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Multidrug-resistant *Klebsiella pneumoniae*: challenges for treatment, prevention and infection control

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**ABSTRACT**

Introduction: Management of antimicrobial resistance in multi-drug-resistant *Klebsiella pneumoniae* (MDR-KP) is a major challenge for clinicians. The optimal treatment option for MDR-KP infections is still not well established. Combination therapies including high-dose meropenem, colistin, fosfomycin, tigecycline, and aminoglycosides are widely used, with suboptimal results. New antimicrobials targeting MDR-KP have been developed during the last decades and are now at various stages of clinical research.

Areas covered: The PubMed database was searched to review the most significant literature on the topic, with a special consideration for articles coming from endemic countries.

Expert commentary: We reviewed the currently available treatment options, discussing the characteristics of new antibiotics with activity against MDR Gram-negative bacteria and the strategies for preventing the spread of MDR-KP. While we wait for real-world data from novel compounds, coordinated efforts in infection control and stewardship programs remain the cornerstone for limiting, or potentially reversing, conditions that favor the spread of MDR-KP.

1. Introduction

Management of antimicrobial resistance in Gram-negative bacteria, included multi-drug-resistant *Klebsiella pneumoniae* (MDR-KP), currently represents a major challenge in the field of infectious diseases [1,2]. Europe, Italy, Greece and Turkey are currently considered ‘endemic’ for carbapenemase-producing Enterobacteriaceae (CPE) and constantly face severe cases of infection admitted from autochthonous sources. Conversely, the majority of other European countries has been classified as ‘epidemic’ and is characterized by sporadic outbreaks [3]. Coordinated efforts between infection control strategies and stewardship programs currently represent essential tools for limiting or potentially reversing conditions that favor CPE spread [4,5].

Infections due to MDR-KP have been associated with mortality rates higher than 40–50% in clinical practice—particularly among critically ill patients and solid organ transplant recipients—and delayed prescription of an adequate antibiotic treatment is a recognized risk factor for increased mortality [6,7]. Unfortunately, the optimal treatment option for MDR-KP infections is still not well established. Combination therapies including colistin, fosfomycin, tigecycline, and aminoglycosides have been the most widely used during last years, although with unsatisfactory results [8]. New antibacterials targeting MDR-Gram negative bacteria (MDR-GNB) have been developed during the last decades and are now at various stages of clinical research.

We have reviewed the possible strategies for prevention of MDR-KP spread and the currently available treatment options, discussing the characteristics of new antibiotic compounds with activity against MDR-GNB and their potential role in everyday clinical practice.

2. Risk factors for MDR-*Klebsiella pneumoniae* colonization and screening strategies

Asymptomatic rectal carriage of MDR-KP is currently considered the main reservoir for ongoing transmission and represents a key point for the implementation of infection control measures [9]. For this reason, European guidelines strongly recommend the adoption of active screening cultures (ASC) programs based on local epidemiology in epidemic settings with MDR-KP outbreaks. Specifically, screening swabs at hospital admission (particularly when risk factors for MDR-KP colonization are present and in high-risk wards, such as oncology-hematology and intensive care unit (ICU)) followed by weekly surveillance swabs in patients at high-risk for MDR-GNB carriage (e.g. patients with prolonged hospitalization, prolonged antibiotic therapy and the ones with indwelling devices, undergoing surgery or admitted to ICU) are recommended. Conversely, in endemic settings ASC should not be considered a basic measure to control the spread of MDR-GNB [10]**. Both in epidemic and in endemic settings, however, the implementation of targeted screening cultures in high-risk patients and active surveillance of patients with epidemiological links to a case of MDR-GNB colonization or infection are suggested [10]. Gagliotti *et al.* evaluated the effect of implementation of an active screening strategy in a tertiary Italian hospital. A rectal swab was performed at hospital admission in...
all patients transferred from other hospitals or long-term health facilities, in patients hospitalized in the previous 60 days and in the ones admitted to intensive care and postacute units. Overall, 1687 patients were screened and 65 (3.9%) tested positive for MDR-KP. Interestingly, 5.1% of case contacts tested positive for MDR-KP, confirming that case contacts screening represents an essential surveillance component for detecting asymptomatic carriers of MDR-KP [11].

However, the implementation of these recommendations into the everyday clinical practice, as well the early identification of colonized patients, still represents a challenge for the clinicians. A possible concern is represented by the low sensitivity of rectal cultures for the identification of MDR-GNB, which varies between 42% and 78%; moreover, the mean time between surveillance cultures collection and results is approximately five days, leading to potential delays in infection control measures implementation [12]. Duration of gut colonization represents another concern with important implications in the definition of screening programs. A recent study suggests that approximately 50% of patients achieve a spontaneous decolonization within 3 months, and approximately 25% have a persistent colonization after 6 months [13]. Possible risk factors for persistent colonization were readmission, duration of hospitalization, positive clinical cultures, use of carbapenems, catheter use, low functional status and long-term care facility stay [14].

Although many risk factors for MDR-KP colonization have been reported, previous exposure to broad-spectrum antibiotics, particularly carbapenems, seemed to be the most clinically relevant determinant for MDR-KP colonization [15–17]. Particularly, even a brief exposure to imipenem (1–3 days) was found to be a major risk factor for imipenem-resistant pathogens carriage status [18]. Gahrbi et al. conducted a retrospective study at a single teaching hospital during the period 2004–2014 to investigate the role of antibiotic consumption in predicting MDR-KP outbreaks. In this study meropenem consumption during the previous year was significantly correlated with the incidence of OXA-48-producing K. pneumoniae, suggesting that antimicrobial consumption may provide a key warning indicator to anticipate increased incidence of carbapenem-resistant organisms [19].

Other reported risk factors for MDR-KP colonization are prolonged hospitalization [20], ICU admission, indwelling urinary catheter [21], receipt of chemotherapy [22], CVC placement [22,23], prior surgery [24], mechanical ventilation [24], previous hospitalization [25], previous vancomycin-resistant Enterococcus spp. (VRE) colonization [23], high Charlson score [20], older age [26], bedridden status [27], solid organ transplant recipient status [28] and the presence of a local MDR-KP outbreak [11].

Duodenoscope used to perform ERC has been recently recognized as an additional potential source of carbapenem-resistant Enterobacteriaceae (CRE) transmission, with approximately 15% of patients developing infection or colonization by CRE when the procedure is carried out using a contaminated duodenoscope. Biliary stent placement, diagnosis of cholangiocarcinoma and active inpatient status have been advocated as the major risk factors for CRE transmission in this setting [29]. A recent study showed that duodenoscopes might remain culture positive for high-risk pathogens, including KP, in approximately 4% of cases, despite standard high-level disinfection and reprocessing [30]. During recent years many outbreaks related with contaminated duodenoscopes have been reported [31,32].

3. Risk factors for MDR-KP infection

Infections due to MDR-KP have been associated with mortality rates up to 50%, with major risk factors for mortality being bacteremia, clinical presentation with septic shock, inadequate empirical antimicrobial therapy, chronic renal failure, high APACHE III score and colistin-resistant isolates [21,33,34]. The prompt identification of patients at risk for MDR-KP infection is crucial to allow the early prescription of an adequate empiric antibiotic therapy, which is a key factor for mortality reduction [21]. However, the identification of patients harboring an infection due to MDR-KP represents a challenge in clinical practice, because risk factors are generic and frequently do not allow a reliable risk stratification.

Colonized status seems to be a key determinant for the development of MDR-KP infection [9]. A recent study found that gut colonization at ICU admission was significantly associated with an increased infection risk (16% vs. 3% among colonized and non-colonized patients, respectively). Moreover, approximately 50% of MDR-KP infections were caused by the patients’ own strain, suggesting the endogenous origin of infection, and 48% of screened patients with infections were positive for prior colonization [35]. ICU admission, abdominal invasive procedure, chemotherapy or radiation therapy and number of additional colonization sites have been identified as independent risk factors for MDR-KP bacteremia among MDR-KP rectal carriers [36]. Alarming data have been recently reported in the subgroup of liver transplant recipients, with progression from colonization to infection in approximately 98% of cases, with mortality rates associated with MDR-KP infection up to 75% [28].

Oral gentamicin decolonization might represent a tool for prevention of infection development among MDR-KP intestinal carriers, particularly in patients not receiving concomitant systemic antibiotic treatment [37]. Tascini et al. showed that administration of oral gentamicin (80 mg four times daily for 7–14 days) among patients with KPC-KP gut colonization resulted in overall decontamination rate of 68%. The incidence of KPC-KP infections was significantly lower among successfully decolonized patients compared with persistent carriers (15% vs. 73%, P < 0.001) during the 6-month period of follow-up, although no differences in overall mortality were found. Decontamination rate was significantly higher in patients receiving oral gentamicin only, compared to patients receiving a concomitant systemic antibiotic therapy (96% vs. 44%, P < 0.001) [38]. Similar data have been reported by other authors [39–41]. Taken together, these data suggest that gut decolonization with oral gentamicin might be a useful option to reduce the risk of infections due to MDR-KP in patients with gut colonization and an expected increased risk for MDR-KP development [e.g. patients undergoing solid organ transplantation or hematological patients undergoing a hematopoietic stem cell transplant (HSCT)], but attention should be paid to the risk of antimicrobial resistance selection [42,43].

Additional reported risk factors for the development of invasive infections due to MDR-KP are solid organ transplant recipient status, steroid use, mechanical ventilation, presence
4. Infection control measures and prevention of interpatient transmission

MDR-KP is characterized by the ability to spread clonally within healthcare institutions, leading to nosocomial outbreaks [46]. Knowledge of transmission modality represents a key factor to understand the role of infection control measures. The World Health Organization (WHO) in 2006 published a document issuing that cross-transmission represents the most important mechanism for nosocomial MDR-GNB spread through five steps: (a) presence of microbes on patient skin and/or in environment; (b) transfer of these organisms to health care workers (HCWs) hands; (c) microbe survival on HCWs’ hands; (d) incorrect hand cleansing by HCWs; (e) cross-transmission to other patients [47].

Infection control measures have the main purpose to interrupt one or more steps in cross-transmission from colonized and/or infected patients to susceptible ones. Current European guidelines recommend the following infection control strategies to limit MDR-KP cross-transmission: (1) implementation of hand hygiene (HH) education programs (moderate evidence, strong recommendation); (2) implementation of contact precaution (CP) for all HCWs and patient encounters with the use of gloves and gowns before entering the room and prompt removal after patient’s, followed by HH (moderate evidence, strong recommendation); (3) use of isolation, single rooms for all patients known to be colonized or infected with MDR-KP (moderate evidence, strong recommendation), when possible; when single isolation room is not available, patient’s cohorting should be considered; (4) environmental cleaning and, when available, dedicate non-critical medical items for use on individual patients colonized or infected with MDR-KP (moderate evidence, conditional recommendation) [10]. Microbiological surveillance with identification of single pathogens. It is important to consider, however, that these infections often occur in patients with poor overall conditions and/or infected patients or clusters of patients who are infected or colonized with MDR-GNB and systematic collection and analysis of data, together with prompt and systematic use of alert codes to allow early introduction of CP measures are also recommended [10]. In a recent prospective study conducted in France, an infection control program was implemented in a 21,000-bed multihospital institution for controlling the spread of carbapenemase-producing Enterobacteriaceae (CPE) and glycopeptide-resistant Enterococcus faecium, aiming to evaluate factors associated with outbreaks occurrence. In multivariate analysis, occurrence of outbreaks was significantly lower when CPs and dedicated nursing staff were implemented around index cases within the first 2 days of hospitalization [48]. During outbreaks, attention should also be paid to identification of potential environmental reservoirs, such as sinks, which have recently pointed out as possible sources for ongoing MDR-KP transmission [49].

Implementation of antimicrobial stewardship programs is suggested by current guidelines with the aim to plan interventions for restriction of antibiotic use and limit the selective pressure that drives the further emergence of resistance [10]. Antimicrobial stewardship programs demonstrated to be effective in reducing the use of selected antimicrobials (included carbapenems) and in increasing antimicrobial prescription adequacy; however, clear evidence of efficacy of this approach in reducing MDR-KP rates is limited and further studies are needed [50–52].

5. Antibiotic treatment for multidrug-resistant Klebsiella pneumoniae infections

The choice of an adequate antibiotic regimen for the treatment of infections due to MDR strains of K. pneumoniae is a challenge for physicians [53], considering that patients, in many cases, develop serious infections and complications [54]. Moreover, these infections affect not only critically ill patients hospitalized in ICU but also patients from other wards with multiple comorbidities. As a matter of fact, no large multicenter trials have evaluated the real effectiveness and safety of the common antibiotic regimens used in the clinical practice for the treatment of MDR infections [55]. Recently, in the AIDA trial [56], a randomized, controlled, superiority trial conducted in six hospitals in Israel, Greece, and Italy investigated the superiority of combination therapy with colistin plus meropenem vs. colistin alone. No differences in term of outcome in patients treated with a combination therapy compared to monotherapy for infections due to carbapenem-resistant pathogens was shown, especially for Acinetobacter spp., including bloodstream infections, ventilator-associated pneumonia (VAP) and/or hospital-acquired pneumonia (HAP). Another trial is still ongoing [57] and will assess whether colistin alone is superior to combination of colistin plus meropenem, with the limit of the real efficacy of an antibiotic regimen with colistin alone, considering the high risk of emergence of colistin-resistant strains. However, these trials are a first step to an evidence-based antibiotic treatment of MDR organisms, especially carbapenem-resistant pathogens. It is important to consider, however, that these infections often occur in patients with poor overall conditions and frequently hospitalized in ICU, with an important difficulty in designing and conducting randomized trials testing combinations of antibiotics and/or new drugs. Proposed algorithm for management of antibiotic therapy for MDR-Kp infections is reported in Figure 1.

6. The role of antibiotic combination therapy

Conversely to what is reported in the AIDA trial, the superiority of combination therapy compared to monotherapy has been confirmed in several retrospective studies. Tzouvelekis et al. conducted a retrospective study [58] including 20 studies (including observational studies and case series) that analyzed the treatment of carbapenem-resistant Enterobacteriaceae using different regimens. The lowest mortality (18.8%) was
reported in the group of patients treated with a combination regimen, including a carbapenem. Other studies confirmed these results, conducted in Italy, 125 KPC-Kp BSI were analyzed, reporting that combination therapy with meropenem plus colistin plus tigecycline was associated with lower mortality compared to monotherapy or other combination therapies. These observations were confirmed in 661 KPC-Kp BSI observed in critically-ill patients, but this data was not confirmed for less complicated infections, including BSI secondary to urinary source or in non-critically ill patients. Of interest, these studies confirmed the utility of a meropenem-based regimen in the treatment of these infections, although carbapenem MIC remained as an important factor in choosing or not meropenem in combination antimicrobial regimens against MDR-KP and other CRE. The choice of the best combination regimen for the treatment of CRE remains a matter of debate. As matter of fact, co-administration of different antibiotics may also lead to important adverse effects, including Clostridium difficile infection, selection of further resistances, or nephrotoxicity. Furthermore, the use of antibiotics in combination in not confirmed and may not be necessary in patients that are stable or non-critically ill. The INCREMENT study, involving 33 centers worldwide constituting the largest database on infections due to MDR Enterobacteriaceae, confirmed that a combination therapy was more effective only in critically ill patients. Crucial points for patients’ outcome in the choice and efficacy of antibiotics in combination, however, include the administration of at least two antibiotics with in vitro activity, as initial or definitive therapy, and obtaining source control, especially in infections that are from abdominal sources. Data supporting these observations in KPC-Kp infections have been reported extensively. Various antibiotic combinations that are active against KPC-Kp, including gentamicin, tigecycline, trimethoprim-sulfamethoxazole, or double-carbapenem therapy are reported in the literature. Finally, optimal treatment duration for KPC-Kp infections remains unclear: retrospective studies reported mean durations of 2 weeks of treatment, but randomized controlled trials to assess optimal duration are awaited and support the evidence that prolonged treatments are not necessary.

7. Considerations about ‘old’ antibiotics for the treatment of multidrug-resistant Klebsiella pneumoniae infections

Colistin used was initially limited for its nefrotoxicity and neuropotency from the '70; nowadays, due to the in vitro efficacy against MDR Gram-negative bacteria, its use has been resumed and represent with carbapenem a backbone of combination antibiotic regimens for these severe infections. Colistin
pro-drug, sodium solistimethate, is then hydrolyzed to colistin, the active principle, and renally excreted. A reduction of colistin dose is indicated for creatinine clearance <50 ml/min. For normal renal function the standard dosing is 9 MU loading dose followed by 4.5 MU twice daily [66]. In a recent randomized trial [72] the use of aerosolized colistin alone for the treatment of VAP lead to the similar results compared to intravenous colistin, but with less collateral effects. In other retrospective studies the results on colistin use were conflicting: in a 2013 multicenter study [73] the use of colistin was associated with lower mortality compared to other regimens, while in a 2015 study [71] increased mortality was associated with colistin use. Another study, analyzing colistin monotherapy compared to colistin-containing combination therapy, found no difference in term of survival [65]. However, even if results remain conflicting about the real efficacy of colistin in the treatment of KPC-Kp infection, this antibiotic still represents an important option for the treatment of these severe infections due to in vitro susceptibility and its bactericidal activity.

Unfortunately, colistin toxicity and the worrisome rising of the colistin-resistant strains can limit the use of this drug. In 2013, emergence of colistin resistance was associated with increased mortality [74]. A dramatic increase in the rates of colistin resistance were reported over a 4-year period (from 10% in 2010 to almost 30% in 2014. A high mortality correlated with colistin resistance was confirmed in a case-control study [75]. In China, in 2016, a plasmid mediating colistin-resistance was identified [76] and its spread subsequently confirmed in other reports worldwide [77–79].

In this scenario, treatment options for MDR-KP infections remains often limited and include tigecycline, gentamicin, fosfomycin, trimethoprim-sulfamethoxazole, and rifampin alone or in combination.

Due to the low rate of resistance reported in literature, tigecycline is usually used with colistin plus meropenem in combination. Increased tigecycline doses (up to 200 mg/24h with a 400 mg loading dose) have been proposed [80,81] without evident adverse effects. However, tigecyclin resistance has been reported [82–84].

Gentamicin is usually active in vitro against KPC. Data about its use as monotherapy have been reported in infections secondary to urinary source [85]. The use of gentamicin in combination therapy, if susceptible, has been associated with increased survival [58,59]. In an outbreak of colistin- and carbapenem-resistant K. pneumoniae infections, targeted therapy with gentamicin was associated with survival [86]. For this reason, some authors considered gut decontamination with gentamicin potentially useful for prevention of infection due to KPC-Kp strains [38].

Along with other ‘old antibiotics’ such as colistin and gentamicin, fosfomycin was considered a therapeutic option for KPC-Kp infections; in vitro susceptibility was reported in XDR strains [87] and its use was recommended in combination regimens [88]. Unfortunately, no clinical trials have investigated fosfomycin use alone or in combination and MIC values are very difficult to determine. In the setting of XDR isolates, fosfomycin is used in combination regimens at a dose of 16 to 24 g/24 h [89].

In a retrospective study including 14 patients with infections caused by trimethoprim-sulfamethoxazole-susceptible KPC-Kp strains, this drug was reported effective in combination therapies or even in monotherapy [90]. However, trimethoprim-sulfamethoxazole resistance is usually high and the side effects (like agranulocytosis) are often not compatible with some patients (e.g. hematologic) and further studies are needed for the assessment of its real effectiveness. Finally, rifampin associated with polymyxin B plus meropenem showed synergistic activity in vitro but there are limited studies in clinical practice [91].

8. Spotlight on ‘new’ antibiotics for the treatment of multidrug-resistant Klebsiella pneumoniae infections

The need of new drugs to target KPC-Kp is considered urgent and, in response to the spread of MDR microorganisms, new antibiotics have been developed in recent years. These new drugs have also an important role as salvage therapy for severe infections, in the setting of PDR strains of K. pneumoniae and other MDR pathogens (Table 1).

8.1. Ceftazidime-avibactam

Among new compounds, β-lactam and β-lactamase inhibitors were proposed for the treatment of these severe infections [92].

Ceftazidime-avibactam is a recently approved combination of a well-known antipseudomonal third generation cephalosporin with a new β-lactamase inhibitor combination, licensed for IAI, HAP/VAP and UTI. Ceftazidime-avibactam is able to inhibit class A, C and some D Ambler class- β-lactamases [93]. The combination of avibactam with aztreonam has been reported to be effective in vitro also for MBLs producers [94]. Its activity has been compared to best available therapy in a randomized trial [95] investigating its use in ceftazidime-resistant strains. A non-inferiority trial on the use of ceftazidime-avibactam in pneumonia found no difference compared to meropenem [96].

Whether ceftazidime-avibactam should be used alone or in combination for KPC-Kp infections is a matter of debate. The drug is licensed to be used alone for HAP/VAP and UTI and in association with metronidazole for IAI. Reports from real-world studies reported ceftazidime-avibactam efficacy both in combination therapy [97] and in monotherapy, including difficult-to-treat infections and critically-ill patients [98,99]. Recently, Gaibani et al. [100] reported the in vitro efficacy of ceftazidime-avibactam used in combination with imipenem or meropenem. Of importance, combination with a carbapenem is out from the strategy of a carbapenem-sparing antibiotic regimen; for this reason, waiting for clinical trials, ceftazidime-avibactam should be used eventually in combination with gentamicin, fosfomycin, tigecycline, or colistin. The use of ceftazidime-avibactam has been associated with the emergence of resistant strains in several reports [101,102]. In critically-ill patients, the use of extended infusion of ceftazidime-avibactam may be considered as a potential option [103].

8.2. Meropenem-vaborbactam

Among new antimicrobials, meropenem-vaborbactam is the only combination of a carbapenem and a class A— and class C—β-lactamase inhibitor [93]. Meropenem-vaborbactam is a potent inhibitor of serine β-lactamases due to the high affinity between
studies have demonstrated the role of relebactam to restore imipenem’s activity against KPC-producing CRE, including *K. pneumoniae*, and to reduce imipenem MICs in *P. aeruginosa*, particularly in strains with depressed OprD expression and increased AmpC expression [111]. Conversely, the addition of relebactam to imipenem did not seem to provide any adjunctive benefit against *A. baumannii* and *S. maltophilia* [112].

A Phase-III study evaluating the efficacy and safety of imipenem-relebactam (200/100 mg to 500/250 mg, based on renal function) compared to colistimethate sodium for the treatment of imipenem-resistant bacterial infections, including HAP, VAP, cIAIs and cUTIs, has recently been completed and results are pending [113]. A non-inferiority, Phase-III trial evaluating the efficacy and safety of imipenem-relebactam compared to piperacillin-tazobactam for the treatment of HAP and VAP [114] is currently ongoing.

### 8.4. Plazomicin

Plazomicin is a new generation semisynthetic aminoglycoside displaying a dose-dependent bactericidal activity and *in vitro* activity against MDR Gram-positive [115] and -negative bacteria. Plazomicin showed a better activity, with MIC50 and MIC90 values of 0.25 and 1 mg/L, compared to gentamicin, tobramycin and amikacin, and synergistic effect in association with meropenem, colistin and fosfomycin, but not with tigecycline [116]. Another *in vitro* study [117], confirmed plazomicin good activity compared with other antibiotics, with only a NDM-1-producing *K. pneumoniae* strain resistant to plazomicin; moreover, its efficacy was confirmed in KPC-KP strains expressing the mcr-1 gene of the colistin-resistance [118].

### 8.5. Cefiderocol

Cefiderocol is a new generation siderophore cephalosporin based on the mechanism of bacterial cell entry binding to ferric iron [119]. Cefiderocol demonstrated *in vitro* activity against ESBL producing Enterobacteriaceae, CRE and meropenem-resistant *P. aeruginosa*, *Stenotrophomonas maltophilia*, and *A. baumannii*, and is currently in Phase III of clinical development. The APEKS-NP trial is a clinical study on nosocomial pneumonia, to compare cefiderocol vs. meropenem (both in association with linezolid), in adults with HAP, VAP and HCAP caused by Gram-negative pathogens [120]. In addition, a Phase-III trial (CREDIBLE-CR) has been started in 2017 to provide the evidence of cefiderocol efficacy in patients with serious infections (HCAP, HAP, VAP, cUTI, and bloodstream infections, BSI) caused by carbapenem-resistant Gram-negative bacteria. In this trial, cefiderocol is compared with best available therapy including up to three

### 8.3. Imipenem-relebactam

Relebactam (formerly known as MK-7655) is a β-lactamase inhibitor similar to avibactam and active against Ambler class A and class C β-lactamases but not against MBL [111]. *In vitro*

### Table 1. New antibiotics for the treatment of MDR *Klebsiella pneumoniae* infections.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose, administration route</th>
<th>Indications and ongoing trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefiderocol</td>
<td>2 g q8h, IV</td>
<td>BSI, HCAP/HAP/VAP, cUTI</td>
</tr>
<tr>
<td>Cefazidime/avibactam</td>
<td>2.5 g q8h, IV</td>
<td>IAI, HAP/VAP, cUTI</td>
</tr>
<tr>
<td>Meropenem/vaborbactam</td>
<td>2 g/2 g q8h, IV</td>
<td>cUTI</td>
</tr>
<tr>
<td>Imipenem/relebactam</td>
<td>500 mg/250–125 mg q6h, IV</td>
<td>cUTI, cIAI, HCAP/VAP, cUTI</td>
</tr>
<tr>
<td>Plazomicin</td>
<td>15 mg/kg q24h, IV</td>
<td>BSI, HABP, VAP, cUTI</td>
</tr>
<tr>
<td>Aztreonam/avibactam</td>
<td>6500 mg ATM/2167 mg AVI</td>
<td>cUTI</td>
</tr>
<tr>
<td>Eravacycline</td>
<td>1 mg/kg q12h, IV</td>
<td>cIAV</td>
</tr>
<tr>
<td>Cefaroline/avibactam</td>
<td>600/600 mg q24h, IV</td>
<td>No ongoing trials</td>
</tr>
<tr>
<td>Cefepime/zidebactam</td>
<td>Not yet established</td>
<td>Phase I (NCT02352140; NCT02707107; NCT02942810)</td>
</tr>
<tr>
<td>Nacubactam/ETX2514</td>
<td>Not yet established</td>
<td>BSI (NCT03182504)</td>
</tr>
</tbody>
</table>

IV, intravenous; BSI, bloodstream infection; HCAP, healthcare-associated pneumonia; HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia; cUTI, complicated urinary tract infection; UTI, urinary tract infection; IAI, intra-abdominal infection; cIAI, complicated intraabdominal infection.

the serine-based active sites of β-lactamases and boronates, leading to the formation of a covalent complex and inhibition of β-lactamases enzymes [104,105]. *In vitro* studies confirmed the ability of vaborbactam to reduce MIC to meropenem [105] and a low rate of adverse events [106]. The TANGO I trial [107] assessed the non-inferiority of meropenem-vaborbactam compared to piperacillin-tazobactam in complicated UTI, including acute pyelonephritis. For cUTI meropenem-vaborbactam has been licensed by the FDA since 2017 [108], while results are pending about the efficacy of meropenem-vaborbactam for HAP, VAP and bactere mia compared to the best available therapy [109] and in HAP and VAP compared to piperacillin-tazobactam [110].

### Table 2. Published cases about intestinal decolonization from carbapenemase-producer pathogens with fecal microbiota transplantation.

<table>
<thead>
<tr>
<th>Age/Sex</th>
<th>Mechanism of resistance</th>
<th>Previous targeted antibiotic therapy</th>
<th>PPI</th>
<th>Via</th>
<th>AE</th>
<th>Time to negativity</th>
<th>Follow-up</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>82/F</td>
<td>OXA-48 Kp</td>
<td>Yes (Colistin + gentamicin)</td>
<td>No</td>
<td>NGT</td>
<td>No</td>
<td>7 days</td>
<td>2 weeks</td>
<td>158</td>
</tr>
<tr>
<td>51/M</td>
<td>NDM-Kp ESBL-E</td>
<td>No</td>
<td>Yes</td>
<td>NDT</td>
<td>Mild diarrhea, Abdominal discomfort</td>
<td>10 days</td>
<td>4 weeks</td>
<td>157</td>
</tr>
<tr>
<td>14/F</td>
<td>KPC-Kp</td>
<td>No</td>
<td>Yes</td>
<td>NDT</td>
<td>NR</td>
<td>NR</td>
<td>18 months</td>
<td>159</td>
</tr>
</tbody>
</table>

PPI, proton pump inhibitor; NDT, naso-duodenal tube; NGT, naso-gastric tube; NR, not reported; AE, adverse effect.
antibacterial agents for carbapenem-resistant Gram-negative bacteria with either a polymyxin-based or non-polymyxin-based regimen [121].

8.6. Aztreonam-avibactam

Aztreonam/avibactam is a combination of a monobactam active against a broad spectrum of Gram-negative pathogens and avibactam, a non-β-lactam β-lactamase inhibitor with activity against Ambler class A and C—β-lactamases and certain class D—β-lactamases. This combination is actually under evaluation in different studies: a Phase-I study [122] and Phase-II REJUVENATE study on pharmacokinetic, safety and tolerability for the treatment of clAIs in hospitalized adults [123]. A Phase-III comparative study to compare the performance of aztreonam/avibactam with or without metronidazole vs. meropenem with or without colistin for the treatment of serious infections (including HAP and VAP) due to Gram-negative bacteria is currently ongoing [124].

8.7. Eravacycline

Eravacycline is a novel fluorocycline with broad-spectrum activity against both Gram-positive and Gram-negative resistant pathogens, including Enterobacteriaceae expressing different classes of β-lactamases (particularly ESBL, KPC and OXA), with a 2- to 4-fold greater activity than tigecycline [125,126]. Eravacycline is active also against anaerobic pathogens [127], but, like tigecycline, it is not effective against P. aeruginosa, although it shows an excellent activity against Acinetobacter baumannii [128].

Eravacycline could be available intravenously and orally, representing a good choice for oral switch and early discharge [129]. In a recent Phase III, randomized, double-blind, multicenter study eravacycline was found to be non-inferior compared to ertapenem for the treatment of patients with clAIs [130].

8.8. Ceftaroline/avibactam

The combination of ceftaroline and avibactam further extends the antimicrobial spectrum to include ESBL-, KPC-producing Enterobacteriaceae, and anaerobes, with a limited activity P. aeruginosa and A. baumannii [131].

A Phase-II study comparing treatment with ceftaroline/avibactam vs. doripenem for the treatment of adult patients with cUTI has recently been completed [132]. Although no studies investigating the role of ceftaroline/avibactam for the treatment of MDR-KP infections are currently available, ceftaroline/avibactam represents a potential option for the treatment of these infections.

8.9. Cefepime-zidebactam

Cefepime/zidebactam (WCK5222) is a new antibiobic combination on the pipeline: it includes a fourth generation cephalosporin with a new molecule formerly known as WCKS107, inhibiting class A (therefore including KPC), class C, some class D β-lactamases, some PBP2 and PBP3 in in vitro studies [133,134]. Phase-I trials are assessing the safety and the PK/PD profile of zidebactam alone [135] or in combination with cefepime [136,137] also in patients with renal impairment [138].

8.10. Nacubactam (OP0595, RO7079901, RG6080)

Nacubactam is a diazabicyclooctane (DBO) serine β-lactamase inhibitor, similar to avibactam in its class A and class C β-lactamases inhibition. With a PBP2 activity, it has an intrinsic bactericidal activity [138]. In vitro studies suggest to use in combination due to the high risk of resistance [139,140].

The combination with meropenem showed in vitro activity against class B, D and KPC Enterobacteriaceae [141]. A Phase-II study investigating the lung penetration of meropenem/nacubactam has been recently completed [142]. In vivo studies are needed to confirm this data.

8.11. ETX2514

ETX2514 is a β-lactamase inhibitor with an intrinsic bactericidal activity, like nacubactam. This activity was tested in combination with sulbactam, that is active in vitro against serine β-lactamases, with a specific activity against A. baumannii [143]. It is being currently tested in the treatment of cUTI [144].

9. Non-antibiotic therapeutic approach: fecal microbiota transplantation

Fecal microbiota transplantation (FMT) is a relatively new technique that, in infectious diseases, found its first use in the context of recurrent C. difficile infection (CDI). Since 2013, several reports confirmed the very high rate (>90%) of clinical cure in patients undergoing FMT [145,146]. For this reason, guidelines recommend FMT in the management of recurrent CDI [147], and many stool banks, like OpenBiome [148] in North America, are now available.

However, preparation and way of administration are not standardized, and in literature are reported many experiences: oral capsules [149], nasogastric tube [150], colonscopy [151], enteroscopy [152], retention enema [151]. Of importance, frozen oral capsules seem to be effective and safe as fresh samples [153,154]. Considering the good success in the treatment of recurrent CDI, many authors have proposed the use of FMT also in patients colonized or infected, especially in ICU, by MDR pathogens, since the intestine is the main reservoir of these pathogens. Studies have been conducted in ESBL colonized patients [155] showing decolonization success in about 40% of patients after the first treatment, in absence of relevant adverse effects. Nevertheless, these first experiences seem to evidence that immunocompromised patients would not benefit from this treatment.

Two large studies are ongoing for FMT in decolonization from MDR pathogens; one of these [156] will be completed in July 2020, and it will investigate the efficacy of FMT on the colonization with MDR organisms in subjects with recurrent MDR infections in order to prevent further recurrences. The FMT will be administered by retention enema and stools will be analyzed at 30 days, 6 months, and 12 months post-FMT and compared with the pre-FMT samples. Of interest, a
prospective single-center study [157], in patients with blood disorders, colonized by MDR pathogens and treated with FMT instilled intra-duodenally, showed a decolonization in over 75% of patients, especially if no concomitant antibiotic therapies were administered. Decolonization seems to be easier for ESBL or OXA-48 strains rather than KPC pathogens. Adverse effects were rare and included vomiting or transient diarrhea. Recolonization with the same MDR organism occurred in only 3/15 (20%) patients [158,159]. See Table 2.

10. Conclusions
Infections caused by MDR-KP are burdened by high mortality and are often associated with increased risk of inadequate antimicrobial therapy. Both in endemic and epidemic context, a high risk of MDR-KP spread is recognized among wards and among different hospitals. Various infection control and antimicrobial stewardship measures are recommended in order to limit MDR-KP spread, including performance of ASCs in high-risk patients, implementation of HH and CP and patient’s isolation, education programs, and limitation of antimicrobial overuse, especially for carbapenems. Sufficient data support the use of a combination therapy in the treatment of these infections. However, the role of new drugs, like ceftazidime-avibactam recently licensed for the treatment of MDR Enterobacteriaceae, should be assessed with evaluation about the use as monotherapy or in a combination antibiotic regimen.

11. Expert commentary
MDR-KP represents an important cause of healthcare-related infections, with high rate of septic shock and mortality. Management of infections due to these strains currently represents a major challenge in the field of infectious diseases, and countries of Mediterranean area, like Italy, Greece and Turkey, are currently considered ‘endemic’ for CPE.

Risk factors for acquisition of these infections and predictors of outcome were evaluated in large, multicenter studies, representing an important source of information for physicians; these infections have been associated with mortality rates up to 50%, with high incidence of bacteremia and septic shock. The choice of an appropriate antibiotic therapy and the adequate source control, especially in deep abdominal infections, represent a crucial point to improve outcome of these infections. Considering that MDR-KP is one of the most important infection in ICU patients and elderly patients, hospitalized in medical wards, screening strategies and infection control measures appear mandatory to avoid the spread of these strains. Moreover, knowledge of transmission modality represents a key factor to understand the role of infection control measures, and knowledge of local epidemiology of antibiotic resistance, with the support of fast and molecular microbiology, is essential to optimize the choice of antibiotic regimens. The use of PK/PD data and therapeutic drug monitoring can drive the antibiotic choice as well as dosage optimization, especially in critically-ill patients. The optimization of antibiotic dosing, especially in ICU patients is a further challenge in dealing with KP infections. The use of therapeutic drug monitoring (TDM) and beta-lactam continuous infusion should be considered for a tailored therapy. This approach allows to use meropenem up to a MIC ≤ 64 mg/L [160,161]. The use of multiplex PCR to detect the specific carbapenemase gene may have therapeutic consequences. To note, ceftazidime/avibactam is active against KPC, while it should not be used for MBL-KP [162,163].

In this scenario, the optimal therapy for treatment of MDR-KP has not been established yet. Old antibiotics such as colistin, aminoglycosides, and fosfomycin have been used in combination regimens, often associated with high-dose carbapenems. Although there are observational studies supporting the use of combination therapies vs. monotherapy, the efficacy of these regimens appears suboptimal and the results comparing the two strategies remain conflicting.

Based on these data, the need of new drugs to target MDR-KP was considered urgent and new antibiotics have been developed in recent years. These new drugs have also an important role as salvage therapy for severe infections, in the setting of PDR strains of Enterobacteriaceae and other MDR pathogens. Currently, ceftazidime-avibactam represents a novel option for the treatment of MDR-KP (except MBL-producing strains) and showed encouraging in vitro results and promising preliminary real-world data. Further studies, however, are necessary to confirm the efficacy of ceftazidime-avibactam in serious MDR-KP infections and to determine if a combination therapy is necessary to avoid the emergence of resistance. Other molecules, belonging to well-known antibiotic classes or showing new mechanisms of action, are currently at various stages of clinical development and may represent promising options for the treatment of serious infections caused by MDR-KP and other resistant Gram-negative pathogens. Until further studies become available, however, coordinated strategies and common efforts in infection control and stewardship programs remain the cornerstone for limiting, or potentially reversing, conditions that favor the spread of MDR-KP.

12. Five-year view
It is expected that, in the next five years, infection control measures will be implemented and risk factors for acquisition of MDR-KP will be definitely assessed. Fast microbiology will be the milestone for an early diagnosis, especially in the setting of critically-ill patients. Research studies will be conducted to analyze clinical efficacy of the new antibiotic options, compared with ‘old’ antibiotic regimens, in real clinical practice. In particular, should be assessed the role of these new antibiotics, especially ceftazidime-avibactam, as monotherapy or in combination, with data about dosage optimization. Finally, the emergence of strains resistant to new antibiotics should be rapidly recognized.

Key issues
- MDR-KP represents an important cause of healthcare-related infections, with high rate of septic shock and mortality.
- Risk factors for acquisition of this infection and predictors of outcome were evaluated in large, multicenter studies, representing an important source of information for physicians.
• Screening strategies and infection control measures are an essential tool to avoid the spread of MDR-KP.
• Local epidemiology of antibiotic resistance, with the use of fast and molecular microbiology, is important to optimize the choice of antibiotic regimens.
• The use of PK/PD data and therapeutic drug monitoring can drive the antibiotic choice as well as dosage optimization, especially in critically-ill patients.
• Sufficient data support the use of a combination therapy in the treatment of these infections. The role of new drugs, like ceftazidime-avibactam recently licensed for the treatment of MDR Enterobacteriaceae, should be assessed with evaluation about the use as monotherapy or in a combination antibiotic regimen.

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Declaration of interest
In the past five years, M Bassetti has participated in advisory boards and/or received speaker honoraria from Achaogen, Angelini, Astellas, AstraZeneca, Bayer, Basilea, Cidara, Gilead, Melinta, Menarini, MSD, Nabriva, Paratek, Pfizer, Roche, The Medicine Company, Shionogi, Tetraphase, VenatoRX, and Vifor. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Papers of special note have been highlighted as either of interest (+) or of considerable interest (++) to readers.
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The article presents the current recommendations regarding screening and other infection control measures to prevent the spread of MDR-Gram negative pathogens.


This study described for the first time the importance of antibiotic combination therapy.

This study is based on a large multicenter database.


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