Resistant Gram-Negative Urinary Tract Bacterial Infections

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Abstract

Urinary tract infection (UTI) is one of the most common infections in both the community as well in hospital settings. It is mostly caused by Gram-negative bacteria (GNBs). Over the past two decades, GNBs have developed complex mechanisms of resistance against most of the potent antibiotics. This has been a global challenge which has been identified by the World Health Organization as "one of the greatest threats to human health." This crisis is mostly attributed to the overuse and misuse of these medications, as well as lack of new drug antimicrobials by the pharmaceutical industry. This resulted in prolonged hospital stay, marked increase in the cost as well as increase in morbidity and mortality. Furthermore, it increases the risks and complications of urological procedures. In this chapter, we review the management of the most common and challenging group of resistant Gram-negative organisms, the extended-spectrum β-lactamases producing organisms (ESBL) and the carbapenem-resistant organisms (CRE/CRP). The latter group includes carbapenem-resistant *Enterobacteriaceae* (CRE), as well as *Pseudomonas aeruginosa* carbapenemases (CRP). When treating these infections, clinicians have few effective antimicrobials options. A critical step in managing these organisms is the early recognition and appropriate empiric therapy. Both showed morbidity and mortality benefits.

Keywords: urinary tract infection (UTI), Gram-negative bacteria (GNBs), complicated urinary tract infections (CUTIs), extended-spectrum β-lactamases producing organisms (ESBL), carbapenem-resistant organisms (CRE/CRP), carbapenems, ceftazidime-avibactam, colistin, fosfomycin, *Enterobacteriaceae*

1. Introduction

Urinary tract infection is the second most common infectious presentation in community as well as in hospital settings. It has been estimated that 150 million people are diagnosed with

UTI each year worldwide [1]. It is mostly caused by GNBs. Over the past two decades, GNBs have developed complex mechanisms of resistance against most of the potent antibiotics. This has been a global challenge which has been identified by the World Health Organization as "one of the greatest threats to human health" [2]. This crisis is mostly man-made as it is attributed to the overuse and misuse of these medications, as well as a lack of new drug development by the pharmaceutical industry seeking better profitable agents.

This resulted in prolonged hospital stay, marked increases in the cost as well as increase in morbidity and mortality [3–6]. Furthermore, bloodstream infections associated with severe complicated urinary tract infections (CUTIs) are associated with high mortality rates of 20–50% among critically ill patients. Many urological procedures are complicated with such infectious manse, frustrating the surgeons and the patients [7].

Multiple mechanisms that enable the organism to become resistant include enzymatic transformation, modification of site of action, active efflux from the cell interior and, the prevention of entry of the molecules into the cell [8].

There are different confusing terminologies in addressing this process. An international panel of experts developed the following definitions: multidrug-resistant (MDROs) means acquiring nonsusceptibility to at least one agent in three or more antimicrobial categories, extensively drug-resistant (XDR) is nonsusceptible to at least one agent in all, but two or fewer antimicrobial categories, and pan-drug-resistant (PDR) isolates are nonsusceptible to any of the available antimicrobial classes [1, 9, 10].

The term "ESKAPE" was one of the former descriptions of pathogens that cause the majority of hospital infections while effectively "escaping" the effects of available therapeutics. Other terms include "SPICE organisms" which include many Gram-negative bacteria that have inducible, chromosomal AmpC β-lactamase genes. The resistance to antibiotics may not be detectable initially, but appears after a period of exposure to β-lactam antibiotics (during therapy or after).

We are focusing in this review on the most common and challenging groups of resistant Gram-negative organisms, the ESBL, and the CRE, as well as CRP. The other highly resistant organism, such as *Acinetobacter baumannii*, less frequently causes urinary tract infection and its therapy is even more complicated [11–13].

When treating these infections, clinicians have a few effective antimicrobials to choose from and many are associated with significant adverse effects. A critical step in managing these organisms is the early recognition and appropriate empiric therapy. Both showed morbidity and mortality benefits. In this chapter we will review the available data on managing UTIs caused by ESBL and the CRE/CRP.

2. Materials and methods

The purpose of this chapter is to review the available data on managing UTIs caused by resistant Gram-negative bacteria. Clinical trials and review articles (in English) were

identified from a Medline search (2000–2017), in addition to laboratory data and abstracts from international Conferences.

2.1. Definition: ESBL organisms

The term ESBL was originally applied to plasmid-encoded β-lactamases that are capable of inactivating extended-spectrum cephalosporins and are inhibited by β-lactamase inhibitors, such as clavulanic acid. *Enterobacteriaceae*, primarily *Escherichia coli* and *Klebsiella pneumoniae*, are among the most frequently producing bacteria [9].

ESBLs are plasmid-encoded or chromosomally encoded β-lactamases with broad activity against penicillins and cephalosporins. They are a diverse group of bacterial enzymes that break down and inactivate most β-lactam antibiotics. They are inhibited by the available β-lactamase inhibitors (clavulanic acid, sulbactam, avibactam, and tazobactam) and do not affect cephamycins (e.g., cefoxitin and cefotetan) or carbapenems. β-Lactamases are divided into A, B, C, and D classes according to their amino acid sequence homology (Ambler classification) [14].

These bacteria are usually multi-resistant, as they are frequently capable of resisting other antibiotics, such as the aminoglycosides, tetracyclines, and trimethoprim/sulfamethoxazole though other mechanisms, leaving few treatment options [3]. As these resistant genes are plasmid-mediated, they can be easily disseminated to other bacterial species [15–17]. UTIs caused by these organisms are seen at alarming rates in both hospital infection and in the community settings [15, 18, 19].

Although 95–100% ESBL organisms are still considered sensitive to carbapenems, rapid emergence of carbapenem resistance has been documented globally, and was linked to the over usage of these agents [20].

2.2. Epidemiology

Surveillance in Asia, Latin America, and Europe revealed dramatically increasing resistance to cephalosporins among *E. coli* and *Klebsiella* spp. [21]. In a large study in Turkey (SMART), the rate of ESBL in *E. coli* isolated from urine samples was high (50% hospital isolates and 38% community acquired isolates) [22, 23].

In one study, 21,414 positive urine cultures were collected from a University hospital in the UK. There were 1420 ESBL-positive specimens. There were a 44% increase, from 4.6 to 6.6%, of the ESBL-positive organisms over 2 years.

Multidrug resistance were detected in 75% of ESBL + *Klebsiella* spp. against >6 antibiotic classes [24].

In the CHINET surveillance system data from 2005 to 2014, ESBL production among *E. coli* isolates was between 51.7 and 55.8% [25].

The spreading of such isolates in the community is well documented, so containment of this type of bacterial infection will be real challenging [23]. There were many outbreaks caused by these organisms all over the globe with high morbidity and mortalities [17].

2.3. Risk factors

Many studies have implicated broad-spectrum cephalosporins as the major class associated with ESBL production; others considered fluoroquinolone and β-lactam-β-lactamase inhibitor combinations, as the main risk factors for ESBL infections [26]. Other risk factors include nursing home residence, diabetes, recurrent UTIs, male gender, prolonged hospitalization, intensive care admission, and urinary catheterization [19, 24, 27–29].

Prospective cohort study of 225 healthy German volunteers traveling to 53 different countries (mostly in Asia, Africa, and S. America) evaluated the risk of ESBL colonization. Stool samples were collected before and after traveling. The isolates were examined phenotypically and by PCR amplification sequencing. Among 191 participants that were ESBL-negative before travel, 30% were colonized by ESBL-producing *E. coli* after returning home [29, 30].

The use of antibiotics in farm animals as growth promoters is linked to this global disaster. In a recent study from India, 18 poultry farms were surveyed, 16 of them reported using antimicrobials for growth promotion. There were 1556 *E. coli* isolates, collected and tested. The prevalence of ESBL-positive strains in broiler farms was 87% [31]. Multiple studies have shown the benefit of early identifications of this organism, to offer the appropriate empiric therapy. A simple predicting score for early recognition was recently published. Four risk factors were identified; each was given a score of one. Scores above 2 had a sensitivity of (84%) and a specificity of (92%). These variables include recent antimicrobial use (OR, 15.29), recent invasive procedures (OR, 12.33), nursing home residents (OR, 27.77), and frequent emergency department visits (OR, 9.98) [32].

2.4. Mechanism of resistance

The most common mechanisms include enzymatic inactivation, target modification, reduced permeability, and active efflux. Antibiotic resistance can be intrinsic to specific microorganisms, which can be explained by their inherent characteristics. Point mutations on β-lactamase genes are responsible for emergence of ESBLs. These new genes could be transmitted through small mobile genetic element DNA (plasmid, transposons) to other bacteria from same or other species [5, 8].

A more distinct type of ESBL including CTX-M-type, AmpC, and carbapenemase, can confer phenotypic resistance that widens the resistance abilities against more antibiotics than the classical isolates [33].

2.5. Detection

These organisms are capable of resisting most of the third-generation cephalosporins but they are inhibited by clavulanate. This is the basis of detecting these organisms using routine laboratory tests such as double disk diffusion test or E-test. The size of zone of inhibition around one or more of the β-lactam-containing discs toward the clavulanic acid-containing disc is indicative of some ESBL producers [34, 35].

The detection of specific genes by PCR and sequencing are commonly used for final confirmation of ESBL producers. A commercially available multiplex real-time PCR can detect the predominant class A β-lactamase genes bla_{CTX-M}, bla_{SHV}, bla_{TEM}, and CIT-type AmpCs with high sensitivity and it is much faster than routine cultures [36].

2.6. Carbapenem resistant organisms

The carbapenems are the most potent agents with wide spectra of coverage. They are the most dependent agents in critical infectious syndromes. However, resistance to these agents has increasingly been reported worldwide, rendering them increasingly ineffective. These organisms are also capable of resisting other classes of antibiotics (aminoglycosides, fluoroquinolone, and co-trimoxazole), due to the frequent coexistence of other resistance genes on the same mobile genetic elements, rendering them superbugs. The most recent example is the emergence of colistin resistant genes in isolates which are already resistant to the carbapenems.

K. pneumoniae carbapenemase (KPC-class A) was the first CRE enzyme to be reported in 2001. New Delhi metallo-β-lactamase (NDM-class B) is one of the most recently reported metallo-enzymes. It has spread widely in the Indian sub-continent and now worldwide. The oxacillinase-48 type (OXA-48-class C) has been identified mostly in Mediterranean and southern European countries. Other mechanisms of resistance include efflux pump over activity (pumping the antibiotics out of the bacterial cell), hyper production of AmpC β-lactamase in the already highly resistant ESBL organisms, and changes in porin permeability [8].

Infections with such resistant isolates resulted in high morbidity, prolonged hospital stay, and mortality [37, 38]. In a pooled analysis of the 9 studies (985 patients), the mortality rate was higher among CRE-infected than carbapenem susceptible *Enterobacteriaceae*-infected patients (RR 2.05, 95% CI 1.56–2.69). The authors calculated 26–44% of deaths from 7 studies attributable to carbapenem resistance [39]. The rate was even higher (61%) in patients infected with KPC-expressing *K. pneumoniae* who received initially ineffective therapy [40].

2.7. Epidemiology

A multicenter observational study in 11 hospitals from 7 Latin American countries that included 255 patients with bacteremia was reported. Twenty-three percent of the isolates were CRE/CRP [38].

According to the latest data collected by the European Antimicrobial Resistance Surveillance Network (EARS-Net), the rate of CRE rose from 6.2% in 2012 to 8.1% in 2015 [41].

CRE are more prevalent in Italy and Greece. In an active surveillance study, rectal swabs (and clinical samples) were collected from 15,104 hospitalized patients (over 2 years). *K. pneumoniae* CRE was detected in 496 consecutive non-replicated samples [42].

In a Greek study, 3449 *K. pneumoniae* isolates were recovered over 10 years. Among them, 1668 (48%) were CRE-producing. Sixteen percent of the isolates were resistant to colistin [43].

2.8. Detection

These include antimicrobial susceptibility testing, modified Hodge testing, and inhibitor-based testing. In 2015, the CDC-CRE surveillance definition was revised to one of two criteria: (1) resistance to any carbapenem according to current CLSI breakpoints (MIC ≥ 2 for ertapenem or ≥4 for doripenem, meropenem, or imipenem) or (2) demonstration of carbapenemase production. Several phenotypic assays are available commercially detecting carbapenemase production from bacterial culture within hours. The Carba NP test has high sensitivity and specificity that can differentiate between class A, B, and C CRE. In one study, its specificity and sensitivity were almost 96% [44].

There are many commercially available PCR-based testing for early recognition and confirmation.

2.9. Therapy of urinary tract infections caused by MDROs

2.9.1. ESBL-producing β-lactamases

In general and for serious life threatening infections, the carbapenems are the drugs of choice for infections caused by these organisms [12, 35]. However, the surge in using the carbapenems, resulted in the evolution of CRE/CRP, so there were multiple recent trials evaluating, carbapenem-sparing are regimens, mostly for less severe infections [12, 45–48].

2.9.2. CRE/CRP

In general, there is no clear consensus on managing these organisms. The available data are drawn from expert opinion or from small trials. There are few controlled trials that determined the best therapeutic so far [49, 50].

In the following sections, we will review the available data on different classes of antibiotics that have been used in managing ESBL, and then if applicable, will discuss their roles in treating CRE/CRP.

2.9.2.1. Carbapenems

They have a broad spectrum of antimicrobial activity more than any other classes of antimicrobials, and are potent bactericidal (ertapenem lakes anti-pseudomonas activities) [51–54].

In multiple non-randomized studies that included large number of patients with bacteremia, sepsis, and other serious infections, they showed high cure-improvement rates with great safety profile [54, 55].

Studies of the pharmacokinetic/pharmacodynamics data also showed superiority of this class of antibiotic in achieving the proper concentration above the bacterial minimal inhibitory concentrations (MICs) [56].

In vitro activities against many ESBL isolates are well documented against large collections of ESBL producing *Enterobacteriaceae* and *P. aeruginosa* isolates [57].

For treating CRE/CRP, limited data on combination regimens involving carbapenems (if MICs ≥ 8 mg/L) adding colistin or high-dose tigecycline or aminoglycoside or even triple combinations, seem to confer decent therapeutic advantage over monotherapy. For organisms with higher MIC, a combination of two or even three antibiotics may be needed.

In a recent meta-analysis of 22 studies of using, the most common regimen, carbapenems plus colistin or polymyxin had mortality advantages [38].

On the other hand, a retrospective study of 436 patients were recruited in the INCREMENT study-cohort (26 tertiary hospitals from 10 countries). The main outcome variable was 30 day all-cause mortality in patients with CRE/CRP bloodstream infection. Overall mortality was not different between those receiving combination therapy and monotherapy (35% vs. 41%) [58].

Synergy is another potential benefit arising from the use of antibiotic combinations.

Tigecycline with colistin, colistin with a carbapenem, fosfomycin with a carbapenem, fosfomycin with an aminoglycoside, and a carbapenem with an aminoglycoside have been reported as antibiotic combinations effectively administered to series of patients infected with carbapenemase-producing *Enterobacteriaceae* [4].

Efforts have been exerted to limit the usage of their precious agents by using alternative regimens whenever [46].

2.9.2.2. Piperacillin-tazobactam (PTZ)

PTZ is a broad-spectrum drug combination used in serious infections. However, the extensive usage of this agent accelerated the emergence of resistance [48, 59].

Some ESBL *E. coli* producers' isolates might have high in vitro susceptibility to PTZ; however, its clinical utility in serious UTIs, especially when associated with bacteremia, has been controversial. In a prospective, randomized, open-label comparison of the therapeutic efficacy of (PTZ), cefepime, and ertapenem in nosocomial UTIs with ESBL producers, 66 participants were evenly randomized to the PTZ and ertapenem treatment groups (cefepime arm was eliminated because of high treatment failure rate). The clinical and microbiological responses to both antibiotics were similar around 94% [60].

Similar non-inferiority of PTZ to carbapenems was shown in a retrospective analysis of bloodstream infection by an ESBL-producing organism, if susceptible in vitro [61].

In a post hoc analysis of patients with bloodstream infections due to ESBL producing isolates from 6 published prospective cohorts, the effect of amoxicillin-clavulanic acid, PTZ, and

carbapenems were compared. The mortality rates at day 30 were much higher with the first 2 antibiotics than with carbapenems [62].

In a retrospective observational study, 331 patients with ESBL bacteremias were evaluated. Empiric therapy with PTZ was used in 48% while 52% received carbapenems. The adjusted risk of death (14-day mortality) was 1.92 times higher for patients receiving empiric PTZ compared with carbapenem therapy (95% confidence interval, 1.07–3.45) [63].

In an editorial that tried to explain these controversial results, the authors mentioned various variables including the inoculum of the bacteria in the bloodstream, the sources of bacteremia (less fatal if from UTIs than central line infections), selection bias inherent to observational studies, and the presence of different genetic and virulence of the included bacteria [35].

A large recent multicenter randomized controlled open-label non-inferiority trial, MERINO trial, comparing meropenem (standard arm) against PTZ in adult patients with bacteremia caused by *E. coli* or *Klebsiella* spp., is ongoing, and hopefully, it will provide better answer to these conflicting data [61].

2.9.2.3. Cephalosporins

Cephalosporins have been less effective than comparative regimens in treating severe/serious infections with ESBL-producing bacteria. They are rapidly hydrolyzed by many ESBLs stains [60].

In many clinical studies, it was associated with a trend toward clinical and microbiological failure, as well as a trend of increased mortality [64, 65].

Despite their in vitro activities, there are reports of mutations and/or acquiring plasmids encoding AmpC-resistant genes during therapy with these agents. Others concerns about this agent failure include the decreased activity with high bacterial load (inoculum effect) and the failure to meet necessary pharmacodynamics targets due to inadequate dosing and/or interval schedules [50].

The most studied agent in this class is the cefepime. In the above-mentioned recent prospective, randomized, open-label that compared (PTZ), cefepime, and ertapenem in nosocomial UTIs, the microbiological and therapeutic efficacies of cefepime in febrile nosocomial urinary tract infection with ESBL *E. coli* were much less than the other competitors at 33% [60].

Data is more clear in patients with serious infections associated with ESBL-producing organisms' bloodstream infections. In a recent study, the mortality risk was 2.87 times higher for patients receiving cefepime compared with carbapenems (95% confidence interval (0.88–9.41) [66].

Another retrospective study included adult patients with BSI due to ESBL-producing *K. pneumoniae* or *E. coli*. In multivariate analysis, using cefepime as empirical therapy was associated with a trend toward an increased mortality risk, while empirical carbapenem therapy was associated with a trend toward decreased mortality [65].

There is few data from limited studies (with small number of participants) that showed cefepime is effective if used against in vitro susceptible ESBL-producing *Enterobacteriaceae* and as a de-escalation therapy in patients with uncomplicated UTIs [53, 67].

There are less robust data for the efficacy of other cephalosporins, cefmetazole (a cephamycins), in treating patients with extended-spectrum β-lactamase producing [68].

2.9.2.4. Aminoglycosides

Aminoglycosides are very potent antibiotics; however, their use is associated with significant renal and auditory toxicities. They have been successful in treating ESBL-UTIs as a mono-therapy or in combinations with other agents. Combinations with other agents were effective in the treatment of CRE/CRP infections if the strain is susceptible to aminoglycosides [69].

Many of the plasmids that carry ESBL-producing genes also carry genes encodes resistant to aminoglycosides, mostly against tobramycin and gentamicin. In contrast, amikacin has retained high susceptibility rates, particularly against *E. coli.*

In a small study of UTI caused by highly resistant ESBL (also resistant to nitrofurantoin, fosfomycin, and quinolones and trimethoprim/sulfamethoxazole), amikacin intramuscular injections for 10 days achieved clinical success in 97.2%. Overall bacteriological success rate was 94.1% on the 7–10 days after treatment [70].

In a review of 20 studies evaluating CRE infections therapy, combination of aminoglycosides and carbapenems displayed the lowest mortality rate (11.1%) [71].

2.9.2.5. Fluoroquinolones

In many parts of the world, *E. coli* fluoroquinolone resistance rates are >20% among patients with community-acquired uncomplicated UTI and 50% among patients with complicated infections. The rate of resistance is even higher against *Klebsiella* spp. up to 70% in one recent international surveillance study [8, 72].

The co-existing of ESBL and fluoroquinolone resistant is extremely high in some areas of the world, in those who uses quinolones prophylaxis and in returned travelers to theses endemic areas [73]. Therefore, they are in general not recommended in the setting of high ESBL isolates [74].

Sitafloxacin is the newest member (fourth generation) of the fluoroquinolone family of antibiotics which has a broad-spectrum activity including many anaerobes [75]. In a recent prospective randomized controlled trial, comparing the clinical and bacteriological efficacy of sitafloxacin and ertapenem for non-bacteremic acute pyelonephritis caused by ESBL-EC was evaluated. Carbapenems were initially given to all patients, and then were randomized to one of the study drugs. The 2 arms were equal in the rates of clinical and microbiological cure [76].

These data suggest that fluoroquinolones may no longer be effective as first-line therapy for Gram-negative UTI in hospitalized patients and definitely in ESBL-producing organisms.

2.9.2.6. Trimethoprim/sulfamethoxazole

Although treatment with trimethoprim/sulfamethoxazole was traditionally effective in treating UTIS, the evolution of resistance is a current major concern. The Infectious Diseases Society of America guideline recommends against using it if local bacterial resistance rate is ≥20% [77]. Genes that encode for ESBLs are usually found on large plasmids accompanied by genetic determinants of resistance against multiple classes of antibiotics, such as aminoglycosides, sulfonamides, and fluoroquinolones. TMP-SMX is not recommended as an empiric treatment option of UTIs caused by resistant strains of *E. coli* or *K. pneumoniae* that reaches 40–66% in some areas in the world [78].

2.9.2.7. Tigecycline

Tigecycline has potent activity against a vast majority of organisms including Gram-negatives, Gram-positives, and anaerobes. It has almost susceptibility rates of 100% against ESBL-producing *E. coli*, however less potency against *K. pneumoniae* isolates producing. However, its use has concerning safety issues [11, 79]. Insufficient urinary excretion of the unchanged drug (15–22% of the dose) has prompted recommendations to avoid tigecycline for UTIs therapy [80, 81].

In a systematic review of the literature, 14 patients received tigecycline for UTIs caused by MDR Gram-negative bacilli. In 12 patients, there were initial microbiological clearance. Eleven patients had evidence of clinical response. However, there were post-therapy growth of tigecycline-resistant organisms in 2 cases [81].

Few studies tried to overcome this obstacle by using higher than the recommended dose for highly resistant organisms (initial dose of 200 mg one time followed by 100 mg every 24 h) [82].

The efficacy of tigecycline is further limited by increasing in vitro resistance in CRE. Serum and urinary levels of tigecycline are low, and most experts discourage the use of tigecycline as monotherapy for bloodstream or urinary tract infections [83].

This agent has no activity against *Pseudomonas*, *Proteus*, *Providencia*, and *Morganella.*

2.9.2.8. The polymyxins

The polymyxins are antibacterial agents that are produced from different strains of *Bacillus polymyxa*. Colistin and polymyxin B are available commercially; both have similar chemical structures and antibacterial activity in vitro, however they differ in their pharmacokinetic profiles. They can cause significant nephrotoxicity (reported in 20–60%) and neurotoxicity [69]. However, the spreading of extensively resistant Gram-negative bacteria as well as the paucity of newer effective antimicrobials let to the extensive usage of these agents as a last resort [84]. The vast majority of ESBL-producing *E. coli* and *K. pneumoniae* are susceptible to these drugs.

Currently, they are the backbone of most of the regimens used against the CRE/CRP organisms. Common combination regimens include tigecycline, carbapenem, minocycline, rifampicin, aminoglycosides, ampicillin/sulbactam, and piperacillin-tazobactam. Large clinical trials are underway to clarify the use of polymyxin different combinations [85].

Polymyxin B is administered directly as the active antibiotic, whereas colistin methanesulfonate is converted in vivo to colistin. The optimal dosing of these agents is still controversial.

Higher doses of colistin were proposed for managing serious CRE/CRP associated infections.

A recent systematic review that included 22 studies (observational studies as well as randomized controlled trials) of polymyxin-based combination therapy in adult patients with infections caused by CRE/CRP was published. The primary outcome was a 30-day mortality. Mortality was significantly higher with polymyxin monotherapy compared with combination therapy of polymyxin with tigecycline, aminoglycosides or fosfomycin, of 1.57 (95% CI = 1.06–2.32). However, the authors caution about the low quality of the evidence [86].

The mechanism of colistin resistance can be generally classified intrinsic or acquired by a recently recognized plasmid-mediated resistance gene [87].

In November 2015, plasmid-borne colistin resistance gene mcr-1 was initially identified in animal and clinical samples from China. As of September 2016, the mcr-1 gene was detected in 35 countries worldwide in human sources in 22 countries [88]. This created a real lethal superbug.

2.9.2.9. Fosfomycin (Fosf)

This agent has gained attention, as it has activities against both Gram-positive and Gram-negative MDR and XDR bacteria [89, 90–94]. It exhibits bactericidal activity against many Gram-positive and Gram-negative pathogens including many of the ESBL-producing *E. coli* and *K. pneumoniae* [91]. Fosf achieves very high concentrations within the urine and is therefore an excellent agent for cystitis, but it is not recommended for treating pyelonephritis or bacteremias due to inadequate concentrations in the blood. However, small studies have shown great results in using Fosf in complicated UTIs [95]. It is currently approved by the American Food and Drug Administration for the treatment of uncomplicated cystitis as a one-time dose of 3 g. Several studies have shown clinical efficacy in the treatment of ESBL cystitis when the dosing is extended to 3 g every 48–72 h for 3 doses [96].

A meta-analysis that evaluated the antimicrobial activity, or the clinical effectiveness of Fosf, reviewed 17 studies. Out of a total of 5057 clinical isolates of *Enterobacteriaceae*, 4448 were ESBL producers. Almost 90% of the isolates were susceptible to Fosf. Eighty percent of 748 *K. pneumoniae* isolates produced ESBL and were susceptible to Fosf [94].

In a prospective study of 47 patients with UTI caused by *E. coli*-ESBL-producing organisms, the outcome was evaluated. Fosfomycin was used in 27 patients and 20 patients received meropenem. The clinical and microbiological success was similar in 2 groups; however, the

costs were significantly lower in the Fosf group (p < 0.001). Fosfomycin was used orally 3 g sachet every other night total of 3 doses, while meropenem was used as a dose for 14 days [95].

In a retrospective study, 60 patients were treated for MDR UTI. There were cases infected with *Enterobacteriaceae*, *P. aeruginosa*, and *VRE*. The clinical response rate was 55%. Chronic kidney disease was associated clinical failure (p = 0.04) [92].

For the carbapenem-producing organisms, a very few clinical data on using this agent are available.

In Europe, an intravenous Fosf formulation is available. In a small (in 11 ICU patients) European study, intravenous Fosf (2–4 g q6 h) in combination with other antibiotics was associated with good bacteriological and clinical outcomes in all patients with carbapenem-resistant *K. pneumoniae* infections [96].

In an in vitro study, 365 isolates out of 2229 urine samples were evaluated. ESBL producers were detected in 65% were, 16% were carbapenem-resistant *Enterobacteriaceae*, almost 95% of the total isolates were susceptible to Fosf [97].

A recent, albeit pessimistic, data came from China. A study collected 233 clinical isolates CRE/CRP *Carbapenem Resistant Enterobacteriaceae/Carbapenem Resistant Pseudomonas* at four different hospitals. Forty-five percent of the strains (105/233) were resistant to Fosf. Plasmid-mediated fosfomycin-modifying enzymes fosA, fosA2, fosA3, and fosA5 genes were identified [98].

2.9.2.10. Nitrofurantoin

Another oral antimicrobial agent that can be considered for the treatment of ESB cystitis is nitrofurantoin. One study showed clinical cure rates of 69% in patients with ESBL cystitis in which all isolates were also resistant to SMX/TMP and ciprofloxacin [99].

Nitrofurantoin should only be used for lower UTI and should be avoided in patients with a creatinine clearance less than 60 (few studies accepted GFR more than 40) mL/min as reduced renal function results in decreased active drug within the urine [100]. It is contraindicated in pregnancy.

2.9.2.11. Cefoperazone-sulbactam

In a larger in vitro study, against the GNBs, a total of 18,386 organisms including 13,224 *Enterobacteriaceae* and 3536 *Pseudomonas* were collected (2013–2014) as part of the SENTRY Antimicrobial Surveillance Program. Cefoperazone/sulbactam inhibited 94% of *Enterobacteriaceae* [101]. There are limited clinical data on the usefulness of this agent against ESBL or CRE/CRP organisms in the urinary tract.

2.9.2.12. Ceftazidime-avibactam (Cef-Avb)

Ceftazidime, a third-generation cephalosporin, when combined with avibactam has potent activities against β-lactamase-producing Gram-negative pathogens including ESBL, AmpC

β-lactamases, and *CRE*. Currently, Cef-Avb is approved for complicated UTIs (limited to patients without other treatment options in the empiric and documented treatment of MDROs).

In an in vitro study, it was tested against collection of international urinary isolates (1797 isolates were collected from 159 medical centers). All ESBL isolates as well as meropenem-non-susceptible *E. coli* and *K. pneumoniae* isolates were susceptible to Cef-Avb [102].

In another study, 34,062 isolates of *Enterobacteriaceae* from patients (with mostly UTIs) were collected (International Network for Optimal Resistance Monitoring, surveillance from 39 countries). Overall, 99.5% of isolates were susceptible to Cef-Avb. It was also active (99.9%) against molecularly confirmed ESBL-producing, plasmid-mediated AmpC-producing (100%), and ESBL- and AmpC-producing (100%). It lacks activity against the metallo-β-lactamase producers (NDM-1 enzyme) [103].

The REPRISE, an international, randomized, open-label trial, recruited 333 patients from 16 countries worldwide. The study recruited patients mostly with complicated UTIs caused by ceftazidime-resistant *Enterobacteriaceae* or *P. aeruginosa*. They were randomly assigned, 165 to Cef-Avb and 168 to best available therapy. The overall proportions of patients with a clinical cure were similar in the 2 arms [104].

In another clinical study, Cef-Avb was compared to imipenem-cilastatin in hospitalized adults with serious complicated UTI due to Gram-negative pathogens. Patients were allowed to switch to oral ciprofloxacin after at least 4 days on the study drug. Patients in the Cef-Avb group had a better microbiological response (70% vs. 71%) [105].

The RECAPTURE study recruited 033 patients, who were randomized in 2 arms, 393 received Cef-Avb and 417 received doripenem, with possible oral antibiotic switch (total duration was 10–14 days). Combined symptomatic resolution/microbiological were similar in the 2 arms (70.2% vs. 66.2%, respectively) [106].

In a recent study, the outcome of therapy with ceftazidime-avibactam (38 patients) was compared to the outcome of therapy with colistin (99 patients) with CRE infections. Most patients received additional anti-CRE agents as part of their treatment. All-cause hospital mortality at 30 days and after were 9% vs. 32%, respectively [107].

Salvage therapy: in a case series of 36 patients, mostly with life-threatening infections received Cef-Avb as a salvage therapy. The causative organisms were CRE (2 were CRP). In 65.8% of patients, other concurrent antibiotics were used. More than 70% of the patients experienced clinical and/or microbiological cure [108].

Resistance: in less than 2 years since its approval, resistant strains have been isolated. Cef-Avb-resistant *K. pneumoniae* emerged in 3 patients after using Cef-Avb for 10–19 days [109].

2.9.2.13. Ceftolozane-tazobactam (Cef-Taz)

This agent was approved in 2015 for the treatment of complicated urinary tract infections (adults with limited or no other therapeutic options) [110]. There are many in vitro studies that

demonstrated activity against Gram-negative and Gram-positive microorganisms, including *E. cloacae*, *E. coli*, *K. oxytoca*, *K. pneumoniae*, *Proteus mirabilis*, *P. aeruginosa* as well as coverage of most ESBL-producing organisms and some anaerobes [110, 111].

Cef-Taz was tested in vitro against 3851 *P. aeruginosa* isolates collected from 32 U.S. hospitals. It was active against 97.0% of the isolates, which was better than 7 other broad spectra antibiotics. A total of 363 isolates were classified as extensively drug resistant; Cef-Taz was active against 76.9% of these isolates [112].

The ASPECT is a randomized, double-blind, double-dummy, non-inferiority trial over 25 countries. 1083 patients enrolled, of whom 82% had pyelonephritis. Patients were randomly assigned to receive Cef-Taz or intravenous high-dose levofloxacin for 7 days. Overall, the composite cure rates were higher in the Cef-Taz group than in the levofloxacin. In a subgroup analysis, clinical cure was seen in 90% compared with 73% in patients with ESBL-producing uropathogens [113].

2.9.2.14. Ceftaroline/avibactam

Ceftaroline is a cephalosporin with broad-spectrum activity against Gram-positive and Gram-negative organisms. When Ceftaroline combined with avibactam, it gains activities against many ESBL-producing organisms in vitro. It was tested in one study against 272 ESBL *Enterobacteriaceae* strains. All isolates were inhibited by ceftaroline-avibactam at ≤4 μg/mL; however, it exhibited limited activity against *Acinetobacter* spp. and *P. aeruginosa* [114].

There are no clinical studies that tested the activity of this agent on UTIs caused by any MDROs.

2.9.2.15. Ceftriaxone + sulbactam + disodium edetate (Elores)

It is a novel molecule, which combines β-lactam plus β-lactamase inhibitor. It has shown activities against many resistant Gram-negative bacterial infections. There is a limited data on its spectrum, usage (mostly in India), and its role in urinary tract infections in specific.

In one study, Elores activity was compared to other comparators (including carbapenems) in treating various infectious syndromes. There were 2500 patients enrolled in the study, in which 24% of the patients had UTIs (no specifics on severity or the causative organisms). The clinical cure/improvement was achieved in 98%. There was no clear description on the types or the incidence of resistant organisms in the study [115].

2.10. ESBL and CRE urinary tract infections with pregnancy

Few studies have been conducted regarding the prevalence of ESBL-producing organisms in pregnant women. In Ireland, a low figure of 1.63% of pregnant patients was colonized with ESBL organisms (perianal). Similar rates were seen in a Norwegian study (2.9%) [116].

Higher rates have been reported in other countries: 5.4% in Argentina and 15% in India [117]. In India, 47% in *E. coli*-related UTIs in pregnant patients were ESBL-producing *E. coli* [117–119].

Peripartum maternal transmission of ESBL organism to newborn infants was documented [120].

Recently, first outbreak of a CTX-M ESBL-producing *E. coli* in an Irish neonatal intensive care unit was reported. This outbreak was mediated by mother to neonate transmission [121].

Carbapenem are the drugs of choice for treating complicated UTIs and pyelonephritis due to ESBL pathogens in pregnancy [122]. In small studies, orally administered fosfomycin have been used to treat cystitis with ESBL pathogens with good success.

A case control study compared outcomes in pregnant women with ESBL-UTIs. Suboptimal treatment was noted in the majority of cases involving ESBL-UTIs (89%, n = 40), which was far more likely than what was observed for non-ESBL infections. Data support the importance of more aggressive treatment and follow-up of pregnant women with ESBL-UTIs to prevent secondary clinical pyelonephritis [123].

There are very limited data on CRE/CRP UTI in pregnancy. A case report of community-acquired pyelonephritis caused by KPC-producing isolate was reported in Australia [124].

Authors were refrained from using colistin, because of its toxicity in pregnancy (category C). Tigecycline was not considered either (category D). Rather, they added cefepime, which is regarded as safe in pregnancy (category B) and offers potential synergistic activity with fosfo-mycin, which is also an inhibitor of cell wall synthesis. In that study, the isolate was resistant to cefepime in vitro. By using 6 g/day as a continuous infusion, they estimated that levels in plasma of 20–30 μg/mL were maintained; moreover, cefepime achieved a very high concentration in the urine. Therefore, it has been reasoned that concentrations of cefepime sufficient to inhibit the growth of *K. pneumoniae* (MIC >32 μg/mL) would be maintained in the urine and genitourinary tract. This approach was successful, as proven by sterile urine cultures (obtained weekly while the patient was on cefepime and 6 weeks after the end of therapy) and the absence of symptoms.

For these challenging cases, a new drug (see above), ceftazidime-avibactam, has shown great activities against most of the ESBL and many of the CRE/CRP organisms. This novel agent is safe during pregnancy. However, there are no randomized trials to show this activity, and it should be considered as a salvage therapy [125].

2.11. Duration of therapy

The optimal length of treatment UTI with highly resistant organisms has not been extensively studied. As there are many different causes of underlying abnormality, a simple recommendation cannot be made. 10 to 14 days of antibiotics are usually recommended for patients with bacteremia, hypotension, and other signs of severe sepsis. Recent clinical trials included

complicated urinary tract infections with resistant organisms that have used the study drugs for 10–14 days [93, 105, 106].

2.12. Infection-control

A successful infection program should be able to recognize, screen, and isolate both colonized and infected patients. Standard and transmission-based precautions are strictly applied at all times. Other basic measures including hand hygiene, use of personal protective barriers, and aggressive environmental cleaning are very beneficial. Implementation of simple items-bundles (multiple-drug resistant bundles MDROs) have shown to be very effective in controlling outbreaks.

Hospital-wide vs. high risk areas (ICU, dialysis centers) (routine vs. on outbreaks based) and clinical and bacteriological surveillance have been useful in early identifications and isolation of index cases. The use of molecular technologies including polymerase chain reaction (PCR) optimized the surveillance process [14].

A strict protocol including the above-mentioned interventions showed a great success in reducing the nosocomial spreading of the highly resistant organisms. During the intervention, nosocomial CRE acquisition in acute care declined from a monthly high of 55.5 to an annual low of 4.8 cases per 100,000 patient-days (p < 0.001) [126].

2.13. Antimicrobial stewardship

Multidisciplinary program including physicians, pharmacists, and microbiologists that aims to control the usage of antimicrobial is mandatory. In one study, carbapenem use was strictly restricted through antimicrobial stewardship in an effort to control MDROs spreading in an ICU setting. The study protocol also included strict environmental cleaning and disinfection in addition to basic infection control measures. The rate of hospital acquired MDRO *Acinetobacter* decreased from 22.82 cases per 1000 patient-days to 2.68 cases per 1000 patient-days after the protocol implementation (p < 0.001) [127].

2.14. Summary of recommended therapy

2.14.1. ESBL producing organisms

In general, carbapenems are the most reliable treatment for infections caused by ESBL-producing bacteria. As shown above, the over usage of these agents resulted in the emergence of the CRE. Multiple trials have shown other effective-carbapenem sparing regimens.

We proposed the following:

A. Uncomplicated cystitis caused by ESBL producing *E. coli* and without any indwelling catheters or obstruent: fosfomycin would be effective (and approved) therapy. In cystitis caused by other ESBL producing organism, fosfomycin alone was associated with significant clinical and microbiological failures.

On the other hand, our (and others) clinical exercise with monotherapy and single dose of fosfomycin was also associated with high rates of relapse. We also have great concerns about the rapid progression of fosfomycin resistance. This will require further research.

Meanwhile, we are proposing fosfomycin 3 g oral sachets twice a week for 3–4 doses with nitrofurantoin 100 mg twice a day for 10 days (if susceptible).

 B. For complicated UTIs: monotherapy with carbapenems, piperacillin-tazobactam, amino-glycosides or ceftazidime-avibactam would be effective.

2.14.2. CRE/CRP producing organisms

Treatment of carbapenem-resistant organisms is a real challenge because of limited choices for effective reliable regimens. There are no randomized controlled trials evaluating different antibiotic options for carbapenemase producers. There are many observational studies; combination therapy appears to be superior to single-drug therapy. Combinations of a polymyxin, tigecycline, and meropenem have met with the greatest success. Meropenem has been used in these combinations despite a lack of in vitro susceptibility. Recently ceftazidime-avibactam is showing promising results. It has good activity against (nearly) all class A and class C β-lactamases as well as OXA-48 carbapenemases. However, it lacks activity against the metallo enzymes.

If we can summarize the data above:

2.15. For complicated UTIs/critically ill patients

1. Aminoglycosides (amikacin or gentamicin) or colistin.

    Plus: a carbapenem or

2. Ceftazidime-avibactam (single agent).

3. Tigecycline plus colistin or aminoglycosides: have been tried in few trials.

4. Triple combinations including aminoglycoside, carbapenem, colistin, rifampicin, tigecy-cline, and fosfomycin have demonstrated synergistic or bactericidal effects in few small studies.

Even with the above-mentioned regimens, failure of therapy is very common, as tigecycline and polymyxin do not have good clearance in the urine.

3. Conclusion

The rapid and global spread of antimicrobial-resistant organisms in recent years is a global challenge. The overuse of antimicrobial use in humans and animals coupled with increased

global connectivity facilitated the transmission of Gram-negative infections harboring extended-spectrum β-lactamases. When treating these infections, clinicians have a few effective antimicrobials to choose from and many are associated with significant adverse effects. Definitive therapy should always be guided by susceptibility testing. Expert consultation with an infectious disease specialist is recommended.

Declaration of interest

The authors report no conflicts of interest.

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