis and septic shock, it prevents one patient death [52]. The appropriateness of early empiric antibiotics is driven by local hospital-resistance patterns. At times,

selection of the most appropriate empiric antimicrobial regimen may be difficult for the clinician based, appropriate history, comorbidities, risk factors for resistant pathogens, and the complexity of patient transitions of care. Clinicians for decades have depended on phenotypic testing that detects the activity of enzymes (i.e., hydrolysis of antibiotics such as beta-lactams *in vitro*) to provide definitive guidance on antimicrobial therapy. These tests provide the clinician pathogen identity with sensitivity, which may have a turn-around time of up to 72 h. As mentioned above, timing of appropriate antimicrobial therapy is key for patient survival in the critically ill, especially with septic shock. New technological advancements in both phenotypic and genotypic testing (molecular tests that detect the resistance mechanisms of a specific gene) commonly known as “rapid diagnostics” will be able to provide detailed information within several hours versus current standards (48–72 h) [53–56].

See **Tables 2** and **3**.

Procalcitonin (PCT) is an inflammatory biomarker that is an acute phase reactant that reflects host response to bacterial infections. PCT synthesis is up regulated in the presence of bacterial toxins and certain bacterial pro-inflammatory mediators such as TNF α (tumor necrosis factor alpha), interleukin (IL)-1b, IL-6. PCT is neutral to cytokines that are normally released for viral

Rapid nonnucleic acid–based tests and other phenotypic tests (MHT/CIM)			
Manufacturer/product name	Methodology	Detection results	Turnaround time
BioMérieux Rapidec Carba -NP	Detects pH shifts by phenol red indicator that occurs when imipenem is hydrolyzed	Detects (w/o distinction) all three types of carbapenemases: Class A: KPC Class B: NDM/VIM/IMP Class D: OXA	<2 h (after positive culture growth, ~24–48 h)
BioMérieux MALDI-TOF MS Vitek—MS (matrix-assisted laser desorption ionization time of flight mass spectrometry)	Detects change in native carbapenem mass	Provides bacterial (or fungal) identification at the species, genus, or group level (detects carbapenemase activity)	2–4 h
Modified Hodge test (MHT)	CLSI suggested phenotypic confirmatory test. Enhanced growth = (+) for carbapenemase production No enhanced growth = (-) for carbapenemase production	Only confirms the presence of carbapenemases (does not identify specific carbapenemase (i.e., KPC vs. NDM))	18–24 h (after positive culture growth, ~24–48 h)
Carbapenemase Inactivation method (CIM)	Phenotypic confirmatory test	Only confirms the presence of carbapenemases (does not identify specific carbapenemase (i.e., KPC vs. NDM))	If results required within same day can be read after 6 h, but prefer reading results after 12–24 h (after positive culture growth, ~24–48 h)

Table 2. Rapid diagnostic testing methodologies.

Rapid nucleic acid–based tests (molecular test)					
Manufacturer/ product name	Methodology	Specimen type	Organisms identified	Resistance mechanisms identified	Turnaround time
BioFire Diagnostics LLC/ Film Array® Blood Culture Identification Panel (BCID)	Multiplex PCR (detects 23 bacterial species, four resistance mechanisms and <i>Candida</i> spp.)	Blood Other FDA Cleared Panels: Respiratory, GI, Meningitis	Gram-positives: <i>Staph/Strep</i> / <i>Enterococcus</i> / <i>Listeria</i> Gram-negatives: <i>Enterobacteriaceae</i> , <i>Pseudomonas aeruginosa</i> , and <i>Acinetobacter</i> species. Fungus: <i>Candida</i> spp.	<i>mecA</i> <i>vanA/vanB</i> <i>bla</i> _{KPC}	1 h (after blood culture positivity, ~8–24 h)
Nanosphere/ Verigene®	Microarray (detects 15 different Gram- positive targets and 14 different Gram-negative targets (including nine resistance mechanisms)	Blood Other FDA Cleared Panels: Respiratory, GI	Gram-positives: <i>Staph/Strep</i> / <i>Enterococcus</i> / <i>Listeria</i> Gram-negatives: <i>Enterobacteriaceae</i> , <i>Pseudomonas aeruginosa</i> , and <i>Acinetobacter</i> species	<i>mecA</i> <i>vanA/vanB</i> IMP/KPC/NDM OXA/VIM/ CTX-M ESBLs	2.5 h (after blood culture positivity, ~8–24 h)
Cepheid GeneXpert Carba R	“On demand” PCR	Rectal swabs	Gram-negative: <i>Enterobacteriaceae</i> , <i>Pseudomonas aeruginosa</i> , and <i>Acinetobacter</i> species	IMP/KPC/NDM/ OXA*/VIM *(Includes OXA- 48, OXA-181, OXA-232)	48 min (can test directly from clinical specimen)

Table 3. Rapid diagnostic testing methodologies.

infections such as interferon- γ . PCT concentrations are undetectable (less than 0.05 ng/mL). However, PCT is immediately released within 2–4 h upon exposure to bacterial toxins. The plasma half-life of PCT is approximately 24 h. Concentrations in the literature have varied for infected patients; however, as higher max concentrations of PCT are released during infection, this tends to correlate with a higher incidence of mortality. In the critically ill baseline PCT levels should be obtained with signs and symptoms of infection as a means of trending. A low PCT level or an ample decrease from baseline along with clinical review during the course of therapy should be interpreted to discontinue antimicrobial therapy. This methodology is part of an antimicrobial stewardship program, which reduces unnecessary antibiotics and also decreases duration. PCT has been proven to effective and safe in various critically ill patients. Many published studies have evaluated the utility of a PCT-guided strategy for determining the appropriate time to discontinue and/or de-escalate antibiotics in patients with varying severity of illnesses with documented infections. These studies have resulted in decreased unnecessary use of antibiotics [50].

8. Treatment

As described earlier, prompt administration with appropriate empiric broad-spectrum antibiotics within 1 h of recognizing sepsis or septic shock has shown to improve survival. The surviving sepsis guidelines recommend initial selection of antimicrobial therapy to broad or “shot gun” approach. This approach ensures that the likely pathogen will be covered. If not, survival may decrease as much as fivefold for septic shock if the initial empiric regimen fails to cover the offending pathogen [50]. The choice of empiric antimicrobial therapy depends on factors related to clinical status, the patient’s history, and local epidemiologic factors (see below). Due to the high mortality associated with inappropriate initial therapy, empiric treatment choices should be broad initially, with constant evaluation to de-escalate the regimen once cultures and results have been determined. The guidelines also address several factors in determining the appropriate antimicrobial regimens:

- a) The site of infection, pathogen profile, and antimicrobial pharmacokinetics and pharmacodynamics (PK/PD) as it relates to penetration at the site.
- b) Prevalence of pathogens in the community, hospital, and specific hospital locations, i.e., critical care unit by means of surveillance is an important determinant.
- c) The resistance patterns of prevalent pathogens in the form of antibiograms or surveillance programs.
- d) Status of the patient, i.e., immunocompromised patients such as HIV infection, splenectomy, neutropenia, congenital defects of immunoglobulin, complement, or leukocyte dysfunction.
- e) Age and patient comorbidities, the presence of invasive devices that compromise the host defenses [50].

Since majority of the patients with severe sepsis do have some form of immunocompromised status, the broad-spectrum antibiotics should be initiated [50]. Clinicians should assess these statuses of β -lactam and carbapenem resistance in their local communities. Physicians should also consider adding another Gram-negative coverage to cover *Pseudomonas* or *Acinetobacter* infections [57]. It holds true for covering for MRSA infections in patients with suspicion or risk factors for those infections. In patients who are immunocompromised with immunosuppressive medications, neutropenia, liver or renal failure, on total parenteral nutrition the coverage for the candida infection needs to be considered [58].

Dosing patients with severe sepsis and septic shock should be centered on pharmacokinetics/pharmacodynamics (PK/PD) and drug properties as per the recommendation of surviving sepsis committee [50]. In most instances, the inability to achieve a therapeutic response can be attributed to the failure of optimizing PK/PD, i.e., failure of target attainment by means of reduced initial dosing or inadequate achievable troughs with subsequent dosing [59]. For optimum dosing for fluoroquinolones and aminoglycoside, it requires to optimize the peak plasma level. For aminoglycoside, it can be achieved by 5–7 mg/kg daily gentamicin dose or

equivalent. For fluoroquinolones, one should consider dosing for ciprofloxacin at 600 mg, every 12 hourly and for levofloxacin at 750 mg Q 24 hourly [60–62].

For vancomycin, trough levels of 15–20 mg/L have been advocated. In addition, drugs with a low volume of distribution such as vancomycin and colistin, a higher loading dose is suggested [63–65]. For the β -lactams, it is the time when the plasma concentration of the drug should be above the pathogen minimum inhibitory concentration (MIC) level. It is suggested to have the $T > MIC$ (time above the minimum inhibitory concentration) of 60% and greater to have good efficacy, but among patients with sepsis a level of $T > MIC$ of 100% may be needed. This is achieved by prolonging the infusion either as an extended or continuous infusion [50, 66].

In regard to the duration of antimicrobial therapy, per surviving sepsis guidelines, the duration of 7–10 days is adequate for most serious infections associated with sepsis and septic shock. In the 2016, management of adults with hospital-acquired and ventilator-associated pneumonia, 7 days are appropriate for those patients that respond to therapy early on and show clinical improvement (see below). Longer courses can be appropriate for patients who are slow responders or immunocompromised patients, and patients with MDR organisms, some fungal, or viral infections or MRSA [50]. Patients with endocarditis, osteomyelitis and larger abscesses may also require longer duration of therapy [50].

Multidrug-resistant pathogens are associated with increased morbidity and mortality and are certainly challenging to treat. We have described the surviving sepsis guidelines and recently published the 2016 Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: Clinical Practice Guidelines by the Infectious Diseases Society of America. These guidelines make recommendations for the diagnosis and treatment of Hospital-acquired pneumonia (HAP) and Ventilator-associated pneumonia (VAP) and are evidence-based derived from systematic literature reviews (**Table 4**).

Detailed pathogen recommendation is beyond the scope of this chapter, but we included an extensive review on Minocin IV. Minocin IV has an FDA approved indication for *Acinetobacter spp.* and not referenced in the guidelines above, but it has been used with success against *Acinetobacter*, including MDR and XDR strains. MINOCIN® (minocycline) [67] IV has been reformulated, the new formulation contains magnesium sulfate heptahydrate and can be infused in as low as 100 mL to as high as 1000 mL over 60 min. It has a new pH of 4.5–6.0 when diluted.

Resistance to β -lactams has resulted in the resurrection of shelf toxic agents, i.e., the polymyxins. Tigecycline and sulbactam are not FDA approved for treatment of infections due to *Acinetobacter*. A recent meta-analysis evaluating the use of tigecycline against *Acinetobacter* infections disfavor its use due to an associated higher in-hospital mortality (OR = 1.57, 95% CI 1.04–2.35; $P = 0.03$) [68].

Tetracyclines, as a class, have shown consistent *in vitro* activity against *Acinetobacter* [20, 21]. Increasing levels of multidrug resistance with *Acinetobacter* have led clinicians to reevaluate certain tetracyclines with good *in vitro* activity. Studies of minocycline in *Acinetobacter* infections have shown clinical success ranging from 67 to 88% [21, 69–73]. Minocycline has approved breakpoints for *Acinetobacter* set forth by the Clinical and Laboratory Standards Institute (CLSI) [54]. These breakpoints are shown in **Table 5**.

A. Gram-positive antibiotics with MRSA activity	B. Gram-negative antibiotics with antipseudomonal activity: β -lactam-based agents	C. Gram-negative antibiotics with antipseudomonal activity: non- β -lactam-based agents
Glycopeptides Vancomycin 15 mg/kg IV q8-12h (Consider a loading dose of 25–30 mg/kg \times 1 for severe illness)	Antipseudomonal penicillins Piperacillin-tazobactam 4.5 g IV q6h	Fluoroquinolones Ciprofloxacin 400 mg IV q8h Levofloxacin 750 mg IV q24h
OR	OR	OR
Oxazolidinones Linezolid 600 mg IV q12h	Cephalosporins Cefepime 2 g IV q8h Ceftazidime 2 g IV q8h	Aminoglycosides Amikacin 15–20 mg/kg IV q24h Gentamicin 5–7 mg/kg IV q24h Tobramycin 5–7 mg/kg IV q24h
	OR	OR
	Carbapenems Imipenem 500 mg IV q6hd Meropenem 1 g IV q8h	Polymyxins Colistin 5 mg/kg IV \times 1 (loading dose) followed by 2.5 mg \times (1.5 \times CrCl + 30) IV q12h (maintenance dose) Polymyxin B 2.5–3.0 mg/kg/d divided in 2 daily IV doses
	OR	
	Monobactams Aztreonam 2 g IV q8h	

Notes: Please refer to these guidelines for the complete table, HAP recommendations and detailed pathogen recommendations that can be found at: <https://www.thoracic.org/statements/resources/tb-opi/hap-vap-guidelines-2016.pdf>

Table 4. Summary of recommendations for suggested empiric treatment options for clinically suspected ventilator-associated pneumonia.

MIC (μ g/mL)	Interpretation
≤ 4.0	Susceptible (S)
8.0	Intermediate (I)
≥ 16.0	Resistant (R)

Table 5. Clinical and Laboratory Standards Institute MIC and disk breakpoints available for minocycline and *Acinetobacter* spp.

CLSI recommends separate *Acinetobacter* susceptibility results for minocycline since surrogate testing with other tetracyclines will underestimate susceptibility. Several retrospective studies have documented that lower mortality rates seen with combination therapy are used against MDR *A. baumannii* infections.

Minocycline IV has been used in combination therapy to achieve synergistic activity and to maximize antimicrobial activity in severely ill patients, or to prevent emergence of resistance [74]. Minocycline and colistin combinations demonstrated bactericidal and synergistic

activity against imipenem-resistant *A. baumannii* and MDR *A. baumannii* clinical isolates [75]. Combinations of minocycline plus meropenem and minocycline plus colistin were found to be synergistic *in vitro* against XDR *A. baumannii*. The package insert (PI) has an initial dose of 200 mg, with subsequent doses of 100 mg administered over 60 min every 12 h. Minocycline is very lipophilic compared to other tetracyclines. It has a very unique pharmacokinetic/pharmacodynamic profile (PK/PD) [67]:

- a) Peak concentrations following 200-mg load (mean) = 4.18 µg/mL (range, 2.52–6.63 µg/mL).
- b) Trough concentration of (1.4–1.8 µg/mL) with 100-mg dosing every 12 h.
- c) These achievable peak and trough serum concentrations with standard human doses of minocycline intravenous exceed the mutant prevention concentration of 1 µg/mL, which has been reported with *Acinetobacter*.
- d) Half-life of 15–23 h.
- e) The mean concentration of minocycline in lung parenchyma has been reported to be 378% of that in plasma.
- f) Urinary excretion 11%.
- g) Renal dysfunction does not appear to alter the maximum serum concentrations of minocycline.
- h) Bactericidal activity in combination with carbapenems or colistin against *A. baumannii*.

9. Importance of antimicrobial stewardship programs, outcomes, and new regulatory mandate from the Joint Commission (7 CDC elements)

According to the World Health Organization (WHO), “Antimicrobial resistance threatens the effective prevention and treatment of an ever-increasing range of infections caused by bacteria, parasites, viruses, and fungi.” The Centers for Disease Control and Prevention (CDC) has identified that 20–50% of all antibiotics prescribed in the U.S. acute care hospitals are either inappropriate or unnecessary. The CDC has also stated that “Antibiotics are among the most commonly prescribed medications in nursing homes. Up to 70% of long-term care facilities’ residents receive an antibiotic every year [76].”

White House held the antibiotic stewardship program in June, 2015, in which the Joint Commission participated along with more than 150 major healthcare organizations and other relevant organizations for helping to implement changes over the next 5 years to decrease the rate of emergence of antibiotic-resistant bacteria, to help detect the resistant strains, help preserve the efficacy of existing antibiotics, and also more importantly regulate to prevent the spread of resistant infections [76].

The Joint Commission has also developed the antimicrobial stewardship standard for hospitals, critical access hospitals, nursing care centers, ambulatory care organizations, and

Official Publication of Joint Commission Requirements New Antimicrobial Stewardship Standard
 Applicable to Hospitals and Critical Access Hospitals Effective January 1, 2017 Medication Management (MM)
 Standard MM.09.01.01 The critical access hospital has an antimicrobial stewardship program based on current
 scientific literature.

1. Leaders establish antimicrobial stewardship as an organizational priority. (See also LD.01.03.01, EP 5)
Note: Examples of leadership commitment to an antimicrobial stewardship program are as follows:

- Accountability documents
- Budget plans
- Infection prevention plans
- Performance improvement plans
- Strategic plans
- Using the electronic health record to collect antimicrobial stewardship data

3. The critical access hospital educates patients, and their families as needed, regarding the appropriate use of antimicrobial medications, including antibiotics. (For more information on patient education, refer to Standard PC.02.03.01)

Note: An example of an educational tool that can be used for patients and families includes the Centers for Disease Control and Prevention's Get Smart document, "Viruses or Bacteria—What's got you sick? At <https://www.cdc.gov/antibiotic-use/community/pdfs/Viruses-or-Bacteria-Factsheet-Eng.pdf>

2. The critical access hospital educates staff and licensed independent practitioners involved in antimicrobial ordering, dispensing, administration, and monitoring about antimicrobial resistance and antimicrobial stewardship practices. Education occurs upon hire or granting of initial privileges and periodically thereafter, based on organizational need

4. The critical access hospital has an antimicrobial stewardship multidisciplinary team that includes the following members, when available in the setting:

- Infectious disease physician
- Infection preventionist(s)
- Pharmacist(s)
- Practitioner

Note 1: Part-time or consultant staff are acceptable as members of the antimicrobial stewardship multidisciplinary team

Note 2: Telehealth staffs are acceptable as members of the antimicrobial stewardship multidisciplinary team

5. The critical access hospital's antimicrobial stewardship program includes the following CDC core elements:

- Leadership commitment: Dedicating necessary human, financial, and information technology resources.
- Accountability: Appointing a single leader responsible for program outcomes. Experience with successful programs shows that a physician leader is effective.
- Drug expertise: Appointing a single pharmacist leader responsible for working to improve antibiotic use.
- Action: Implementing recommended actions, such as systemic evaluation of on-going treatment need, after a set period of initial treatment (for example, "antibiotic time out" after 48 h).
- Tracking: Monitoring the antimicrobial stewardship program, which may include information on antibiotic prescribing and resistance patterns.
- Reporting: Regularly reporting information on the antimicrobial stewardship program, which may include information on antibiotic use and resistance, to doctors, nurses, and relevant staff.
- Education: Educating practitioners, staff, and patients on the antimicrobial program, which may include information about resistance and optimal prescribing. (See also IC.02.01.01, EP 1 and NPSG.07.03.01, EP 5)

Note: These core elements were cited from the Centers for Disease Control and Prevention's Core Elements of Hospital Antibiotic Stewardship Programs (<https://www.cdc.gov/antibiotic-use/healthcare/pdfs/core-elements.pdf>)

<p>6. The critical access hospital’s antimicrobial stewardship program uses organization-approved multidisciplinary protocols (for example, policies and procedures). Note: Examples of protocols are as follows:</p> <ul style="list-style-type: none">• Antibiotic Formulary Restrictions• Assessment of Appropriateness of Antibiotics for Community-Acquired Pneumonia• Assessment of Appropriateness of Antibiotics for Skin and Soft Tissue Infections• Assessment of Appropriateness of Antibiotics for Urinary Tract Infections• Care of the Patient with <i>Clostridium difficile</i> (c. -diff)• Guidelines for Antimicrobial Use in Adults• Guidelines for Antimicrobial Use in Pediatrics• Plan for Parenteral to Oral Antibiotic Conversion• Preauthorization Requirements for Specific Antimicrobials• Use of Prophylactic Antibiotics <p>8. The critical access hospital takes action on improvement opportunities identified in its antimicrobial stewardship program. (See also MM.08.01.01, EP 6)</p>	<p>7. The critical access hospital collects, analyzes, and reports data on its antimicrobial stewardship program Note: Examples of topics to collect and analyze data on may include evaluation of the antimicrobial stewardship program, antimicrobial prescribing patterns, and antimicrobial resistance patterns</p>
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Adopted from https://www.jointcommission.org/assets/1/6/New_Antimicrobial_Stewardship_Standard.pdf.

Table 6. The New Joint Commission antimicrobial stewardship standard: MM.09.01.01.

office-based surgery practices in standard with the following governmental and professional organizations: Centers for Medicare & Medicaid Services (CMS), the CDC, and the Society for Healthcare Epidemiology of America (SHEA) (**Table 6**).

10. Future pipeline in phase III development

There has been emergence and increase of MDR pathogens. Efforts have been made toward adequate treatment, daily de-escalation regimen as well as antibiotic stewardship programs. The pipeline for the new drugs is still sparse. **Table 7** illustrates the antibiotics that are in the phase 3 trials. Only very few have an expected activity against the CDC urgent threat potential (**Table 7**).

11. Conclusion

Antimicrobial resistance has risen at threatening levels within the past few decades and has contributed to an economic burden on healthcare expenditures. Several governmental agencies including the WHO, CDC, and the White House are focused on combating antimicrobial resistance at various steps. Acquisition of multidrug-resistant organisms in patients has established an

Drug name	Development phase	Company	Drug class	Expected activity against resistant Gram-negative ESKAPE pathogens?	Expected activity against a CDC urgent threat pathogen? ⁴
Zabofloxacin	Phase 3	Dong Wha Pharmaceutical Co. Ltd	Fluoroquinolone	No	No
S-649266	Phase 3	Shionogi Inc.	Cephalosporin	Yes	Yes
Omadacycline	Phase 3	Paratek Pharmaceuticals Inc.	Tetracycline	Yes	Possible
Lefamulin (BC-3781)	Phase 3	Nabriva Therapeutics AG	Pleuromutilin	No	No
Imipenem/cilastatin+relebactam (MK-7655)	Phase 3	Merck & Co. Inc.	Carbapenem+novel beta-lactamase inhibitor	Yes	Yes
Iclaprim	Phase 3	Motif Bio PLC	Dihydrofolate reductase (DHFR) inhibitor	No	No
Cadazolid	Phase 3	Actelion Pharmaceuticals Ltd.	Quinolonyl- oxazolidinone	No	Yes
Taksta (fusidic acid)	Phase 3	Cempra Inc.	Fusidane	No	No
Carbavance (vaborbactam+meropenem)	Phase 3	Rempex Pharmaceuticals Inc. (wholly owned subsidiary of the Medicines Co.)	Meropenem+novel boronic beta-lactamase inhibitor	Yes	Yes
Baxdela (delafloxacin)	Phase 3	Melinta Therapeutics Inc.	Fluoroquinolone	Possible	Possible
Eravacycline	Phase 3	Tetraphase Pharmaceuticals Inc.	Tetracycline	Yes	Yes
Plazomicin	Phase 3	Achaogen Inc.	Aminoglycoside	Yes	Yes
Solithromycin	Phase 3	Cempra Inc.	Macrolide (fluoroketolide)	No	Yes

Source: Adopted with permission from: <http://www.pewtrusts.org/~media/assets/2016/05/antibiotics-currently-in-clinical-development.pdf>. Full table for drugs in phase 1 and phase 2 is available from this site.

Table 7. New antibiotics currently in clinical development.

independent risk factor for mortality. Clinical expertise, risk stratification, surveillance, infection control, and the use of rapid diagnostics may be key to early identification of resistant pathogens; furthermore, appropriate antimicrobial selection and dose optimization via PK/PD are critical in improving outcomes and survival. Various studies have demonstrated the correlation between survival and appropriate early initial antibiotics. Antimicrobial stewardship programs have been shown to reduce antimicrobial resistance and are now considered a regulatory mandate. CMS and TJC have developed guidance for accreditation as it relates to demonstrating an effective antimicrobial stewardship program, including developing publicly reportable measures.

In recent years, we have seen high-level resistance to last-line agents such as carbapenems. Inappropriate usage and a reduced antimicrobial pipeline have driven this crisis. Several companies are dedicated to the research and development of new antimicrobials for our armamentarium in combating multidrug-resistant organisms and preventing a preantibiotic era. Education will be vital across all healthcare disciplines, including to patients, as this will ultimately ensure optimal prescribing.

Conflict of Interest

Salim Surani has no conflict of interest to disclose. Mauricio Rodriguez is an employee of Medicine Company. No conflict persists pertaining to this chapter.

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References

- [1] Ventola CL. The antibiotic resistance crisis: Part 1: Causes and threats. *P & T: A Peer-Reviewed Journal for Formulary Management*. 2015;**40**(4):277-283 [PMID: 25859123 PMCID: 4378521]
- [2] Ventola CL. The antibiotic resistance crisis: Part 2: Management strategies and new agents. *P & T: A Peer-Reviewed Journal for Formulary Management*. 2015;**40**(5):344-352 [PMID: 25987823 PMCID: 4422635]

- [3] Boucher HW, Talbot GH, Bradley JS, Edwards JE, Gilbert D, Rice LB, Scheld M, Spellberg B, Bartlett J. Bad bugs, no drugs: No ESKAPE! An update from the Infectious Diseases Society of America. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*. 2009;**48**(1):1-12 [PMID: 19035777 DOI: 10.1086/595011]
- [4] Talbot GH, Bradley J, Edwards Jr JE, Gilbert D, Scheld M, Bartlett JG, Antimicrobial availability task force of the infectious diseases society of A. Bad bugs need drugs: An update on the development pipeline from the Antimicrobial availability task force of the infectious diseases society of America. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*. 2006;**42**(5):657-668 [PMID: 16447111 DOI: 10.1086/499819]
- [5] Antibiotics Resistance Threat in the US. US Department of Health & Human Services; Centers for Disease Control and Prevention [Internet]. 2013. Available from: <http://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf> [Accessed: March 16, 2017]
- [6] President Advisory Council on Combating Antibiotic-resistant Bacteria. HHS. Gov. 2015. Available from: [http://www.hhs.gov/ash/advisory.committees/paccarb/\\$](http://www.hhs.gov/ash/advisory.committees/paccarb/$) [Accessed: March 16, 2017]
- [7] Detsis M, Karanika S, Mylonakis E. ICU acquisition rate, risk factors, and clinical significance of digestive tract colonization with extended-spectrum beta-lactamase-producing enterobacteriaceae: A systematic review and meta-analysis. *Critical Care Medicine*. 2017;**45**(4):705-714. [PMID: 28157141 DOI: 10.1097/CCM.0000000000002253]
- [8] Vardakas KZ, Rafailidis PI, Konstantelias AA, Falagas ME. Predictors of mortality in patients with infections due to multi-drug resistant Gram negative bacteria: The study, the patient, the bug or the drug? *The Journal of Infection*. 2013;**66**(5):401-414 [PMID: 23142195 DOI: 10.1016/j.jinf.2012.10.028]
- [9] Munoz-Price LS, Poirel L, Bonomo RA, Schwaber MJ, Daikos GL, Cormican M, Cornaglia G, Garau J, Gniadkowski M, Hayden MK, Kumarasamy K, Livermore DM, Maya JJ, Nordmann P, Patel JB, Paterson DL, Pitout J, Villegas MV, Wang H, Woodford N, Quinn JP. Clinical epidemiology of the global expansion of *Klebsiella pneumoniae* carbapenemases. *The Lancet Infectious Diseases*. 2013;**13**(9):785-796 [PMID: 23969216 PMCID: 4673667 DOI: 10.1016/S1473-3099(13)70190-7]
- [10] Guh AY, Bulens SN, Mu Y, Jacob JT, Reno J, Scott J, Wilson LE, Vaeth E, Lynfield R, Shaw KM, Vagnone PM, Bamberg WM, Janelle SJ, Dumyati G, Concannon C, Beldavs Z, Cunningham M, Cassidy PM, Phipps EC, Kenslow N, Travis T, Lonsway D, Rasheed JK, Limbago BM, Kallen AJ. Epidemiology of carbapenem-resistant enterobacteriaceae in 7 US communities, 2012-2013. *Journal of the American Medical Association*. 2015;**314**(14):1479-1487 [PMID: 26436831 DOI: 10.1001/jama.2015.12480]
- [11] Spellberg B, Rex JH. The value of single-pathogen antibacterial agents. *Nature Reviews Drug Discovery*. 2013;**12**(12):963 [PMID: 24232373 PMCID: 4012226 DOI: 10.1038/nrd3957-c1]

- [12] van Duin D, Perez F, Rudin SD, Cober E, Hanrahan J, Ziegler J, Webber R, Fox J, Mason P, Richter SS, Cline M, Hall GS, Kaye KS, Jacobs MR, Kalayjian RC, Salata RA, Segre JA, Conlan S, Evans S, Fowler Jr VG, Bonomo RA. Surveillance of carbapenem-resistant *Klebsiella pneumoniae*: Tracking molecular epidemiology and outcomes through a regional network. *Antimicrobial Agents and Chemotherapy*. 2014;**58**(7):4035-4041 [PMID: 24798270 PMCID: 4068524 DOI: 10.1128/AAC.02636-14]
- [13] Lin MY, Lyles-Banks RD, Lolans K, Hines DW, Spear JB, Petrak R, Trick WE, Weinstein RA, Hayden MK, Centers for Disease C, Prevention Epicenters P. The importance of long-term acute care hospitals in the regional epidemiology of *Klebsiella pneumoniae* carbapenemase-producing enterobacteriaceae. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*. 2013;**57**(9):1246-1252 [PMID: 23946222 DOI: 10.1093/cid/cit500]
- [14] Kim UJ, Kim HK, An JH, Cho SK, Park KH, Jang HC. Update on the epidemiology, treatment, and outcomes of carbapenem-resistant acinetobacter infections. *Chonnam Medical Journal*. 2014;**50**(2):37-44 [PMID: 25229014 PMCID: 4161759 DOI: 10.4068/cmj.2014.50.2.37]
- [15] Munoz-Price LS, Weinstein RA. Acinetobacter infection. *The New England Journal of Medicine*. 2008;**358**(12):1271-1281 [PMID: 18354105 DOI: 10.1056/NEJMra070741]
- [16] Cerqueira GM, Peleg AY. Insights into *Acinetobacter baumannii* pathogenicity. *IUBMB Life*. 2011;**63**(12):1055-1060 [PMID: 21989983 DOI: 10.1002/iub.533]
- [17] Bennett JE, Raphael D, Blaser MJ. Mandell, Douglas and Bennett's Principles and Practices of Infectious Disease. 8th ed. Philadelphia: Saunders; 2014
- [18] Al-Anazi KA, Abdalhamid B, Alshibani Z, Awad K, Alzayed A, Hassan H, Alsayiegh M. *Acinetobacter baumannii* septicemia in a recipient of an allogeneic hematopoietic stem cell transplantation. *Case Reports in Transplantation*. 2012;**2012**:646195 [PMID: 23259136 PMCID: 3504248 DOI: 10.1155/2012/646195]
- [19] Al-Anazi KA, Al-Jasser AM. Infections caused by *Acinetobacter baumannii* in recipients of hematopoietic stem cell transplantation. *Frontiers in Oncology*. 2014;**4**:186 [PMID: 25072028 PMCID: 4095644 DOI: 10.3389/fonc.2014.00186]
- [20] Castanheira M, Mendes RE, Jones RN. Update on *Acinetobacter* species: Mechanisms of antimicrobial resistance and contemporary in vitro activity of minocycline and other treatment options. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*. 2014;**59**(Suppl 6):S367–S373 [PMID: 25371512 DOI: 10.1093/cid/ciu706]
- [21] Denys GA, Renzi PB, Koch KM, Wissel CM. Three-way comparison of BBL CHROMagar MRSA II, MRSASelect, and spectra MRSA for detection of methicillin-resistant *Staphylococcus aureus* isolates in nasal surveillance cultures. *Journal of Clinical Microbiology*. 2013;**51**(1):202-205 [PMID: 23135930 PMCID: 3536262 DOI: 10.1128/JCM.02022-12]
- [22] Doi Y, Park YS, Rivera JI, Adams-Haduch JM, Hingwe A, Sordillo EM, Lewis 2nd JS, Howard WJ, Johnson LE, Polsky B, Jorgensen JH, Richter SS, Shutt KA, Paterson DL.

Community-associated extended-spectrum beta-lactamase-producing *Escherichia coli* infection in the United States. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*. 2013;**56**(5):641-648 [PMID: 23150211 PMCID: 3563390 DOI: 10.1093/cid/cis942]

- [23] Ben-Ami R, Schwaber MJ, Navon-Venezia S, Schwartz D, Giladi M, Chmelnitsky I, Leavitt A, Carmeli Y. Influx of extended-spectrum beta-lactamase-producing enterobacteriaceae into the hospital. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*. 2006;**42**(7):925-934 [PMID: 16511754 DOI: 10.1086/500936]
- [24] Ben-Ami R, Rodriguez-Bano J, Arslan H, Pitout JD, Quentin C, Calbo ES, Azap OK, Arpin C, Pascual A, Livermore DM, Garau J, Carmeli Y. A multinational survey of risk factors for infection with extended-spectrum beta-lactamase-producing enterobacteriaceae in nonhospitalized patients. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*. 2009;**49**(5):682-690 [PMID: 19622043 DOI: 10.1086/604713]
- [25] Denisuik AJ, Lagace-Wiens PR, Pitout JD, Mulvey MR, Simner PJ, Tailor F, Karlowsky JA, Hoban DJ, Adam HJ, Zhanel GG, Canadian Antimicrobial Resistance A. Molecular epidemiology of extended-spectrum beta-lactamase-, AmpC beta-lactamase- and carbapenemase-producing *Escherichia coli* and *Klebsiella pneumoniae* isolated from Canadian hospitals over a 5 year period: CANWARD 2007-11. *The Journal of Antimicrobial Chemotherapy*. 2013;**68**(Suppl 1):i57-i65 [PMID: 23587779 DOI: 10.1093/jac/dkt027]
- [26] Harris PN. Clinical management of infections caused by Enterobacteriaceae that express extended-spectrum Beta-lactamase and AmpC enzymes. *Seminars in Respiratory and Critical Care Medicine*. 2015;**36**(1):56-73
- [27] Stuart RL, Kotsanas D, Webb B, Vandergraaf S, Gillespie EE, Hogg GG, Korman TM. Prevalence of antimicrobial-resistant organisms in residential aged care facilities. *The Medical Journal of Australia*. 2011;**195**(9):530-533 [PMID: 22060088]
- [28] Ha YE, Kang CI, Cha MK, Park SY, Wi YM, Chung DR, Peck KR, Lee NY, Song JH. Epidemiology and clinical outcomes of bloodstream infections caused by extended-spectrum beta-lactamase-producing *Escherichia coli* in patients with cancer. *International Journal of Antimicrobial Agents*. 2013;**42**(5):403-409 [PMID: 24071027 DOI: 10.1016/j.ijantimicag.2013.07.018]
- [29] Kollef MH, Chastre J, Fagon JY, Francois B, Niederman MS, Rello J, Torres A, Vincent JL, Wunderink RG, Go KW, Rehm C. Global prospective epidemiologic and surveillance study of ventilator-associated pneumonia due to *Pseudomonas aeruginosa*. *Critical Care Medicine*. 2014;**42**(10):2178-2187 [PMID: 25054674 DOI: 10.1097/CCM.0000000000000510]
- [30] Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, Harbarth S, Hindler JF, Kahlmeter G, Olsson-Liljequist B, Paterson DL, Rice LB, Stelling J, Struelens MJ, Vatopoulos A, Weber JT, Monnet DL. Multidrug-resistant, extensively drug-resistant and pan drug-resistant bacteria: An international expert proposal for interim standard definitions for acquired resistance. *Clinical Microbiology and Infection: The Official*

- Publication of the European Society of Clinical Microbiology and Infectious Diseases. 2012;**18**(3):268-281 [PMID: 21793988 DOI: 10.1111/j.1469-0691.2011.03570.x]
- [31] Hirsch EB, Tam VH. Impact of multidrug-resistant *Pseudomonas aeruginosa* infection on patient outcomes. *Expert Review of Pharmacoeconomics & Outcomes Research*. 2010;**10**(4):441-451 [PMID: 20715920 PMCID: 3071543 DOI: 10.1586/erp.10.49]
- [32] McCarthy K. *Pseudomonas aeruginosa*: Evolution of antimicrobial resistance and implications for therapy. *Seminars in Respiratory and Critical Care Medicine*. 2015;**36**(1):44-55 [PMID: 25643270 DOI: 10.1055/s-0034-1396907]
- [33] Huang SS, Datta R, Platt R. Risk of acquiring antibiotic-resistant bacteria from prior room occupants. *Archives of Internal Medicine*. 2006;**166**(18):1945-1951 [PMID: 17030826 DOI: 10.1001/archinte.166.18.1945]
- [34] Drees M, Snyderman DR, Schmid CH, Barefoot L, Hansjosten K, Vue PM, Cronin M, Nasraway SA, Golan Y. Prior environmental contamination increases the risk of acquisition of vancomycin-resistant enterococci. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*. 2008;**46**(5):678-685 [PMID: 18230044 DOI: 10.1086/527394]
- [35] Wilks M, Wilson A, Warwick S, Price E, Kennedy D, Ely A, Millar MR. Control of an outbreak of multidrug-resistant *Acinetobacter baumannii*-calcoaceticus colonization and infection in an intensive care unit (ICU) without closing the ICU or placing patients in isolation. *Infection Control and Hospital Epidemiology*. 2006;**27**(7):654-658 [PMID: 16807837 DOI: 10.1086/507011]
- [36] Nseir S, Blazejewski C, Lubret R, Wallet F, Courcol R, Durocher A. Risk of acquiring multidrug-resistant Gram-negative bacilli from prior room occupants in the intensive care unit. *Clinical Microbiology and Infection: The Official Publication of the European Society of Clinical Microbiology and Infectious Diseases*. 2011;**17**(8):1201-1208 [PMID: 21054665 DOI: 10.1111/j.1469-0691.2010.03420.x]
- [37] Shaughnessy MK, Micielli RL, DePestel DD, Arndt J, Strachan CL, Welch KB, Chenoweth CE. Evaluation of hospital room assignment and acquisition of *Clostridium difficile* infection. *Infection Control and Hospital Epidemiology*. 2011;**32**(3):201-206 [PMID: 21460503 DOI: 10.1086/658669]
- [38] Dancer SJ, Carling PC. All that glistens may be neither gold nor clean. *The Journal of Hospital Infection*. 2010;**76**(2):177-178 [PMID: 20691502 DOI: 10.1016/j.jhin.2010.06.008]
- [39] Dancer SJ. Controlling hospital-acquired infection: Focus on the role of the environment and new technologies for decontamination. *Clinical Microbiology Reviews*. 2014;**27**(4):665-690 [PMID: 25278571 PMCID: 4187643 DOI: 10.1128/CMR.00020-14]
- [40] Huang SS, Septimus E, Kleinman K, Moody J, Hickok J, Avery TR, Lankiewicz J, Gombos A, Terpstra L, Hartford F, Hayden MK, Jernigan JA, Weinstein RA, Fraser VJ, Haffenreffer K, Cui E, Kaganov RE, Lolans K, Perlin JB, Platt R, Program

- CDCPE, Network AD, Healthcare-Associated Infections P. Targeted versus universal decolonization to prevent ICU infection. *The New England Journal of Medicine*. 2013;**368**(24):2255-2265 [PMID: 23718152 DOI: 10.1056/NEJMoa1207290]
- [41] Patient Safety 2015. National Quality Forum, 2015. 2015. Available from: <http://www.qualityforum.org/qps/2720> [Accessed: July 3, 2017]
- [42] Commission TJ. New Antimicrobial Stewardship Standard. 2016. Available from: http://www.jointcommission.org/assets/1/6/hap-cah_antimicrobial_prepub.pdf [Accessed: July 3, 2017]
- [43] Forum NQ. National Quality Partners Playbook: Antibiotic Stewardship in Acute Care. National Quality Forum. 2016. Available from: http://www.qualityforum.org/nqp/antibiotic_stewardship_playbook.aspx [Accessed: July 2, 2017]
- [44] Storr J, Twyman A, Zingg W, Damani N, Kilpatrick C, Reilly J, Price L, Egger M, Grayson ML, Kelley E, Allegranzi B, Group WHOGD. Core components for effective infection prevention and control programmes: New WHO evidence-based recommendations. *Antimicrobial resistance and Infection Control*. 2017;**6**:6 [PMID: 28078082 PMCID: 5223492 DOI: 10.1186/s13756-016-0149-9]
- [45] Ferrer R, Martin-Loeches I, Phillips G, Osborn TM, Townsend S, Dellinger RP, Artigas A, Schorr C, Levy MM. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: Results from a guideline-based performance improvement program. *Critical Care Medicine*. 2014;**42**(8):1749-1755 [PMID: 24717459 DOI: 10.1097/CCM.0000000000000330]
- [46] Tenover FC. Mechanisms of antimicrobial resistance in bacteria. *The American Journal of Medicine*. 2006;**119**(6 Suppl 1):S3-S10; discussion S62-70 [PMID: 16735149 DOI: 10.1016/j.amjmed.2006.03.011]
- [47] Jacoby GA, Munoz-Price LS. The new beta-lactamases. *The New England Journal of Medicine*. 2005;**352**(4):380-391 [PMID: 15673804 DOI: 10.1056/NEJMra041359]
- [48] Bush K, Jacoby GA. Updated functional classification of beta-lactamases. *Antimicrobial Agents and Chemotherapy*. 2010;**54**(3):969-976 [PMID: 19995920 PMCID: 2825993 DOI: 10.1128/AAC.01009-09]
- [49] Li XZ, Ma D, Livermore DM, Nikaido H. Role of efflux pump(s) in intrinsic resistance of *Pseudomonas aeruginosa*: Active efflux as a contributing factor to beta-lactam resistance. *Antimicrobial Agents and Chemotherapy*. 1994;**38**(8):1742-1752 [PMID: 7986004 PMCID: 284631]
- [50] Rhodes, A., Evans, L.E., Alhazzani, W., Levy, M.M., Antonelli, M., Ferrer, R., Kumar, A., Sevransky, J.E., Sprung, C.L., Nunnally, M.E. and Rochwerf, B. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. *Intensive care medicine*. 2017;**43**(3):304-377. [DOI: 10.1007/s00134-017-4683-6]

- [51] Kumar A, Ellis P, Arabi Y, Roberts D, Light B, Parrillo JE, Dodek P, Wood G, Kumar A, Simon D, Peters C, Ahsan M, Chateau D, Cooperative Antimicrobial Therapy of Septic Shock Database Research G. Initiation of inappropriate antimicrobial therapy results in a fivefold reduction of survival in human septic shock. *Chest*. 2009;**136**(5):1237-1248 [PMID: 19696123 DOI: 10.1378/chest.09-0087]
- [52] Vazquez-Guillamet C, Scolari M, Zilberberg MD, Shorr AF, Micek ST, Kollef M. Using the number needed to treat to assess appropriate antimicrobial therapy as a determinant of outcome in severe sepsis and septic shock. *Critical Care Medicine*. 2014;**42**(11):2342-2349 [PMID: 25072764 DOI: 10.1097/CCM.0000000000000516]
- [53] Lutgring JD, Limbago BM. The problem of carbapenemase-producing-carbapenem-resistant-enterobacteriaceae detection. *Journal of Clinical Microbiology*. 2016;**54**(3):529-534 [PMID: 26739152 PMCID: 4767976 DOI: 10.1128/JCM.02771-15]
- [54] CLSI Performance Standards for Natimicrobial Susceptibility Testing (note: document pages 56, 63, 67, 122-35). Clinical Laboratory Standard Institute; 2016 [Internet]. Available from: http://shop.clsi.org/site/sample_pdf/M100s26_sample.pdf [Accessed: July 2, 2017]
- [55] Laboratory Detection and Reporting of Carbapenem-resistant Enterobacteriaceae (CRE): Specifically, slides 37-54. CLSI Outreach Working Group (ORWG) [Internet]. 2016. Available from: <http://clsi.org/wp-content/uploads/sites/14/2013/11/orwg-cre-laboratory-role-5.30.16.pdf> [Accessed: July 2, 2016]
- [56] Banerjee R, Humphries R. Clinical and laboratory considerations for the rapid detection of carbapenem-resistant Enterobacteriaceae. *Virulence*. 2016;**0**(0)1-13 [PMID:27168451 DOI:10.1080/21505594.2016.1185577]
- [57] Micek ST, Welch EC, Khan J, Pervez M, Doherty JA, Reichley RM, Kollef MH. Empiric combination antibiotic therapy is associated with improved outcome against sepsis due to Gram-negative bacteria: A retrospective analysis. *Antimicrobial Agents and Chemotherapy*. 2010;**54**(5):1742-1748 [PMID: 20160050 PMCID: 2863648 DOI: 10.1128/AAC.01365-09]
- [58] Pittet D, Monod M, Suter PM, Frenk E, Auckenthaler R. Candida colonization and subsequent infections in critically ill surgical patients. *Annals of Surgery*. 1994;**220**(6):751-758 [PMID: 7986142 PMCID: 1234477]
- [59] Moore RD, Smith CR, Lietman PS. The association of aminoglycoside plasma levels with mortality in patients with gram-negative bacteremia. *The Journal of Infectious Diseases*. 1984;**149**(3):443-448 [PMID: 6715900]
- [60] van Zanten AR, Polderman KH, van Geijlswijk IM, van der Meer GY, Schouten MA, Girbes AR. Ciprofloxacin pharmacokinetics in critically ill patients: A prospective cohort study. *Journal of Critical Care*. 2008;**23**(3):422-430 [PMID: 18725050 DOI: 10.1016/j.jcrc.2007.11.011]
- [61] Barza M, Ioannidis JP, Cappelleri JC, Lau J. Single or multiple daily doses of aminoglycosides: A meta-analysis. *British Medical Journal (Clinical Research ed)*. 1996;**312**(7027):338-345 [PMID: 8611830 PMCID: 2350289]

- [62] Hatala R, Dinh T, Cook DJ. Once-daily aminoglycoside dosing in immunocompetent adults: A meta-analysis. *Annals of Internal Medicine*. 1996;**124**(8):717-725 [PMID: 8633831]
- [63] Rybak MJ, Lomaestro BM, Rotschafer JC, Moellering RC, Craig WA, Billeter M, Dalovisio JR, Levine DP. Vancomycin therapeutic guidelines: A summary of consensus recommendations from the infectious diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*. 2009;**49**(3):325-327 [PMID: 19569969 DOI: 10.1086/600877]
- [64] Steinmetz T, Eliakim-Raz N, Goldberg E, Leibovici L, Yahav D. Association of vancomycin serum concentrations with efficacy in patients with MRSA infections: A systematic review and meta-analysis. *Clinical Microbiology and Infection: The Official Publication of the European Society of Clinical Microbiology and Infectious Diseases*. 2015;**21**(7):665-673 [PMID: 25887712 DOI: 10.1016/j.cmi.2015.04.003]
- [65] Mohamed AF, Karaikos I, Plachouras D, Karvanen M, Pontikis K, Jansson B, Papadomichelakis E, Antoniadou A, Giamarellou H, Armaganidis A, Cars O, Friberg LE. Application of a loading dose of colistin methanesulfonate in critically ill patients: Population pharmacokinetics, protein binding, and prediction of bacterial kill. *Antimicrobial Agents and Chemotherapy*. 2012;**56**(8):4241-4249 [PMID: 22615285 PMID: 3421626 DOI: 10.1128/AAC.06426-11]
- [66] McKinnon PS, Paladino JA, Schentag JJ. Evaluation of area under the inhibitory curve (AUC) and time above the minimum inhibitory concentration (T>MIC) as predictors of outcome for cefepime and ceftazidime in serious bacterial infections. *International Journal of Antimicrobial Agents*. 2008;**31**(4):345-351 [PMID: 18313273 DOI: 10.1016/j.ijantimicag.2007.12.009]
- [67] Minocin (minocycline) for injection. Available from: www.minociniv.com [Accessed: March 15, 2017]
- [68] Ni W, Han Y, Zhao J, Wei C, Cui J, Wang R, Liu Y. Tigecycline treatment experience against multidrug-resistant *Acinetobacter baumannii* infections: A systematic review and meta-analysis. *International Journal of Antimicrobial Agents*. 2016;**47**(2):107-116 [PMID: 26742726 DOI: 10.1016/j.ijantimicag.2015.11.011]
- [69] Chan JD, Graves JA, Dellit TH. Antimicrobial treatment and clinical outcomes of carbapenem-resistant *Acinetobacter baumannii* ventilator-associated pneumonia. *Journal of Intensive Care Medicine*. 2010;**25**(6):343-348 [PMID: 20837632 DOI: 10.1177/0885066610377975]
- [70] Goff DA, Bauer KA, Mangino JE. Bad bugs need old drugs: A stewardship program's evaluation of minocycline for multidrug-resistant *Acinetobacter baumannii* infections. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*. 2014;**59**(Suppl 6):S381-S387 [PMID: 25371514 DOI: 10.1093/cid/ciu593]

- [71] Bishburg E, Bishburg K. Minocycline—An old drug for a new century: Emphasis on methicillin-resistant *Staphylococcus aureus* (MRSA) and *Acinetobacter baumannii*. *International Journal of Antimicrobial Agents*. 2009;**34**(5):395-401 [PMID: 19665876 DOI: 10.1016/j.ijantimicag.2009.06.021]
- [72] Wood GC, Hanes SD, Boucher BA, Croce MA, Fabian TC. Tetracyclines for treating multidrug-resistant *Acinetobacter baumannii* ventilator-associated pneumonia. *Intensive Care Medicine*. 2003;**29**(11):2072-2076 [PMID: 14556048 DOI: 10.1007/s00134-003-1811-2]
- [73] Jankowski CA. A stewardship approach to combating multidrug-resistant *Acinetobacter baumannii* infections with minocycline. *Infectious Disease in Clinical Practice*. 2012;**20**:184-187
- [74] Karageorgopoulos DE, Falagas ME. Current control and treatment of multidrug-resistant *Acinetobacter baumannii* infections. *The Lancet Infectious Diseases*. 2008;**8**(12):751-762 [PMID: 19022191 DOI: 10.1016/S1473-3099(08)70279-2]
- [75] Tan TY, Ng LS, Tan E, Huang G. In vitro effect of minocycline and colistin combinations on imipenem-resistant *Acinetobacter baumannii* clinical isolates. *The Journal of Antimicrobial Chemotherapy*. 2007;**60**(2):421-423 [PMID: 17540671 DOI: 10.1093/jac/dkm178]
- [76] Prevention CfDCA. Core Elements of Hospital Antibiotic Stewardship Program [Internet]. 2016. Available from: <http://www.cdc.gov/getsmart/healthcare/implementation/core-elements.html> [Accessed: July 20, 2016]