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Review Article

Antibiotic regimens for treatment of infections due to multidrug-resistant Gram-negative pathogens: An evidence-based literature review

Mandana Izadpanah[1], Hossein Khalili[1]

[1]Department of Clinical Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

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Corresponding author:
Prof. Hossein Khalili,
E-mail: khalilih@sina.tums.ac.ir

ABSTRACT

Evidences regarding the efficacy of different antibiotic regimens proposed for treatment of multidrug-resistant (MDR) Gram-negative pathogens have been reviewed. Available data in Scopus, Medline, EMBASE, the Cochrane central register of controlled trials, and Cochrane database of systematic reviews have been collected. Several antibiotic regimens are proposed for treatment of MDR Gram-negative infections (defined as nonsusceptibility to at least one agent in three or more antimicrobial categories). The most challenging issue is the treatment of carbapenem-resistant (CR) Gram-negative pathogens. A carbapenem plus either colistin or tigecycline was the most effective regimen for treatment of CR Gram-negative pathogens with low-level resistance (minimal inhibitory concentration [MIC] ≤ 8 mg/L). However, in high-level resistance (MIC > 8 mg/L), combination of colistin and tigecycline showed promising effect.

Keywords: Antibiotic; Gram-negative bacteria; infection; resistant

INTRODUCTION

In the recent years, increasing infections and mortality due to antibiotic-resistant pathogens is a challenging topic. Although this concern exists for both Gram-positive and negative bacteria, because of emergence of the strains resistant to the common antibiotics and absence of new effective antibiotics makes Gram-negative (g–) bacteria on the top of this attention. Available antibiotics have lost their effectiveness in managing these infections. Invasive pathogens may acquire resistance genes which enable bacteria to produce enzymes like beta-lactamase and carbapenemase, express efflux systems, and modify the drug's target site and an alternative metabolic pathway.[1,2]

Multidrug-resistant (MDR) organisms including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci and certain Gram-negative bacilli like *Pseudomonas aeruginosa* (Pa), *Acinetobacter baumannii* (Ab) and *Enterobacteriaceae* (Eb) cause severe and lethal human infections especially in critically ill patients. The term, "ESKAPE," has been proposed to express the majority of nosocomial infections due to resistant pathogens, including *Enterococcus faecium*, *S. aureus*, *Klebsiella pneumonia* (Kp), Ab, Pa, and *Enterobacter* species.[3]

Up to the year 2000, most g-microorganisms were susceptible to carbapenems. Carbapenem-resistant (CR) pathogens became a major clinical challenge within 15–20 years after approval of the first carbapenem.[4-7]

Carbapenamases enzymes, which belong to Ambler class A, B or D beta-lactamases. Class A and D enzymes have a serine-based hydrolytic mechanism,

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including members of the SME, IMI, NMC, GES, and *Klebsiella pneumonia* carbapenemase (KPC) families, of these, the KPC carbapenemases, which found commonly on plasmids in Kp are the most prevalent, while class B enzymes are metallo-beta-lactamases that contain zinc in the active site. The class D carbapenemases consist of OXA-type beta-lactamases frequently detected in Ab. The metallo-beta-lactamases belong to the IMP, VIM, SPM, GIM, and SIM families and have been detected primarily in Pa; however, there are increasing numbers of reports worldwide of this group of beta-lactamases in the Eb.[8]

Choosing the best agent for the treatment of infections caused by these pathogens is one of the most important challenges facing practitioners. Here, evidences regarding the efficacy of different antibiotics and combinations that proposed for treatment of the MDR g-organisms have been reviewed.

METHODS

In this narrative review, available English language data in the following databases have been evaluated: Scopus, Medline, EMBASE, the Cochrane central register of controlled trials, and Cochrane database systematic reviews. The time frame of the review was 1990–2014.

The key words used as search terms were "*Acinetobacter*," "*Klebsiella*," "*Pseudomonas*," "*Enterobacter*," "Eb," "Gram-negative infection," "resistant", "prevention," "MDR," "extended drug-resistant (XDR)," "pan drug-resistant (PDR)," "treatment," and "antibiotic regimen." Randomized clinical trials, prospective or retrospective human studies, case series, and case reports were considered. Non-English language articles (5), as well as *in vitro* and experimental studies (12) were excluded. Finally, 80 articles were recruited in this review.

RESULTS

Multidrug resistant pathogens

Pseudomonas aeruginosa has likely been the first pathogen to exhibit MDR and XDR phenotypes. XDR is defined as nonsusceptibility to at least one agent in all but two or fewer antimicrobial categories. Ab has become one of the major players in the ongoing antibiotic resistance crisis. The challenge, in this case, is due to CR-Ab strains, which are usually resistant to all the available anti-Ab agents except polymyxins. Carbapenem-resistant *Enterobacteriaceae* (CRE, mostly contributed by Kp) represents the most recent and worrisome evolution of the antibiotic resistance crisis. Currently, there are at least four types of carbapenemases that are spreading among Eb worldwide, including the KPC and OXA-48 serine carbapenemases (of molecular class A and D, respectively) and the MBLs of the VIM and NDM types.[9,10]

Extended-spectrum beta-lactamase (ESBL), CR, MDR, XDR, and PDR pathogens are included in this category.[11] The emergence of metallo-beta-lactamases VIM, IMP and NDM (molecular class B), OXA-48 and its derivatives (molecular class D), and KPCs molecular class A is rapidly causing several paradigm shifts in antibiotic therapy against the g-bacteria.[4] ESBL-producing Eb has been increasingly implicated in healthcare-associated infections.[12]

Klebsiella pneumonia carbapenemases are at first detected in the Kp, but later has also been detected in other Eb, including *Escherichia coli*, *Enterobacter* species, *Salmonella enterica*, *Proteus mirabilis*, and *Citrobacter freundii*.[13] Intensive Care Unit (ICU) admission, prolonged broad-spectrum antibiotic therapy, surgery or invasive procedures and immunosuppression are the major risk factors for colonization and subsequent infection with CR-Kp. The fatality rate is highest among patients with blood stream infection (BSI). Inappropriate empirical therapy increased the probability of poor outcome, whereas combination therapy and control of the infection source are associated with improved patient survival.

Treatment options

Limited clinical trials evaluated the role of combination therapy for treatment of MDR Ab. Different combinations of rifampin (RIF), sulbactam, aminoglycosides, colistin methate sulfate (CMS), carbapenems, and other agents have been evaluated against MDR-Ab infections. However, a carbapenem (imipenem, meropenem, or doripenem) is the drug of choice for treating carbapenem-susceptible MDR-Ab infections.[14,15]

In the following sections, case series included the treatment of nosocomial infections caused by resistant pathogens, have been reviewed at first. After that, treatment options for treatment of MDR infections of specific organs including blood stream, respiratory tract, central nervous system (CNS), and urinary tract infections (UTIs) have been separately reviewed.

Case series of nosocomial infections

Sobieszczyk *et al*. reviewed CMS efficacy and safety in the treatment of MDR g-respiratory tract infections. 29 courses of CMS in combination with other antimicrobial agent in 25 critically ill patients were included. Concomitant antibiotics were imipenem or meropenem, amikacin, tobramycin, cefepime, a

quinolone, sulbactam, and aztreonam. In this study, colistin in combination with another antimicrobial agent showed considerable efficacy and safety.[16]

Kasiakou *et al*. assessed the safety and efficacy of CMS in the treatment of nosocomial infections. The most common infections were *Pneumonia* (33.3%), bacteremia (27.8%), UTIs (11.1%) and intra-abdominal infections (11.1%). Ab (51.9%), Pa (42.6%), and Kp (3.7%) strains were isolated pathogens. In-hospital mortality was 24% in this survey. The response was observed in 66.7% (36/54) of the episodes. The results showed that CMS was a relatively safe and effective intervention in for severe hospital-acquired infections due to MDR g-bacteria.[17]

In Saballs *et al*. study, RIF plus imipenem was considered for patients with serious infections due to CR-Ab that were only susceptible to colistin. RIF/imipenem was not an appropriate combination for CR-Ab infections. However, the evaluating efficacy of RIF in combination with other antibiotics should be considered in future studies.[18]

Epidemiology and outcome of XDR-Ab bacteremia have been evaluated by Tseng *et al*. Antibiotic therapy was evaluated in three different regimens; sulbactam, a carbapenem (imipenem or meropenem) and a carbapenem (imipenem or meropenem) plus an aminoglycoside. Clinical outcomes of the patients were not different between the antibiotics' regimens. However, the severity of the illness at the onset of bacteria and the presence of immunosuppression were the only two significant predictors of 30-day mortality.[19]

Oliveira *et al*. evaluated the efficacy and safety of CMS and ampicillin-sulbactam in treating infections caused by CR-Ab. During the study period, 283 infectious episodes caused by CR-Ab were included. 82 and 85 patients received polymyxins and ampicillin-sulbactam, respectively. Remaining episodes were treated with other antibiotic regimens. Treatment with CMS, higher Acute Physiological and Chronic Health Evaluation II (APACHE II) score, septic shock, delay in starting treatment, and renal failure were defined predictors of mortality. On multivariate analysis, prognostic factors for in-hospital mortality were older age, septic shock, and higher APACHE II score. In this study, sulbactam was more effective than CMS.[20]

Efficacy and safety of fosfomycin have been evaluated in critically ill patients with CR-Kp infections. Fosfomycin plus either CMS (n = 6), gentamicin (n = 3) and piperacillin-tazobactam (n = 1) were the combinations used. All-cause ICU mortality was 18.2%. Fosfomycin in combination with other antibiotics showed promising effect in treating infections caused by CR-Kp in the adult critically ill patients.[21]

Efficacy of CMS (3 million IU 3 times a day) and tobramycin (5–6 mg/kg daily) in managing of Ab-induced nosocomial infections in critically ill patients have been compared in a retrospective cohort study by Gounden *et al*. No significant differences in the ICU survival, time to the microbiological response and kidney injury have been detected in the tobramycin and CMS groups.[22]

During a 2-year observational case series of 21 patients infected by PDR g-bacteria, the clinical outcome of CMS containing regimen (47.6%) was compared with the tigecycline-based regimen (33.3%). Treatment response was higher, and duration of hospitalization was shorter in the patients treated with tigecycline compared to the CMS group.[23]

In BSI and Ventilator-associated *Pneumonia* (VAP) due to Ab, Pa, and Kp which were only susceptible to CMS, a 9 MIU loading dose and 9 MIU as a daily dose (in two divided doses) showed acceptable efficacy and relatively low kidney injury.[24] Also in a brief report of an observational study in 22 poly-trauma critically ill patients, tigecycline combined with CMS or gentamicin was effective for the treatment of CR-Kp infections.[25]

Kontopidou *et al*. included 107 patients with 127 infectious episodes, including central venous catheter bacteremia and VAP in a multicenter study. A high failure rate was detected among patients received tigecycline, especially as monotherapy.[26] However, tigecycline is an option for treating severe infections due to CP-Kp.[27,28]

Blood stream infection

Kuo *et al*. reported the efficacy of different antimicrobial regimens for BSIs due to Ab. The results showed a combination of a carbapenem and ampicillin-sulbactam showed better outcome compared with a carbapenem plus amikacin, or a carbapenem alone.[29,30]

Treatment regimens in 47 patients with Ab-BSIs have been retrospectively reviewed by Choi *et al*. Cefoperazone-sulbactam and imipenem-cilastatin were used regimens in 25 and 12 patients respectively. The rates of acceptable response were not statistically different between the groups.[31]

In a prospective observational study, Daikos *et al*. evaluated the role of VIM production on Kp-BSI outcome. A total of 162 patients; 67 (41.4%) and 95 (58.6%) with and without VIM-Kp infections,

respectively, were included. The all-cause 14-day mortality rates were 15.8%, 18.9%, and 42.9% of patients infected with VIM-negative organisms, VIM-positive carbapenem-susceptible organisms, and VIM-positive CR organisms, respectively. The mortality rate was lower in combination therapy with two active drugs; a carbapenem plus either CMS or an aminoglycoside compared to monotherapy. The severity of underlying diseases and CR were independent predictors of death.[32]

Lim *et al*. evaluated the outcomes of patients with MDR-Ab BSIs, who were treated with or without CMS-based regimen. In this study, colistin did not improve the overall hospital mortality in patients who had an MDR-Ab BSIs. A high APACHE II score at ICU admission was the only significant risk factor that predicted mortality.[33]

Tumbarello *et al*. conducted a multicenter retrospective cohort study to evaluate the clinical outcome in 125 patients with BSIs caused by CR-Kp. Inadequate empirical antibiotic therapy was reported as one of the three predicting factors of mortality in BSIs caused by CR-Kp and it is the only one that is potentially modifiable. The other predictors were at admission septic shock and high APACHE III score. Combination therapy with tigecycline, CMS, and meropenem improved survival.[34,35] Zarkotou *et al*. investigated outcomes, risk factors for mortality and impact of appropriate antimicrobial treatment in patients with BSIs caused by KPC producing Kp. Based on the results of the multivariate analysis, the major predictors of infection, mortality were the severity of the baseline condition, older age, and inappropriate treatment. Among them, the only modifiable variable that could be used to improve outcomes is the administration of appropriate treatment. The most common treatment regimen was the combination of colistin with tigecycline, received by nine patients. Colistin was used as monotherapy in seven patients with infection, mortality 66.7% while the tigecycline monotherapy was administered to five patients with infection mortality 40%.[36]

Daikos *et al*. conducted a study to evaluate the clinical outcome of patients with CR-Kp BSIs received different antibiotic regimens. In this study, 103, 72, and 12 patients received combination therapy, monotherapy, and therapy with no active drug, respectively. Severe underlying diseases, septic shock, and treatment with a single active agent were independent predictors of death. Combination therapy provides significant survival benefit, especially when a carbapenem was considered.[37] Another treatment-related factor that can affect the clinical outcome is the time of initiation of effective antibiotic regimen. Prompt initiation of effective antibiotic regimen for severe infections showed an important impact on patients' survival.[35,38]

The clinical characteristics and treatment outcomes of 36 patients with BSIs due to CRE were investigated in a cohort study by Balkan *et al*. The microbiological and clinical responses within the first 7 days of the treatment were the major determinant of 28-day mortality. Colistin-based dual combinations and preferably triple combinations were associated with significantly better outcomes when compared to noncolistin based regimens.[39]

Pneumonia / ventilator-associated Pneumonia

Ventilator-associated *Pneumonia* and tracheobronchitis followed by bacteremia are the most frequent common infectious complications in critically ill patients. Late-onset VAP, which occurs after 4 days of intubation, mainly is induced by MDR bacteria such as MRSA, Ab, Pa, Kp and ESBL g-bacteria.[40] In the empirical treatment of VAP due to the MDR pathogens, local resistance patterns are determining factor. In most cases, CMS and tigecycline are the unique treatment options for VAP caused by MDR pathogens.[41-45]

Garnacho-Montero *et al*. prospectively evaluated efficacy and safety of intravenous (IV) colistin in 35 episodes of VAP due to MDR-Ab. CMS monotherapy was applied to 21 patients (in whom VAP caused by the susceptible pathogen to CMS) and the other patients were treated with imipenem (susceptible to imipenem). In this study, CMS was an effective alternative for imipenem in the management of the CR-Ab.[46]

Experimental studies have shown that that CMS monotherapy was not an ideal option for treatment of CR-Ab associated *Pneumonia*. In one study, 7 critically ill patients with VAP caused by Ab-isolates were treated with either doxycycline or minocycline. The results showed that minocycline or doxycycline may be an option for treating imipenem and ampicillin-sulbactam resistant Ab-*Pneumonia*.[47]

Lee *et al*. compared the efficacy of different antibiotic combinations in 89 patients with PDR-Ab nosocomial infections. A total of 59 patients were treated with a carbapenem plus sulbactam, and 30 patients were treated with a second or third generation cephalosporin, antipseudomonal penicillins, or a fluoroquinolone plus an aminoglycoside. In this study, carbapenem-sulbactam combination significantly decreased minimal inhibitory concentrations (MICs) for PDR-Ab. The clinical outcomes of both groups had not significant differences, either in terms of resolution of infection (25/59, 42% in first group vs. 12/30, 40% in second group) or survival (35/59, 59%

vs. 17/30, 57%). Based on MICs, imipenem-sulbactam reversed resistance in 30% (14/46) of Ab isolates initially intermediate or resistant to imipenem alone. Meropenem-sulbactam had a similar effect in 11% (5/45) of isolates that were intermediate or resistant to meropenem.[48]

Petrosillo *et al*. evaluated efficacy of CMS plus RIF in 14 critically ill patients who were diagnosed with CR-Ab VAP only or VAP plus BSI or surgical site infection (SSI). Five of the patients who had BSI or SSI, also received IV ampicillin–sulbactam. This combination resulted in the microbiological response in 9 (64%) patients with limited adverse effects. Overall, 7 (50%) of 14 patients died, three patients experienced a relapse of their *Acinetobacter* infection and received a second course of colistin–rifampicin; two of these patients died. Thus, therapy with colistin–rifampicin, and with ampicillin–sulbactam in case of susceptibility to this combination, resulted in microbiological clearance of CR-Ab infection with limited side effects.[49]

In another study, efficacy of CMS-RIF combination in the treatment of nosocomial *Pneumonia* or bacteremia due to MDR-Ab been assessed in 29 critically ill patients. This combination showed acceptable efficacy.[50]

High-dose of ampicillin-sulbactam has been proposed for treatment of VAP due to MDR-Ab. CMS (3 MIU every 8 h) and high-dose ampicillin-sulbactam (9 g every 8 h) were comparably safe and effective treatments in the treatment of MDR-Ab VAP.[51]

Tasbakan *et al*. evaluated tigecycline efficacy in treating patients with MDR-Ab *Pneumonia*. Tigecycline was used as monotherapy in 23 cases. It was combined with cefoperazone-sulbactam, netilmicin, and amikacin in 26, 13, and three cases, respectively. Mortality and microbiological eradication rates were not different in the monotherapy group compared with the combination therapy group.[52] Colistin-carbapenem combination improved the clinical response and survival compared to other regimens in solid organ transplant patients with XDR-Ab *Pneumonia*.[53]

Efficacy of CMS alone or in combination with RIF has been evaluated in 210 critically ill patients with XDR-Ab infections by Durante-Mangoni *et al*. The length of hospitalization and mortality was similar in both groups, but the microbiological response was higher in the combination treatment group.[54] In a retrospective analysis, the clinical and microbiological responses to IV colistin or colistin-sulbactam for the treatment of MDR-Ab VAP were assessed in 89 critically ill adult patients. In this study, although it was not statistically significant, the clinical cure rates (40.0% vs. 29.8%) and bacteriological clearance rates (85.7% vs. 72.3%) were better in the combination therapy group than colistin monotherapy.[55]

In McLaughlin *et al*. study, 15 patients with CR-Kp infections were evaluated. Two patients who had received carbapenem monotherapy died. One patient on no-directed therapy was died. Directed therapy was defined as any antibiotic given to a patient in a directed manner after culture results were available. Time to directed therapy was defined as the time in hours from the culture draw to the receipt of antibiotic therapy. However, one patient on cefepime was discharged. Other patients received combination therapy and survived. Combination therapies were included carbapenems, tigecycline, colistin, aminoglycosides, cefepime, piperacillin/tazobactam, and fosfomycin.[56] In a recently matched cohort analysis, it was proposed that colistin-based empiric therapy is superior to the tigecycline-based regimen for treating MDR-Ab *Pneumonia*.[57]

Meningitis

Nosocomial g-bacillary meningitis due to Ab or Pa occurs occasionally in neurosurgical critically ill patients.[58-60]

To treat CNS infections, bactericidal antibiotics should rapidly attain adequate concentrations within the CNS. Hydrophilic drugs, namely beta-lactams and glycopeptides, have low BBB permeability for which the presence of inflamed meninges is associated with an increase in CNS penetration. The new cephalosporins represent the backbone of several antimicrobial regimens for the treatment of bacterial meningitis. Among carbapenems, meropenem represents a drug for which the recommended dosage is 2 g every 8 h, as an IV 3-h infusion, with MIC values 0.25 mg/L. Its disposition into the cerebrospinal fluid (CSF) may increase in the presence of inflamed meninges. Data regarding tigecycline efficacy in meningitis are limited. In the case reports, tigecycline showed good CSF penetration.[61] CSF linezolid concentrations have been found similar to those of the free fraction in plasma.[62] Fosfomycin, rapidly distributes into the CSF and is a potential option in the treatment of multi-resistant Gram-positive and g-infections as well as "difficult-to-treat" bacterial infections. The disposition of trimethoprim and sulfamethoxazole into CSF is higher than beta-lactams, also in the presence of uninflamed meninges because of their lipophilic nature. Fluoroquinolones are able to achieve bactericidal concentrations in CSF. However, for microorganisms with high MIC values, these drugs should be used in combination therapy with other antibiotics. Due to their limited penetration

and risk of toxicities, aminoglycosides are not good choices for treating meningitis.[63]

Colistin and colistimethate sodium represent drugs of choice when the causative microorganisms are MDR strains. However, these drugs should be used in combination with other antibacterial agents, and in selected cases, intraventricular (IVT) administration should be adopted to augment the probability of cure because of modest and variable drug penetration into the CSF.[62]

In a study, 51 cases with nosocomial meningitis due to Ab were followed. A carbapenem (21 cases), ampicillin-sulbactam (4 cases), and other antibiotics (2 cases) were used IV antibiotics. Four patients were treated with IV combination therapy. 19 patients were treated with IV and intrathecal (IT) regimens, CMS (8 cases), carbapenem (4 cases) or only IT aminoglycoside (5 cases), and other regimens (2 cases). 18 patients died. IT amikacin (20 mg/day) was associated with a cure rate of 80%. Although no patient in CMS group (10 mg every 12 h) died, no statistically significant difference in the mortality among the groups was detected.[64]

IT or IVT CMS can be an effective and safe treatment for the management of MDR-Ab meningitis.[65] IVT CMS is the last option for the treatment of CNS infections caused by PDR g-bacteria. The dosages of IVT/IT CMS ranged between 1.6 and 40 mg/day.[66-68]

Falagas *et al*. collected 31 case reports/series, and reviewed 64 episodes of Gram-negative meningitis (34 of them in adults). Monotherapy with CMS via the IT or IVT and combination of systemic and local CMS was used for 11 and 25 episodes, respectively. In other episodes, different combinations were considered. In this report, IT/IVT CMS alone or in combination with systemic antibiotics was effective without considerable adverse effects.[67] Markantonis *et al*. examined the penetration of CMS into the CSF. Only 5% of CMS were detected in the CSF that seems inadequate for treatment of bacterial meningitis.[69]

Khawcharoenporn *et al*. evaluated the efficacy of IT/IVT colistin in CNS infections. The commonly administered dose was 40,000–500,000 IU/day for 2–3 weeks. Sterilization of the CSF was expected within 72 h. Systemic antibiotics were aminoglycosides (amikacin and tobramycin), colistin, imipenem, cefoperazone-sulbactam, ciprofloxacin, and ampicillin-sulbactam. There was no significant difference in the response rate between the IT/IVT CMS monotherapy and combination of IT/IVT colistin and other IV antibiotics. However, as most of the concurrent IV antibiotics (85%) had failed in monotherapy, role of IT/IVT colistin was dominant.[68]

Imberti *et al*. evaluated the pharmacokinetic (PK) parameters of CMS in 9 adult patients developed CNS infections caused by a PDR-Kp (6 patients), PDR-Ab (2 patients) or PDR-Pa (1 patient). In this study, IVT administration of CMS produced concentration by CMS in CSF that never obtained with systemic administration. IVT CMS at doses of ≥5.22 mg/day was defined as appropriate.[66]

Efficacy of IT or IVT of CMS in the management of MDR-Ab and XDR-Ab ventriculitis or meningitis was reviewed in 36 related articles. CMS was administered via the IVT and IT route in 52 and 22 cases, respectively. The exact route was not reported in 7 cases. The median duration of treatment and sterilization of CSF was 18.5 and 4 days, respectively. The response rate was 89%, and reversible local chemical reactions were reported in 9 patients.[70]

Several antibiotic regimens were reviewed for the empiric treatment of Gram-negative meningitis.[71] Meropenem 2 g every 8 h plus IT or IVT of an aminoglycoside (4 mg gentamicin or 30 mg amikacin as daily interval), IV CMS (2.5–5 mg/kg colistin base activity per day [equal to 6.67–13.3 mg/kg CMS]) in two to four divided doses, polymyxin B IV (1.5–2.5 mg polymyxin B base per kg per day in two divided doses) plus IT or IVT aminoglycoside (doses as above) with or without IV or PO rifampicin (600 mg/day) were studied regimens for treatment of CR-Ab meningitis. Removal of shunts and devices is one of the important concerns regarding treatment of meningitis, due to the probability of biofilm formation. Removal of shunt plus use of IV antibiotics caused the cured rate of 75%.[72,73] The recommended duration of antibiotic therapy for acute g-bacterial meningitis is 21 days. However, the administration of antibiotics should continue until CSF becomes culture negative. In patients in whom external ventricular drains or other ready CSF access is not present, repeat lumbar puncture to sample CSF should be done after 4 days of IV therapy, since the median duration of therapy needed to clear the CSF is roughly 3 days.[73]

Urinary tract infections

Many of the resistant g-bacillary infections caused complicated UTIs are acquired in the health-care-related facilities.

Although oral fluoroquinolones are the drug of choice for cystitis and outpatient pyelonephritis, but in inpatient pyelonephritis treatment with a parenteral third generation cephalosporin, cefepime, piperacillin-tazobactam or carbapenem should be considered.[74]

Takeyama *et al*. reported the clinical conditions of three patients with acute pyelonephritis caused

by MDR Pa. One of them treated with aspoxicillin and arbekacin, the other with piperacillin and the third case was treated with ceftazidime and arbekacin. Although none of the causative microorganisms were susceptible to the used antimicrobial agents, the clinical outcomes were all favorable.[75] In a retrospective case series, 21 adult in-patients with bacteriuria caused by KPC-positive organisms were assessed. Aminoglycosides showed promising results in the treatment of CRE UTI.[76] Volkow-Fernández *et al*. proposed that continuous intravesical administration of CMS is another useful way to eradicate an MDR-Ab urinary infection. They administrated colistimethate sodium, 3.5 mg/kg was dissolved in a 500 cm^3 saline solution for 12 h and administered through a triple intravesical catheter with continuous irrigation over 7 days for a patient with a UTI caused by MDR-Ab.[77]

CONCLUSION

Klebsiella pneumonia, Ab, Pa, and *Enterobacter* species are the most common resistant nosocomial g-infections around the word. BSI, *Pneumonia*, especially VAP, CNS infections, and complicated UTI due to these pathogens have been detected as main causes of morbidity and mortality in the hospitalized patients. These bacteria almost always are resistant to the conventional antibiotics. The resistant patterns of these organisms are changing from MDR to PDR pathogens.

Unfortunately, limited options are available for treatment of these infectious. Several variables including a history of antibiotic use, duration of hospitalization, major surgery, immunosuppression, parenteral nutrition, and diabetes are identified as predisposing factors for these infections. Infection control policies and antibiotic stewardships are two major well-evidenced strategies for prevention of antibiotic resistance in hospitals.

Differentiation between causative pathogen from colonization is another important issue in the clinical settings. Unfortunately, appropriate sampling and using rapid detection techniques for identification of pathogenic microorganisms are not available in many hospitals especially in the developing countries. Conventional disk diffusion methods usually are used as antimicrobial susceptibility tests. However, due to changing in the susceptibility pattern of bacteria, especially among MDR g-pathogens, identification of MIC for these microorganisms to selecting appropriate antibiotic regimen is essential.

Several antibiotic regimens are proposed for treatment of MDR g-infections. Most of the regimens are empirical, and some of them are based on the susceptibility patterns. Carbapenems are the treatment of choice for empirical treatment of infections due to ESBL-producing bacteria. The most challenging issue is the treatment of infections due to CR g-pathogens. Several evidences support the use of combination therapy regimens versus monotherapy for treatment of these infections. Tigecycline, polymyxins (polymyxin B, polymyxin E, CMS, carbapenems (imipenem, meropenem, doripenem), aminoglycosides (amikacin, gentamicin, tobramycin), quinolones (ciprofloxacin, levofloxacin), fosfomycin, RIF, ampicillin-sulbactam, piperacillin-tazobactam, and tetracyclines (minocycline and doxycycline) are common antibiotics that were used in the combinations. In these combinations, a carbapenem (always meropenem) plus either CMS or tigecycline was the most effective regimen for treatment of low-level resistant CR-Ab, CR-Kp infections. However, in high-level resistance (MIC > 8 mg/L) combination of CMS and tigecycline showed a better response.[78] For PDR-Ab and PDR-Kp infections combination regimens including two or three effective antibiotics are recommended.

Besides selection of appropriate agent, considering site and type of infection and PK parameters of antibiotics, especially dosing strategies are essentials for designing an effective antibiotic regimen. To treat CNS infections, bactericidal antibiotics should rapidly attain adequate concentrations within the CNS. Aminoglycosides and CMS as backbone of antimicrobial regimens for treatment of g-bacterial meningitis have not good CNS penetration. IT/IVT administration of these antibiotics should be considered. However, carbapenems, tigecycline, fosfomycin, trimethoprim and sulfamethoxazole, RIF, and fluoroquinolones have good CSF penetration. Furthermore, aerosolized CMS and aminoglycosides as adjunct therapy may be helpful in the treatment of severe VAP due to MDR g-bacteria.[55,79]

Following decreasing antibiotic susceptibility of MDR g-microorganisms, high-dose CMS (9 MIU loading followed by 9 MIU/day in two divided doses) were recommended for treatment of severe nosocomial infections, especially VAP.

Increased mortality risk in patients treated with tigecycline was observed in the clinical trials. This may be due to the large volume of distribution and low blood concentration of tigecycline that is not adequate for bacteremia clearance. Optimizing antibiotic dosing with considering PK-pharmacodynamic parameters is one of the strategies to manage resistant pathogens. The available evidences suggest that extended or continuous infusion of carbapenems

or piperacillin-tazobactam is associated with lower mortality.

AUTHORS' CONTRIBUTION

Izadpanah M, was responsible for literature review, data collection and preparing the manuscript draft. Khalili H, was responsible for data analysis and editing the manuscript.

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There are no conflicts of interest.

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