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Antibiotic therapy for pan-drug-resistant infections

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SUMMARY

Antibiotic resistance occurs when microorganisms resist the drugs used against the infection caused by them and neutralize their effects over time using various mechanisms. These mechanisms include preventing drug absorption, changing drug targets, drug inactivating, and using efflux pumps, which ultimately cause drug resistance, which is named pan-drug-resistant (PDR) infection if it is resistant to all antimicrobial agents. This type of drug resistance causes many problems in society and faces the health system with difficulties; therefore their treatment is crucial and encourages doctors to develop new drugs to treat them. PDR Gram-negative bacteria, including *Pseudomonas aeruginosa, Acinetobacter baumannii, Klebsiella pneumoniae*, and *Escherichia coli* are among the most significant resistant bacteria to many antimicrobial agents, and only a limited range of antibiotics, especially synergistically are effective on them. For the therapy of PDR *A. baumannii*, tigecycline in combination with colestimethate, imipenem, amikacin, and ampicillin-sulbactam are the most effective treatments. The utilization of β-lactamase inhibitors such as ceftolozane-tazobactam, ceftazidime-avibactam, or imipenem-cilastatin-relebactam has the most efficacy against PDR *P. aeruginosa*. The PDR *K. pneumoniae* has been treated in the last decades with tigecycline and colistin, but currently, nitrofurantoin, fosfomycin, and pivmecillinam seem to be the most effective agent for the therapy of PDR *E. coli*. While these drugs impressively struggle with PDR pathogens, due to the daily increase in antibiotic resistance in microorganisms worldwide, there is still an urgent need for the expansion of novel medicines and methods of combating resistance.

Keywords: Antibiotic resistance, pan-drug-resistant, *Pseudomonas aeruginosa, Acinetobacter baumannii, Klebsiella pneumoniae, Escherichia coli,* therapy.

INTRODUCTION

The emergence of resistance to various antimicrobial agents in bacteria has endangered human health worldwide, and the reason for this is the lack or absence of antimicrobial agents against them [1, 2]. Antibiotic resistance exists in both Gram-positive and Gram-negative bacteria, and this problem has led to the emergence of new scientific terms in the field of antibiotic resistance [3, 4]. One of these definitions is multidrug-resistant organisms (MDR), which is the resistance of an organism to more than one antimicrobial agent, which makes the treatment ineffective against the infection or delays the treatment and endangers the patient's health [5]. Bacteria categorized as extensively drug-resistant (XDR) are not only

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resistant to multiple antibacterial substances, but also have the inauspicious potential of being resistant to almost all authorized antimicrobials, making them epidemiologically important [6]. Initially, the term XDR was used in medical sciences to broadly explain drug-resistant *Mycobacterium tuberculosis* (XDR MTB) as resistant to the first-line drugs rifampicin and isoniazid, to a fluoroquinolone and at least one of three mentioned second-line drugs, including amikacin, kanamycin, or capreomycin [7].

Among the terms of drug resistance, pan-drug-resistance (PDR) refers to resistance to all antimicrobial compounds [8]. PDR bacterial infections, on the side of the abusage of broad-spectrum antibiotics in clinical utilization, pose a considerable public health menace due to the resistance of pathogenic microorganisms to various antimicrobials [9]. As the problem progresses, these organisms show resistance to all presently utilized antibacterial substances or stay sensitive only to previously used and potentially more toxic agents such as polymyxins and tigecycline, leaving limited and non-optimal choices for the remedy of infections [10]. PDR Gram-negative bacteria, including *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Klebsiella pneumoniae*, and *Escherichia coli* are among the most significant bacteria that show resistance to varied antibacterial substances, and only a limited range of antibiotics are effective on them [11]. These PDR bacteria are widely disseminated in the clinic because of their strong stability, colonization incidence rate, and resistance to antibacterial substances [12]. Since PDR bacteria adopt resistance mechanisms quickly, there is a debate about antibiotic choices concerning the efficacy and susceptibility of resistant strains in clinical utilization. Therefore, it is not easy to describe a standard therapeutic regimen against PDR infections in ill people [13]. The present narrative review will deal with the recent antibiotic advances in treating PDR infections and the most effective methods of treating them.

THE EMERGENCE OF ANTIBIOTIC RESISTANCE

Misuse and overuse of antimicrobial agents are the most significant causes of the expansion of drug-resistant microorganisms [14, 15]. Lack of clean water and sanitation and insufficient infection prohibition and control cause the dissemination of microorganisms, some of which can be resistant to antimicrobial remedies [16, 17]. Antimicrobial resistance mechanisms are classified into four main classes, *i.e.* preventing drug absorption, modifying the target of the drug, drug inactivating, and efflux pump. Intrinsic resistance is due to preventing drug absorption, drug inactivation, using an efflux pump, and, exerting the drug out of the cell. Acquired resistance is due to the modification of the target of drugs, enzymatic inactivation of drugs, and use of efflux pumps (Figure 1) [18]. There are differences in the kinds of mechanisms utilized by Gram-negative bacteria in comparison with Gram-positive ones, because of the diversity in bacterial structure [19]. All four principal mechanisms are utilized by Gram-negative bacteria, whereas Gram-positive bacteria just use preventing drug absorption [20, 21]. The existence of these differences causes variation in the drug resistance of different strains and each strain shows a different pattern of antibiotic resistance and causes variation in the effects of drugs on them [22].

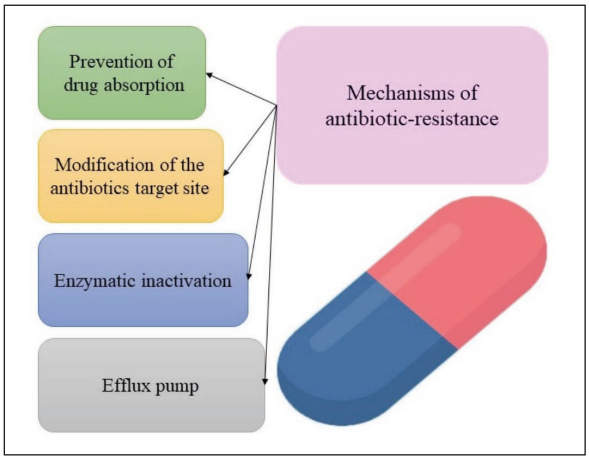

Figure 1 - The most significant mechanisms of antibiotic-resistance.

TREATMENT OF PDR *A. BAUMANNII*

Acinetobacter baumannii, an aerobic, Gram-negative coccobacillus, is considered a crucial nosocomial pathogen because of various drug resistance mechanisms, and it can be a complicated microorganism for physicians to perform therapeutic

measures [23]. It causes multiple infectious disorders, including pneumonia, wound, urinary tract, hematological, and intra-abdominal infections [24]. The number of cases of *A. baumannii* with resistant patterns to carbapenems over a 2-year time is increased [25]. As expected, the emergence and dissemination of PDR *A. baumannii* isolate in hospital settings leads to high mortality rates and is difficult to eradicate [26]. The increasing rate of microorganisms has shown resistance to antibiotics such as carbapenems worldwide, which in past years had high efficacy in the therapy of patients [27]. Non-traditional substances such as polymyxin E and polymyxin B, are utilized for the therapy of patients with pan-drug-resistant *A. baumannii* despite their high toxicities [28-30]. Resistance to these antibacterial substances has also emerged among some strains during treatment with them [31].

Pharmacological measures with newer antibacterial drugs or antimicrobial synergistic combination utilization of drugs have become increasingly crucial in combating these infections. Tigecycline also was authorized for the therapy of complicated skin and gastrointestinal infections caused by susceptible microorganisms [32]. Treatment with tigecycline alone or in simultaneous consumption with other antibacterial substances including imipenem, colestimethate, amikacin, and ampicillin-sulbactam are impressive in treating PDR infection [33]. Another effective synergy was seen in the utilization of imipenem-colestimethate and tigecycline-imipenem combinations. These results demonstrate the importance of the use of synergistic consumption gaining the activity of particular antibacterial substance combinations against PDR *A. baumannii* [34].

TREATMENT OF PDR *P. AERUGINOSA*

P. aeruginosa is a ubiquitous bacterium that can survive under various environmental situations [35]. It not only causes disease in plants and animals but also in humans, causing multiple harsh disorders in immunocompromised patients with cancer and patients suffering from severe burns and cystic fibrosis (CF) [36]. This microorganism is one of the significant organisms responsible for drug-resistant nosocomial infections and is one of the crucial causes of biofilm formation, bacteremia, and pneumonia in hospitalized patients [37, 38]. Multidrug-resistant *P. aeruginosa* was initially seen in patients with cystic fibrosis, and the spreading of them has since been announced among hospitalized patients [39]. *P. aeruginosa* isolates resistant to carbapenems or all antibacterial substances which are accessible for clinical utilization, are related to nosocomial infections and prevalence among patients hospitalized in intensive care units (ICUs) or burn units [40]. In addition to inherent resistance to multiple antimicrobial substances, *P. aeruginosa* acquires resistance quickly to conventional anti-pseudomonal agents such as carbapenems, ceftazidime, penicillins, fourth-generation cephalosporins, aztreonam, and ciprofloxacin following extended utilization of these antimicrobial agents in hospitalized patients, especially those in ICUs [41].

For the remedy of PDR *P. aeruginosa* infection, conventional, antipseudomonal β-lactam antibacterial drugs such as cefepime, ceftazidime, piperacillin-tazobactam, and carbapenems are generally prescribed, sometimes in simultaneous consumption with a second drug from another antibiotic class such as aminoglycoside, fluoroquinolone, polymyxin [42]. When the utilization of conventional β-lactams for *P. aeruginosa* infections may be ineffective due to the suspected PDR, monotherapy with novel β-lactamase inhibitors such as ceftolozane-tazobactam, ceftazidime-avibactam, or imipenem-cilastatin-relebactam over mix therapy with conventional substances is preferable, followed by therapeutic intensification or de- intensification based on *in vitro* susceptibility outcomes [43, 44]. If β-lactamase inhibitors are inaccessible, cefiderocol is the preferable remedy for acute PDR *P. aeruginosa* infections over simultaneous consumption with conventional antibacterial substances [45-47].

TREATMENT OF PDR *K. PNEUMONIAE*

K. pneumoniae is a significant pathogen that often causes nosocomial infections in hospitalized patients. In the past decade, the clinical isolation rate of *K. pneumoniae* has been rising, and in most countries, it has become the second most prevalent clinically isolated Gram-negative bacilli after *E. coli* [48]. The emergence of carbapenem-resistant *K. pneumoniae* causes a complicated problem for public health due to the lack of effective therapeutic options for the therapy of such infections

[49, 50]. *K. pneumoniae* carbapenemase (KPC) is one of the most significant carbapenemases found in *K. pneumoniae*, whose acquisition has contributed to resistance to all β-lactams in this microorganism and the therapy of infections caused by them has faced many problems [51].
Carbapenem-resistant *K. pneumoniae* that has resistance to drugs such as tigecycline and colistin, often known as PDR bacteria or super bacteria, makes the therapy of the infections hard for clinicians [52]. PDR *K. pneumoniae* has been isolated in plenty of health centers of countries worldwide [53]. Most KPC-carrying *K. pneumoniae* strains are MDR and PDR microorganisms that have also resistance to β-lactams, aminoglycosides, fosfomycin, and quinolones [54]. Tigecycline and colistin are two effective antibacterial drugs with high efficacy for treating KPC-producing PDR *K. pneumoniae* infections [55]. Tigecycline was impressive against most KPC-producing *K. pneumoniae* at its initial clinical utilization, and colistin is presently identified as the last solution for the therapy of carbapenem-resistant *K. pneumoniae* strain infections [56, 57].

TREATMENT OF PDR *E. COLI*

E. coli, the type genus of the family Enterobacteriaceae, is the most representative facultative anaerobe microorganism in the human gastrointestinal system. Some strains have developed the capability to cause gastrointestinal, urinary, and central nervous system disorders [58]. Urinary tract infections (UTIs) caused by antibiotic-resistant *E. coli*, especially PDR ones are a growing concern due to the unavailability of appropriate treatment options [59]. Knowledge of the common uropathogens, and local susceptibility patterns, is essential in determining suitable antibiotic therapy for UTIs [60]. The recommended first-line antibacterial substances utilized for acute uncomplicated cystitis in healthy nonpregnant females is a period of nitrofurantoin, fosfomycin tromethamine, or pivmecillinam [61]. High rates of resistance in microorganisms against drugs such as trimethoprim-sulfamethoxazole and ciprofloxacin prevent their utilization as effective remedies for UTIs in multiple countries, especially in patients who utilized them recently or in those who are in facing the infection of extended-spectrum β-lactamases (ESBLs)-producing *E. coli* [62]. Second-line choices include oral cephalosporins such as cephalexin or cefixime, fluoroquinolones, and β-lactams, such as amoxicillin-clavulanate. Running therapy choices for UTIs against *E. coli* with the ability to produce AmpC- β-lactamase include drugs such as fosfomycin, nitrofurantoin, pivmecillinam, fluoroquinolones, cefepime, piperacillin-tazobactam and carbapenems [63, 64]. Therapeutic choices for the UTIs caused by ESBLs-*E.coli* include nitrofurantoin, fosfomycin, pivmecillinam, amoxicillin-clavulanate, finafloxacin, and sitafloxacin, while pivmecillinam, fosfomycin, finafloxacin, and sitafloxacin are oral therapy choices for ESBLs- *K.pneumoniae* [65]. Because the drug resistance of the strains is increasing daily and microorganisms are developing resistance to the drugs used currently, the utilization of new antimicrobi-

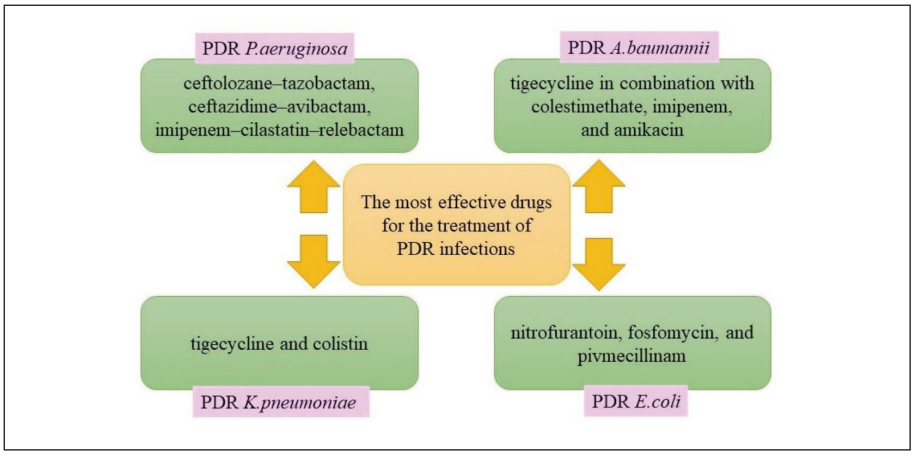

Figure 2 - The most effective drugs for the treatment of PDR infections.

als is essential and it is wisely for the therapy of infections caused by drug-resistant organisms to avoid resistance and prevent the loss of effective therapies (Figure 2) [66].

CONCLUSIONS

Resistance among deadly Gram-negative pathogens has increased to epidemic proportions, especially within hospitals and acute care settings. Infections with drug-resistant microorganisms such as MDR, XDR, and PDR *E. coli, P. aeruginosa, K. pneumoniae,* and *A. baumannii* contribute to alarming high mortality rates in vulnerable populations and add healthcare costs through lengthening hospitalization, use of resources, lost productivity, and high acuity care needs. Addressing this problem requires both infection prevention and appropriate treatment. Knowledge of local patterns of resistance and individual risk factors for resistance will lead to better care for patients. Although there have been worldwide initiatives to expand new antibacterial substances against PDR Gram-negative pathogens, only limited advances have been made in the last few years. We are forced to rely on new combinations of old drugs largely, and our most impressive advances have been with new β-lactamase inhibitors such as avibactam, vaborbactam, and relebactam in simultaneous consumption with old cephalosporins and carbapenems. While these drugs combat PDR pathogens effectively, there is still a consecutive requirement to develop new medicines and methods of combating resistance.

Conflict of interest
None

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