Akram et al. | J Pure Appl Microbiol | 14(3):1639-1647| September 2020
Article 6131 | https://doi.org/10.22207/JPAM.14.3.02

Print ISSN: 0973-7510; E-ISSN: 2581-690X

REVIEW ARTICLE OPEN ACCESS

Treatment of Multi-Drug Resistant Gram-Negative Bacterial Pathogenic Infections

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Abstract

The multidrug-resistant Gram-negative bacteria (MDR-GNB) infections in severely infected patients present numerous difficulties in terms of treatment failure where antibiotics cannot arrest such drug resistant bacteria. Based on the patient's medical history and updated microbiological epidemiology data, an effective empirical treatment remains critical for optimal results to safeguard human health. The aim of this manuscript is to review management of MDR-Gram negative pathogenic bacterial infections. Quick diagnosis and narrow antimicrobial spectrum require rapid and timely diagnosis and effective laboratories in accordance with antimicrobial stewardship (AS) principles. Worldwide, there is an increased emergence of Carbapenem-resistant *Enterobacteriaceae* (CRE), *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*. Recently, novel therapeutic options, such as meropenem/vaborbactam, ceftazidime/avibactam, ceftolozane/tazobactam, eravacycline and plazomicin became accessible to effectively counteract severe infections. Optimally using these delays the emergence of resistance to novel therapeutic agents. Further study is required, however, due to uncertainties in pharmacokinetic/pharmacodynamics optimization of dosages and therapeutic duration in severely ill patients. The novel agents should be verified for (i) action on carbapenem resistant *Acinetobacter baumannii*; (ii) action on CRE of β-lactam/β-lactamase inhibitors dependence on type of carbapenemase; (iii) emergence of resistance to novel antibacterials and dismiss selective pressure promoting development of resistance. Alternative treatments should be approached alike phage therapy or antibacterial peptides. The choice of empirical therapy is complicated by antibiotic resistance and can be combated by accurate antibiotic and their combinations usage, which is critical to patient survival. Noteworthy are local epidemiology, effective teamwork and antibiotic stewardship to guarantee that medications are utilized properly to counter the resistance.

Keywords: Antimicrobial resistance, *Enterobacteriaceae*, Carbapenemase, *Acinetobacter baumannii*, bacteriophage

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(Received: March 03, 2020; accepted: August 28, 2020)

Citation: Akram WM, Menezes GA, Abbas N, Ahmad W, Ahmed AM. Treatment of Multi-Drug Resistant Gram-Negative Bacterial Pathogenic Infections. *J Pure Appl Microbiol.* 2020;14(3):1639-1647. doi: 10.22207/JPAM.14.3.02

INTRODUCTION

Gram-negative pathogens and antimicrobial resistance

Rising incidences of Gram negative bacteria (GNB) have become an immense problem worldwide as it may decrease the therapeutic choices considerably and renders anti-bacterial drugs ineffective. In Gram-negative pathogens, resistance has led into a principal cause of morbidity and mortality and a grave public health concern globally, specifically among *Enterobacteriaceae* family and non-fermenters[1,2]. The expansion of bacterial resistance has grown together with antimicrobial remedy from many years, but merely the GNB have recently begun to exhibit endurance to all regularly employed stages of antimicrobials. Clinicians have been enforced to contemplate different treatment modalities such as combinations of medications or even, to rediscover previous preparations, which had toxicity issues, in addition to suboptimal pharmacokinetics[3].

The three most problematic GNB; extended-spectrum β-lactamase (ESBL) producing *Enterobacteriaceae, Acinetobacter baumannii*, and *Pseudomonas aeruginosa* were identified by the 'antimicrobial availability task force' (these were a group of national experts that were responsible for development in concert with the upsurge in antibiotic resistance, as well as for reviewing trends in antibiotic research. Following this, they were asked to propose various resolutions to warrant the availability of efficient antibiotics in the near future)[4].

Various processes of antimicrobial opposition in GNB have been classified which include efflux pumps, target modification, hydrolyzing enzymes (e.g. β-lactamases). The widespread processes of resistance in GNB are firstly, the β-lactam and β-lactamase inhibitor arrangement such as monobactam (e.g. aztreonam), carbapenems and cephalosporins. Secondly, the β-lactam ring present in penicillin's gets hydrolyzed by β-lactamases[5]. Carbapenem-resistance is utmost predominant in *Acinetobacter* spp., and in *Pseudomonas* spp. but in addition, it is constantly increasing in *Enterobacteriaceae* too, especially *Klebsiella* spp. and is an excellent marker for such situations[1].

Acinetobacter baumannii is the usual carbapenem resistant pathogen linked to nosocomial infections worldwide and its infections are commonly seen to be occurring, especially in severely ill people with either major trauma, significant comorbidities, or immunosuppression. Carbapenem resistance among *A. baumannii* is conferred by multiple coexisting mechanisms, with production of β-lactamases being the predominant one[6].

The recurrent resistance causes reduced therapeutic options, as well as higher mortality. *P. aeruginosa* is a problematic pathogen as it is hard to treat compared to other GNB. In *P. aeruginosa,* major role in carbapenem resistance is played by intrinsic/chromosomal-mediated resistance mechanisms. Typical resistance mechanisms in carbapenem resistant *P. aeruginosa* are variations or loss of the outer membrane proteins. These are required for the uptake of carbapenems, combined with overexpression of the chromosomal cephalosporinase AmpC β-lactamase, up regulation of efflux systems that can acquire resistance to unrelated antibiotic groups[7].

The principal spp. among the cluster of carbapenem resistant *Enterobacteriaceae* (CRE) is *Klebsiella pneumoniae*[8]. The predominant cause of carbapenem resistance in *K. pneumoniae* is the generation of carbapenemases, which additionally affect other antibiotics such as, beta-lactam's. Non-carbapenemase-mediated process of resistance in carbapenem resistant *K. pneumoniae* is rare but, in general, vastly unknown[1].

Intravenous treatment options for MDR GNB

Infections induced by multiple drug resistant (MDR) GNB microorganisms usually happen when there is hidden ailment, damage or hospitalization. MDR GNB might be obtained from different patients on broad-spectrum antibacterial agents for prolonged periods. Infections brought about due to MDR GNB are hard to treat thus may cause increasingly drawn out other effects, for example, pneumonia or septicemia. This can extend the duration of stay in the hospital, eventually leading to fatal outcomes. A few kinds of MDR GNB, for example, *Acinetobacter* spp. colonize in territories of the body with no apparent signs or signs and symptoms[8,9].

Groups of carbapenems like meropenem, imipenem and ertapenem have a variety of roles, one of them is the treatment of lethal infections with Extended Spectrum β-Lactamases (ESBL) and AmpC β-lactamase producing *Enterobacteriaceae* and they are used for empirical treatment of sepsis caused due to GNB. Imipenem has its effects during the emergence of resistance within *P. aeruginosa* but should be avoided in susceptible *Pseudomonas* spp. infections. If any resistance is found, exact levels of meropenem resistance should be immediately tested for and any sign of the accountable class of carbapenemase (e.g. MBL/KPC/OXA48-like) all imipenem or meropenem resistant isolates of *Enterobacteriaceae* should be detected. Preferably, meropenem and imipenem are chosen for empirical therapy of bacteremia (often developing within the urinary tract) because of their advantage to provide a broader spectrum range of treatment. Ertapenem is used in the advent of resistance via porin loss in ESBL- and AmpC β-lactamase producing *Klebsiella* spp. and *Enterobacter* spp. It is also used in a once-daily dosing regimen for outpatient parenteral antimicrobial therapy of susceptible infections. In case the bacteria responsible for the infection eventually do not produce neither ESBLs nor AmpC β-lactamase, narrower-spectrum agents should be used instead of carbapenems[8,9].

Ceftazidime is normally inadequate for treating infections with multi resistant *Enterobacteriaceae,* except certain OXA-48 carbapenemase producing bacterial strains. It remains helpful for infections caused by imipenem or quinolone susceptible *P. aeruginosa* strains. The utilization of ceftazidime in managing diseases caused due to ESBL-or AmpC β-lactamase producing *Enterobacteriaceae* or carbapenemase-producing *Enterobacteriaceae* (CPE), besides for OXA-48 makers, regardless of whether in vitro tests recommendation is to be avoided[10].

Ceftolozane/tazobactam is effective against various GNB, including *Enterobacteriaceae* and *P. aeruginosa*. These drugs have benefit in complicated cases of urinary tract infections (UTI's) and intra-abdominal infections. Ceftolozane is the most vigorous β-lactam against *P. aeruginosa* and it has potentially different uses. Concerning *MIC, ce*ftolozane/tazobactam should be avoided in infections caused due to AmpC β-lactamase producing or KPC producing *Enterobacteriaceae*[9]. Co-amoxiclave is mixture of broad-spectrum antibiotic, amoxicillin and the β-lactamase inhibitor, clavulanic acid. It's efficacy is seen in lower tract UTIs triggered by ESBL-producing bacteria, particularly pathogens that lack co-production of OXA-1 β-lactamase[9].

Cefepime has a greater disappointment level in infections caused by ESBL-producing GNB than carbapenems, provided minimum inhibitory concentrations of (MICs) against cefepime are ≤1 mg/L. The use cefepime for treatment of infection caused by ESBL or AmpC β-lactamase producing microorganism is not advised if inclined to the EUCAST breakpoint of MIC ≤1 mg/L. The longer use of cefepime even at increased dose for isolates is not advised with (i) MIC of 2–8 mg/L (CLSI 'susceptible dose dependent') or (ii) MIC 2–4 mg/L (EUCAST intermediate) or (iii) strains producing both AmpC β-lactamase and ESBLs. Bacteremia caused due to *E. coli* strains barring ESBLs and with MIC ≥2 mg/L but <8 mg/L can be correctly handled with cefepime but the use of cefepime is not advised to treat infections caused by CPE[9].

Fluoroquinolones are advantageous in therapy of complicated UTI caused by *Enterobacteriaceae* residing in intestinal flora and additionally for quinolone-susceptible MDR GNB. Oral or intravenous (IV) fluoroquinolones can be used for the UTIs due to *Enterobacteriaceae* with ESBLs, if there is no conflict *in vitro*; then most ESBL producing strains are resistant to fluoroquinolones (comprising of levofloxacin and ciprofloxacin). Fluoroquinolones are used in combination with at least one of the other agents, trimethoprim/sulfamethoxazole, ceftazidime or tigecycline to treat infections caused by *Stenotrophomonas maltophilia*, as resistance is usual. They can be used orally to handle UTI caused by susceptible MDR GNB[10].

Oral medications used for secondary or tertiary treatment including UTI

The first agent that can be used orally is pivmecillinam, which is the oral formulation of mecillinam. They can be used uniquely to treat lower UTI that are caused by AmpC β-lactamase producing *Enterobacteriaceae*. This drug effectively combats ESBL-producing *E. coli* but not the carbapenemase producers. Individuals

infected with these strains can be treated with carbapenems and then orally followed up on pivmecillinam alone for UTI due to mecillinam's apparent activity *in vitro*[9].

The third generation cephalosporin known as cefixime is an oral formula, which, in contrast to pivmecillinam, is no longer effective by itself for ESBL-producing *E. coli* for the reason that there is resistance to more than one antibacterial agents, including quinolones. Cefixime and co-amoxiclave combined can be used for treating ESBL producing *Enterobacteriaceae*, as supported by *in-vitro* data. These combinations must not be used against pathogens without investigations done to recognize AmpC β-lactamase and ESBL production. The transconjugant form of *E. coli* supports that cefixime in addition to clavulanate is convincing against strains producing CTX-M-15. Other cephalosporins such as cefdinir, ceftibuten and cefpodoxime, likewise indicated synergism with clavulanate, though sulbactam was less successful as a potentiator. Cefixime, not added or added to clavulanate, was not active against AmpC β-lactamase producing pathogens nor would it be relied upon to be active against Carbapenemase-producing *Enterobacteriaceae* (CPE)[9,10].

Nitrofurantoin is generally utilized in uncomplicated UTI. The resistance rate by *E. coli* is low, although new plasmid-intervened tools of defiance are now established. Low concentrations of the antibacterial agent reach the renal tissue and the circulation system but consequently, it is contraindicated if pyelonephritis (upper UTI) or bacteremia is suspected. Resistance of nitrofurantoin is intrinsic in *Morganella morganii* and *Providencia* spp. Furthermore, it is characteristic in *Proteus* spp. and *Serratia* spp. Moreover, antibacterial agent may not have an efficacy in the alkalinized urine that is due to urease-producing pathogens. For example, a lot of urease is produced by these and possibly *Staphylococcus saprophyticus* that is defenseless *in vitro*. Nitrofurantoin resistance is extremely common in CPE[9].

Usually, there are no differences shown in fecal *Enterobacteriaceae* while consuming or following use of nitrofurantoin. Estimated GFR (eGFR) decreases with age and nitrofurantoin must no longer be utilized if it's <45mL/min. A short option of 3 to 7 days might be utilized in individuals with an eGFR of 30 to 44 mL/min/1.73 m^2. Still, it is being used in lower UTIs with MDR organisms while the advantages of nitrofurantoin are expected to exceed the side effects. Repetitive or long-term plans of nitrofurantoin are related to serious pneumonic fibrosis[9].

Fosfomycin is effective in the management of lower UTI caused by MDR *Enterobacteriaceae*. Fosfomycin in given orally either while fasting 2 or 3 hours prior to meals, as the absorption rate is minimized after the ingestion of food, which leads to drop in the concentrations in urine. Uncomplicated cystitis is the only indication for use of oral fosfomycin. The urinary concentration along with its constituents restricts *E. coli multiplication* for at least first 48 hours. Prophylactic regimens of pyelonephritis, in individuals with asymptomatic bacteriuria in pregnancy, and chronic prostatitis consist of oral fosfomycin trometamol. The long and repetitive use of fosfomycin has led to major complication such as plasmid as well as chromosomally mediated resistance in patients[9].

The Next Invention of Agents and Adjuvants against GNB: Antibiotic Hybrids

The existence of the outer membrane makes Gram-negative microorganisms characteristically impervious to numerous antibacterial agents, particularly those with an increased molecular bulk and hydrophobicity. For example, lipopolysaccharide (LPS) structure makes the bacterial outer membrane extra prohibitive to hydrophobic antimicrobials, compared to the inner membrane. With this, we can confer that the hydrophilic carbohydrate part of LPS makes a hydration circle, which is impermeable to the track of hydrophobic molecules through the membrane. The glycopeptide antimicrobial, known as vancomycin, with a subatomic mass of 1449.3 g/mol, does not have any antibacterial action against most GNB. It prevents peptidoglycan synthesis by isolating the peptidoglycan precursors, so glycan cross-linking cannot be done. On the other hand, in gram-positive microbe's, vancomycin has no antibacterial restrictions, as its target is situated at the cell membrane. Nevertheless, it should cross the outer membrane and come to the periplasmic area to evoke its capacity in GNB. This is particularly difficult for vancomycin due

to its defensive membrane barrier, hindering the membrane to be impermeable to all significant glycopeptide antimicrobials[5].

It must be eminent that drug efflux overexpression may be problematic by causing intrinsic resistance to pathogens. It also affects the intracellular dosage of a therapeutic agent. Antibiotics from the oxazolidinone class, for example, linezolid, don't have potent action against most GNB, probably because of permeability obstructions over the outer membrane and/or efflux[5,10].

Pathogens are resistant to anti-microbial monotherapy because of their quick multiplying periods and high transmutation degrees. A few of them, for example, those from *Mycobacterium* spp. class show anti-microbial resilience because of their moderate growth. A mutation that presents general fitness under such antimicrobial stress is proliferated in enduring cells and along these lines offers the formation of a drug resistant approach. It is also evident that a few pathogens under antimicrobial monotherapy might prompt opposition systems that give cross-protection from other clinically irrelevant antibacterial classes[5]. A hybrid antibiotic is defined as a synthetic, established agent capable of eliciting a desired antimicrobial effect and it is made up of two or more pharmacophores. This comprises of agents that are depicted as being either dual-action hybrids, antibiotic conjugates, chimeric, or multivalent/divalent [5,11.]

In the typical hybrid drug approach, a robust non-cleavable molecular linker capable of withstanding enzymatic and non-enzymatic attacks throughout in the body, covalently links the participating therapeutic agents. After arriving into the body, a hybrid drug is relied upon to provoke its antibacterial activity by using both of its pharmacophoric area at the same time. In any case, it ought to be noticed that the advancement of a hybrid medication that can concurrently restrain both targets by using just a particular molecular substance is a difficult task to achieve[12].

The hybrid preparation approach is more prevalent than the prodrug approach because of scarce number of available bacteria specific cleavable linkers, in order to provide a prodrug delivery method. A hybrid agent is relied upon to stay a uni-molecular substance as it journeys to the site of infection and navigates through the bacterial membrane into the internal compartments such as periplasmic and cytosolic space. In any case, contrasts in such methodologies lie by the way they evoke their biotic function. A hybrid prodrug undergoes enzymatic cleavage, as it arrives in the bacterial cell, to yield two useful remedial elements, while a hybrid medication would stay a solitary substance all through its time course. In this way, hybrid medications might be beneficial as far as their drug metabolism and elimination is concerned[12].

Mostly, the antibiotic hydrids against GNB have a fluoroquinolone pharmacophore (for the most part ciprofloxacin). The decision of joining a fluoroquinolone as a principal medication might be credited to its strong substance properties that are constant even under numerous situations. Additionally, it might be simpler to attach fluoroquinolones to other helpful pharmacophore, for instance, β-lactams with slender areas of substance strength. In addition, the well-clarified structure-action association of fluoroquinolone antimicrobial and their expansive range of movement cause them to be an alluring class of anti-toxins[12].

The most encouraging passage is a combined naringenin/ciprofloxacin hybrid (known as hybrid 7) that has a strong antibiotic activity against Gram-positive microbes (MIC50 of 0.29 g/ml against Methicillin Resistant *S. aureus* [MRSA]), GNB (MIC50 of 0.71 g/ml against MDR *E. coli*), and fungi (MIC50 of 0.14 g/ml against amphotericin B-resistant *Candida albicans*)[5,10,13].

Considering their apparent advantages, the idea of antibiotic hybrids is appealing but they are not without a problem. Stubborn chemical synthesis, molecular complexity and the effort required to institute the mode of action and advantage of hybrids over conventional medications make the approach of hybrids daunting[10,13].

Phage therapy/phage lytic proteins as antimicrobial

Rise in multidrug resistant (MDR) clinical pathogens have led to an alarming drop in research and development of new antibiotics, and hence roles of reprogramming of antibiotics, finding alternatives and combinational therapies as future strategies in designing effective antibacterial

agents are being exploited[14-16]. Alternatively, the use of bacteriophage therapy to treat bacterial infections is becoming increasingly popular in field of research. Phage technique, either as a substitute or as a supplement to antibiotic treatments, has proved to be extremely promising in two ways such as the identification of effective antibodies directed against pathogens, as well as for vaccine development. Recent clinical trials have shown great potential in conventional phage therapies that are based upon the mechanism to use naturally occurring phages, which pollute and lyse bacteria at their site of infection. Most importantly, their use has also been vastly studied for public health surveillance, as biosensor phages can be used to detect food and water contaminations, as well as prevent bacterial epidemics[13].

How do bacteriophages perform their function?

Phages are naturally occurring, exceptionally varied, non-living biological beings containing DNA or RNA, surrounded inside a protein capsid. They are not able to reproduce independently and thus, are eventually dependent on bacterial host for survival. There are two steps as to how phages lyse the cell: first, the bacteriophage binds to a certain receptor on the bacterial cell surface. Then, they fuse this substance into the bacterial genome (known as temperate phages) either to duplicate vertically from mother to daughter cell or takeover the bacterial multiplication apparatus to produce the next phage descendants and lyse the cell (known as lytic phages). Immediately after the phage decedent's critical capacity has been reached, depending on the environmental aspects, the lytic proteins then become activated. They hydrolyze the peptidoglycan cell wall, thus releasing novel phage to restart the lytic cycle.[12]

During the lysis of the bacterial host there are two major protein classes engaged by the phage spp. The first is the transmembrane protein known as 'holin' and the second is a peptidoglycan cell wall hydrolase referred to as 'endolysin.' These work collectively in activating bacterial cell lysis. Advancements show that a newly noticed lysin, ABgp46, withholds the capability to lyse many gram-negative and MDR pathogens such as *Salmonella* Typhimurium, *A. baumannii*, *P. aeruginosa*, and *Streptococcus pneumoniae*, among others. This has led to the scientists discover that together, the phage lysins and antibiotics are more effective in abolishing infections in contrast to using antibiotics alone. This has further been proved by the use of *in vitro* and ex vivo phages in *Clostridium difficile*[13].

Most of the time, phages are virulent only to those specific pathogens, which are carrying their complementary receptor, and this regulates lytic phage host range. The foremost usual lytic phages linked with pathogens infecting humans and the gut microbiotas are the Caudovirales (known as the tailed phages) and Microviridae. The tailed phages have double stranded DNA genomes whereas the Microviridae have single-stranded viruses[13].

Contrastingly, lysogenic phages can also be of importance to the bacterial host as the phages incorporate their genetic composition into the bacterial chromosome. This results in encoding for virulence factors (e.g., botulinum toxin, diphtheria toxin and shiga toxin), and antibiotic resistance genes (e.g., β-lactamases)[13].

There is another therapy known as 'conventional phage therapy.' This solemnly focuses on strictly lytic phages that only kill the bacterial host. To treat animals, lytic phages are collected into "phage cocktails" which contain numerous phages that have *in vitro* effectiveness against the bacterial pathogen[13].

Phage lytic proteins as antimicrobials

Current research has used bacteriophages on animal prototypes to examine a range of clinically significant pathogens. The following pathogens have been examined:

- A single dose of phage cocktail was sufficiently used as prophylaxis in *C. difficile* induced ileocecitis, while the control animals obtaining clindamycin passed away within 96 hours. Phage cocktails also drastically compacted *C. difficile* growth *in vitro* and restricted multiplication *in vivo.*
- On oral administration of phage cocktail for patients suffering from gut-derived sepsis, the mortality rate reduced to 66.7%.
- A single strain of phage administered intraperitoneally was adequate to protect vancomycin-resistant *E. faecium*, ESBL producing *E. coli*, as well as imipenem-resistant *P. aeruginosa*.
- Phage cocktails are used to treat antibiotic-

Table 1. Antibacterial agents available for treatment of carbapenemase producing Gram-negative pathogens (Adapted from: Doi, 2019[18] and Chew et al., 2018[19])

SL No.	Agents	IV	Oral	Activity	Pathogens covered	Indications
01	Fosfomycin	Yes	Yes	Class- A, B and D carbapenemases	*Enterobacteriaceae*	• Complicated UTIs & Acute pyelonephritis
02	Ceftolozane-tazobactam	Yes	No	None	*P. aeruginosa*	• Complicated UTIs & Acute pyelonephritis, nosocomial pneumonia and Complicated IAIs
03	Ceftazidime-avibactam	Yes	No	Class- A and D carbapenemases	*P. aeruginosa*	• Complicated UTIs, Acute pyelonephritis, complicated IAIs, Hospital-acquired bacterial pneumonia and VA bacterial pneumonia
04	Meropenem-vaborbactam	Yes	No	Class- A carbapenemase	*Enterobacteriaceae*	• Complicated UTIs & Acute pyelonephritis
05	Plazomicin	Yes	No	Class- A and D carbapenemases	*Enterobacteriaceae*	• Complicated UTIs & Acute pyelonephritis
06	Eravacycline	Yes	No	Class- A, B and D carbapenemases	*A. baumannii* & *S. maltophilia*	• Complicated IAIs
07	Imipenem-cilastatin-relebactam	Yes	No	Class- A carbapenemase	*P. aeruginosa*	• Complicated UTIs, Acute pyelonephritis, complicated IAIs, Hospital-acquired bacterial pneumonia & VA bacterial pneumonia
08	Cefiderocol	Yes	No	Class- A, B and D carbapenemases	*P. aeruginosa*, *A. baumannii* & *S. maltophilia*	• Complicated UTIs, Acute pyelonephritis, hospital-acquired bacterial pneumonia & VA bacterial pneumonia
09	Aztreonam-Avibactam	Yes	No	MβLs (NDM, IMP, or VIM) cocarrying a KPC or OXA- 48-like carbapenemase	*P. aeruginosa*, *A. baumannii* & *S. maltophilia*	• Complicated UTIs, Complicated IAIs, hospital-acquired bacterial pneumonia & VA bacterial pneumonia

Abbreviations: IV- Intravenous, A. baumannii, Acinetobacter baumannii; IAIs, intra-abdominal infections; MβLs, Metallo β- lactamases; UTI, urinary tract infection; KPC, Klebsiella pneumoniae carbapenemase; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase; P. aeruginosa, Pseudomonas aeruginosa; S. maltophilia, Stenotrophomonas maltophilia, VIM, Verona integron-encoded metallo-β-lactamase; VA, ventilator-associated.

resistant *P. aeruginosa* contaminations of the lungs, gastrointestinal tract and skin.

Further studies show likewise favorable outcomes for multidrug-resistant *E. coli*, *Vibrio parahaemolyticus*, *S. aureus*, and *A. baumannii*. These researches have shown that there is a sign that bacteriophages will be able to restore antibiotic sensitivity in antibiotic resistant bacteria, such as multidrug-resistant *P. aeruginosa*[12,13].

Trials on humans have also been conducted using bacteriophages. They have vastly been used in clinical treatment of everyday bacterial pathogens such as *E. coli, S. aureus*, *Streptococcus* spp., *P. aeruginosa*, *Proteus* spp. Both, therapeutic and prophylactic effectiveness has been achieved in cases of surgery and gastroenterology. Recently, a study was conducted where six patients with diabetic foot ulcers unresponsive to antibiotics, received topical application of *S. aureus* - specific phage. The results showed that this was sufficient for recovery in all patients[13].

Biosensor phages

Currently, none of the phage therapy products have been permitted for use to humans in the European Union or The States. Nevertheless, the case is different in food industry. In this, numerous commercial phage formulations are used for bio-control of bacteria and the FDA approves them by being listed under the categorization called "generally considered as safe." The formulations are under use against MRSA, *Salmonella* spp., *E. coli, Listeria monocytogenes*, *Mycobacterium tuberculosis*, *Pseudomonas syringae* and *Campylobacter* spp. These recent studies have suggested that bacteriophage play a strategic role in successfully refining food safety at numerous stages such as in food production and processing, while also reducing the bacterial contamination in vegetables, fruits and dairy products. However, additional study is still required in this aspect[13].

Bioengineered chimeras of phage-derived lytic proteins may be the new era of antibacterials

Chimeric lysine forms by linking the active site of a lysin with a cell wall binding domain. Chimeric lysines are highly skilled of saving animals infected with MRSA bacteremia. They have efficiently been able to avert fatality from *S. pneumoniae* and stop growth of methicillin-sensitive *Staphylococcus aureus* (MSSA) endophthalmitis. However, researches on such bioengineered proteins are still in the early stages[13].

GNB have an impermeable LPS outer membrane; whereas lysins perform through enzymes. They cleave the bacterial cell wall thus, becoming less successful against such microorganisms. As an effort, to overcome its target, bioengineered artificial lysin molecules, termed artilysins, have been manufactured which are able to penetrate the outer membrane. Until now in a nematode gut model, artilysins have successfully decolonized *P. aeruginosa* as well as protected the human keratinocytes when tested with *A. baumannii*[13].

Antibacterial agents available for treatment of multidrug resistant (MDR) Gram-negative pathogens

To summarize the antibacterial agents, available for treatment of multidrug resistant (MDR) Gram-negative pathogens include, amikacin; amoxicillin/clavulanate; ampicillin/sulbactam; aztreonam; cefepime; cefixime and other oral cephalosporins; ceftazidime; ceftazidime/avibactam; ertapenem; fluoroquinolones; fosfomycin; gentamicin; imipenem and meropenem; nitrofurantoin; piperacillin/tazobactam; pivmecillinam; polymyxins (including colistin); temocillin; tigecycline; tobramycin & trimethoprim/sulfamethoxazole. The antibacterial agent used depends on antibiotic policies, empirical use, toxicity and mechanisms of antimicrobial resistance[17-19](Table 1).

CONCLUSION

The choice of empirical therapy is complicated by antibiotic resistance and can be combated by accurate antibiotic and their combinations usage, which is critical to patient survival. Noteworthy are local epidemiology, effective teamwork and antibiotic stewardship to guarantee that medications are utilized properly to counter the resistance.

ACKNOWLEDGMENTS

Not applicable.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

FUNDING

None.

ETHICS STATEMENT

This study was approved by RAKMHSU-REC.

DATA AVAILABILITY

All datasets generated or analyzed during this study are included in the manuscript.

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