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Review

Management of KPC-producing *Klebsiella pneumoniae* infections

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ABSTRACT

Background: Klebsiella pneumoniae carbapenemase (KPC)-producing *K. pneumoniae* (KPC-KP) has become one of the most important contemporary pathogens, especially in endemic areas.
Aims: To provide practical suggestion for physicians dealing with the management of KPC-KP infections in critically ill patients, based on expert opinions.
Sources: PubMed search for relevant publications related to the management of KPC-KP infections.
Contents: A panel of experts developed a list of 12 questions to be addressed. In view of the current lack of high-level evidence, they were asked to provide answers on the bases of their knowledge and experience in the field. The panel identified several key aspects to be addressed when dealing with KPC-KP in critically ill patients (preventing colonization in the patient, preventing infection in the colonized patient and colonization of his or her contacts, reducing mortality in the infected patient by rapidly diagnosing the causative agent and promptly adopting the best therapeutic strategy) and provided related suggestions that were based on the available observational literature and the experience of panel members.
Implications: Diagnostic technologies could speed up the diagnosis of KPC-KP infections. Combination treatment should be preferred to monotherapy in cases of severe infections. For non–critically ill patients without severe infections, results from randomized clinical trials are needed for ultimately

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weighing benefits and costs of using combinations rather than monotherapy. Multifaceted infection control interventions are needed to decrease the rates of colonization and cross-transmission of KPC-KP.
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Introduction

Management of infections caused by multidrug-resistant bacteria greatly affects health costs and has become a major modifier of health expenses in the ongoing antibiotic resistance crisis [1]. *Klebsiella pneumoniae* carbapenemase (KPC)-producing *K. pneumoniae* (KPC-KP), has become one of the most important contemporary pathogens, especially in endemic areas [2–4]. The optimal treatment for KPC-KP, however, is not known, and there are currently no published recommendations for the management of infections by KPC-KP. Given the observational nature of most of the studies on this topic, many of the recommendations listed here arise from the acquired experience of the invited panel members and therefore represent expert opinion.

Purpose and methods

We sought to answer practical questions for physicians dealing with the treatment of KPC-KP infections in critically ill patients in view of the fragmentation in the observational literature on this topic and the lack of randomized clinical trials [5]. A panel of 11 experts developed a list of questions to be addressed; 12 questions were formulated after rounds of discussion between chairs (MB, GP, CV and HG) and panel members. In view of the lack of high-level evidence, panel members were asked to provide narrative answers on the basis of their knowledge and experience in the field. Finally, provided answers were reviewed and discussed by the panel until a consensus was reached. The final summary of selected questions and related answers is presented in Table 1.

Background information for provided answers

How can the laboratory speed up KPC-KP identification and susceptibility testing?

Rapid methods for identification of strains producing KPC and other carbapenemases are important to ensure appropriate and early initiation of specific therapy, as well as the prompt implementation of the most appropriate infection control measures [6]. This is particularly relevant with KPC-KP or other types

Table 1
Clinical question defined by panel and related answers based on expert opinion

Question no.	Question	Answer
1	How can the laboratory speed up KPC-KP identification and susceptibility testing?	Diagnostic technologies could speed up the diagnosis of KPC-KP infections and potentially improve patient outcomes. However, whether they should be introduced into the laboratory workflow remain a choice to be carefully balanced locally, according to the available resources and personnel in each hospital.
2	What is currently the best treatment for KPC-KP infections?	Combination treatment should be preferred to treat KPC-KP infections compared to monotherapy in the case of severe infections and for critically ill patients. For non–critically ill patients without severe infection, results from randomized clinical trials are needed to ultimately weigh the related benefits and costs in terms of induction of resistance.
3	What is the role of carbapenems in the treatment of KPC-KP infections?	Administration of high-dose (e.g. 2 g every hours), prolonged infusion meropenem could be beneficial in KPC-KP infections if MIC is ≤8 mg/L. For MIC up to 32–64 mg/L, meropenem administration should be considered if therapeutic drug monitoring is available to monitor optimal drug exposure.
4	What molecules can be used to treat KPC-KP infections?	Various molecules can be used in combination treatment against KPC-KP, including aminoglycosides, polymyxins, tigecycline, fosfomycin, ceftazidime/avibactam and carbapenems in selected cases (see Table 2).
5	What is the role of nebulized antibiotics in the treatment of VAP and VAT by KPC-KP?	The use of nebulized antibiotics could be useful in selected clinical scenario, especially when there is lung involvement (e.g. use of inhaled colistin in VAP due to carbapenem-resistant pathogens).
6	Is prolonged infusion of β-lactams preferable for KPC-KP?	To achieve pharmacodynamic optimization in KPC-directed regimens, prolonged infusion should be combined with high-dose regimens. To achieve pharmacodynamic optimization in KPC-directed regimens, prolonged infusion should be combined with high-dose regimens.
7	What about source control in patients with KPC-KP infections?	Although data among patients with KPC-KP infections are limited, source control in this population has been associated with favourable outcomes and should be performed promptly whenever possible.
8	What is the optimal duration of treatment for KPC-KP infections?	Treatment duration for KPC-KP infections should vary according to the source of the infection. Factors such as achievement of microbiologic eradication, use of biomarkers and optimization of antibiotic exposure could be used to reduce treatment duration.
9	Can KPC-KP infections be prevented? How?	Multifaceted infection control components are needed to decrease the rates of colonization and cross-transmission of KPC-KP.
10	Who among KPC-KP colonized patients is at increased risk of developing KPC-KP infections?	Proper management of colonized patients, including surveillance and antimicrobial stewardship programs, are essential and contribute to ensure an early and appropriate treatment in patients with signs of infection.
11	Is decolonization a useful strategy in KPC-KP colonized patients?	Decolonization of KPC-KP carriers is currently not supported by large studies and may be considered only in selected cases.
12	What's new in KPC-KP treatment options?	Novel compounds targeting KPC-KP are under investigation and appear promising for their treatment, including meropenem/vaborbactam, imipenem/relebactam, plazomicin, cefiderocol and eravacycline. Among these meropenem/vaborbactam and plazomicin have already demonstrated some interesting and favourable results in treating KPC-KP infections.

KPC-KP, *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae*; MIC, minimum inhibitory concentration; VAP, ventilator-associated pneumonia; VAT, ventilator-associated tracheobronchitis.

of carbapenemase-producing *Enterobacteriaceae* (CPE) infections because commonly used regimens for empiric antimicrobial chemotherapy do not normally cover for multidrug-resistant pathogens, except under specific circumstances (e.g. febrile neutropenia in a patient who is known to be colonized with KPC-KP) [7].

Several new diagnostic technologies have recently become available to allow increased rapidity of microbiologic diagnosis, including matrix-assisted desorption ionization–time of flight mass spectrometry (MALDI-TOF MS), rapid immunochromatography, rapid enzymatic assays (such as the Carba NP test), single-cell automated time-lapse microscopy and molecular biology–based assays [8–10]. These new technologies may be useful to reduce the time for pathogen identification and antibiotic susceptibility test.

MALDI-TOF MS has proven successful in rapid bacterial identification from isolated colonies or monomicrobial blood cultures. MALDI-TOF MS can also be used for rapid detection of some resistance determinants, such as β-lactamases [11]. A mass spectrometric β-lactamase assay represents a functional assay that is based on the direct monitoring of the enzymatic activity of the β-lactamase and can be performed with bacterial cultures or directly from freshly tagged positive blood cultures, with results available after 1 to 4 hours' incubation [11]. Both imipenem and meropenem can be used in these tests, with meropenem being somewhat more efficient [12].

This method, however, cannot identify the type of β-lactamase. Recently the identification of a 11 109 Da MS peak corresponding to a gene product of the bla_{KPC} pKpQIL plasmid was found to be useful in rapid tracking KPC-producing strains [13].

Diagnostic platforms capable of rapid detection of bla_{KPC} genes based on molecular biology techniques are currently available to target carbapenemase genes (e.g. Xpert Carba-R or Check-Direct CPE) in bacterial cultures or rectal swabs [14]. Others can identify bla_{KPC} and other clinically relevant resistance genes directly from positive blood culture (e.g. FilmArray BC-ID or Verigene). Remarkably, in this case, the results are provided in about 1 hour compared to conventional microbiologic methods that may take from 12 up to 72 hours [15]. More recently, a polymerase chain reaction/electrospray ionization-mass spectrometry platform (Iridica) that detects more than 800 bloodstream infection (BSI)-relevant pathogens and also bla_{KPC} genes in approximately 6 hours was developed [16].

It should be noted that detection of resistance mechanisms by molecular biology is useful to rapidly predict potential resistance to some agents, but it does not provide comprehensive information about the resistance phenotype of the infecting strain, and conventional antibiotic susceptibility test remains the cornerstone for selection of definitive treatment regimens and evaluation of adequate or inadequate antimicrobial chemotherapy [17]. However, the rapid detection of some resistance mechanism, and of KPC genes in particular (the presence of which means most of the time resistance to carbapenems and even multiresistance), can be useful for an earlier revision of empiric regimens, which usually do not cover CPE.

Availability of rapid diagnostic methods is associated with decreased length of stay, lower mortality and reduced costs in the long term, provided their implementation is feasible [6]. Indeed, in some cases, these techniques may represent an unaffordable expensive add-on to the routine diagnostic laboratory workflow, in terms of reagents and manpower cost, requiring a 24/7 schedule of sample processing. Furthermore, the information provided for antibiotic susceptibility test is different from conventional minimum inhibitory concentration (MIC) values and must be suitably conveyed to the clinician to avoid confusion. Overall, microbiology laboratories should have protocols for immediate notification of clinical teams whenever a CPE infection is identified.

What is currently the best treatment for KPC-KP infections?

A necessary premise is that only low-level evidence with a high risk of bias is available from observational studies regarding the optimal treatment for KPC-KP infections, thus not allowing definite conclusions to be drawn [5,18,19]. In this light, the following statements are to be weighed cautiously, pending results of randomized clinical trials (NCT01597973 and the AIDA study [20] are, respectively, ongoing and have been recently completed).

Because monotherapy appeared to be associated with higher mortality rates compared to combination therapy for the targeted treatment of KPC-KP in observational studies, the use of combined regimens should be preferred in patients with severe KPC-KP infections [19,21–25]. Indeed, the positive impact of combination therapy on survival might be true only in patients with severe infections compared to less severe BSI and in nonbacteraemic intra-abdominal or urinary tract infections, a fact which is also in line with the favourable survival effect of combinations recently observed only in patients with a high INCREMENT-CPE mortality score [23,25]. In patients at lower risk of mortality, no clear survival benefit of combinations over monotherapy has been demonstrated. In these patients, a conservative combination approach might be used at the beginning, with the option of de-escalating to a simpler regimen in correlation with patient's clinical conditions. However, the risk of inducing further resistance by the use of last-resort antibiotics is a nonnegligible risk, and results from randomized clinical trials are needed for ultimately weighing benefits and costs of using combinations in patients with nonsevere KPC-KP infections.

What is the role of carbapenems in the treatment of KPC-KP infections?

In combination treatment, meropenem may still be considered as an option for possibly enhancing bacterial killing, provided that the MIC of meropenem is $\leq$8 mg/L and that a high-dose and prolonged infusion regimen is administered. With the limitations of the nonrandomized design, a survival benefit by using meropenem-based regimens has indeed been argued in many observational studies, with published data mostly referring to meropenem-including combinations for treating KPC-KP BSI. In large multicentre studies conducted in Italy and Greece, increased survival by using combinations of meropenem was observed when KPC-KP exhibited MICs of $\leq$8 mg/L [23,24]. Smaller case series also suggested that increasing carbapenem dosage, use of prolonged infusion and therapeutic drug monitoring might be helpful for treating KPC-producing organisms with meropenem MICs up to 32 to 64 mg/L [26,27]. However, clinical evidence supporting this possibility is preliminary [26,27], and the combination of two other agents showing *in vitro* activity against the given KPC-KP isolate should be considered as a reasonable alternative to carbapenem-including regimens. The administration of carbapenem-based regimens when facing meropenem MICs of >8 mg/L might be considered for MICs up to 32 to 64 mg/L, provided that therapeutic drug monitoring is available to monitor optimal drug exposure, in view of the risk of futility and perpetuation of resistance selection.

Because carbapenem MICs are important for including or not meropenem in combination antimicrobial regimens against KPC-KP and other CPE, the accurate measurement of carbapenem MICs of KPC-KP is a clinically relevant issue. Unfortunately, automated systems and gradient diffusion tests (which are commonly used for antibiotic susceptibility tests in diagnostic microbiology)

may be inaccurate for measurement of carbapenem MICs with KPC-KP and other CPE [28]. Therefore, we recommend that carbapenem MICs of KPC-KP be determined using the reference broth microdilution methodology [29], covering meropenem concentrations up to at least 32 to 64 mg/L.

What molecules can be used to treat KPC-KP infections?

Complete background information is available as Supplementary Material S1 [30–68]. A summary of the available drugs and their suggested dosage for treating KPC-KP infections is presented in Table 2.

What is the role of nebulized antibiotics in the treatment of ventilator-associated pneumonia (VAP) and ventilator-associated tracheobronchitis by KPC-KP?

Inadequate penetration of intravenous antibiotics that may be used against KPC-KP (including colistin, aminoglycosides and tigecycline) to the epithelial lining fluid have prompted the administration of aerosolized antibiotic therapy in patients with VAP [68]. Clinical outcomes were usually noncomparable between clinical studies as a result of heterogeneity in regimens, indications (i.e. VAP, ventilator-associated tracheobronchitis, colonization), therapeutic approaches (intravenous antibiotic and/or nebulized) and different nebulizing devices used [69,70]. Data on KPC producers are scarce overall.

Because maximal antibiotic delivery depends on the type of aerosol generators, novel drug–device combinations stand out as a promising delivery approach in critically ill patients. A randomized trial compared fixed combination of amikacin and fosfomycin (5:2 ratio) or placebo delivered via the investigational eFlow Inline System (PARI GmbH, Starnberg, Germany) as adjunctive treatment to standard intravenous antibiotics [71]. Distribution of multidrug-resistant and extensively drug-resistant isolates did not differ statistically between the two arms (ten and five KPC-KP were identified in target and control arms, respectively). Although clinical benefit was not demonstrated, resistance selection was prevented and eradication of pathogens was higher in the nebulized arm.

Table 2
Antimicrobial agents against KPC-KP

Drug	Loading dose	Daily dose for normal renal function	Comments
Polymyxins [30–41]			
Colistin[a]	9 million IU	4.5 million IU IV every 12 hours Intrathecal/intraventricular: 125 000–250 000 IU Inhaled: 1 to 3 million IU every 8 hours	For infections caused by organisms with MIC >0.5 mg/L, it is advisable to use colistin as part of combination therapy. For dosage adjustment in patients with renal failure, see Nation et al. [41].
Polymyxin B[b]	Not required	7500–12 500 IU/kg every 12 hours every 12 hours Intrathecal/intraventricular: 50 000 IU every 24 hours	No dose adjustment for renal failure.
Aminoglycosides [42–44] (https://www.uptodate.com/contents/manifestations-of-and-risk-factors-for-aminoglycoside-nephrotoxicity)			Aminoglycosides can be useful as part of combination regimens for treating KPC-KP infections, especially if colistin resistance is documented. Pulse dosing is preferable to multiple daily doses; desired peak serum levels are about 10 times the MIC of the organism. Adjust doses according to Hartford nomogram [43].
Gentamicin	Not required when administered in pulse dosing schemes	5 to 7 mg/kg infused over 1 hour	—
Amikacin	Not required when administered in pulse dosing schemes	15 to 20 mg/kg infused over 1 hour	
Tigecycline	100–200 mg	50–100 mg every 12 hours IV	For BSIs or pneumonia or when tigecycline MIC >0.5 mg/L, higher doses are recommended (loading dose, 200 mg followed by 100 mg every 12 hours), preferably in combination with another agent. Not to be used in urinary tract infections; no concentrations in urine.
Fosfomycin	Not required	18 to 24 g IV in 3 to 4 doses	Fosfomycin could be used in combination treatment for KPC-KP infections administered as 6 to 8 g every 8 hours. Resistance can occur during treatment and should be monitored. Potential of fosfomycin to select resistant mutants precludes use as single agent.
Ceftazidime/avibactam	Not required	2.5 g every 8 hours IV infused over 2 hours	Approved for Hospital and Ventilator acquired pneumonia, complicated intra-abdominal and urinary tract infections and for the treatment of infections due to aerobic Gram-negative organisms in adult patients when other treatments might not work.; active in vitro against Enterobacteriaceae-producing ESBLs, AmpC, KPC, OXA-48. Clinical experience for carbapenem-resistant Enterobacteriaceae is currently limited to case series [55–58]. Despite concerns of resistance selection raised by a few reports that might support the used of ceftazidime/avibactam in combination with other agents for treating KPC-KP infections, whether it should be ultimately used alone or combined remain unclear, and requires further dedicated investigation.
Meropenem	1–2 g	2 g every 8 hours IV infused over 3–6 hours	Meropenem should be used in combination with another active agent; the probability of response is higher when meropenem MIC ≤8 mg/L. Salvage therapy with association of 2 carbapenems, e.g. ertapenem plus either meropenem or doripenem, can be considered when other options are not suitable or available.

BSI, bloodstream infection; ESBL, extended-spectrum β-lactamase; KPC-KP, *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae*; MIC, minimum inhibitory concentration.

[a] One milligram of colistin base activity is contained in 2.4 mg colistimethate, which is equivalent to 30 000 IU.

[b] One milligram of polymyxin B is equivalent to 10 000 IU.

Several studies along with a rigorous meta-analysis performed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Critically Ill Patients Study Group (ESGCIP) [72,73] argue for an unclear clinical benefit of inhaled antibiotic in VAP due to KPC-producers [68]. A potential impact on resistance, however, needs to be further investigated [68,74]. Recently published guidelines recommend the add-on use of inhaled colistin in patients with VAP due to carbapenem-resistant pathogens that are susceptible only to colistin [75]. The recommendation was based on a meta-analysis of four studies reporting that add-on nebulized colistin was associated with improved clinical cure. Non-responding VAP is another indication for add-on nebulized colistin [73].

Is prolonged infusion of β-lactams preferable for KPC-KP?

Prolonged β-lactam infusion is intended to enhance the potency (i.e. *f*T > MIC) of these agents against pathogens with elevated MICs [76]. Because KPC-KP is intrinsically resistant to carbapenems, the use of a pharmacodynamically optimized regimen that utilizes an increased dose and infusion time has been advocated as a technique to maximize *in vivo* exposures [77,78]. Enhancement of *f*T > MIC can be achieved using either continuous (total daily dose infused over a 24-hour period) or prolonged infusions (conventional 0.5-hour infusion prolonged up to 6 hours [79,80]). Carbapenem reduced stability at room temperature and requires frequent replacements of the antimicrobial at each dosing interval [81,82], but it provides pharmacodynamic optimization and more flexibility for the nursing staff in patients receiving polypharmacy and limited intravenous access.

What about source control in patients with KPC-KP infections?

The objective of source control includes the actions to control the foci of infection and to restore optimal function of the site of infection. Source control includes removal of implanted or tunnelled devices, open surgical or percutaneous drainage of infected fluids or abscesses and surgical resection of infected tissues. Time from hypotension to implementation of source control has been found to be highly correlated with outcome. Therefore, interventions to be undertaken for source control within the first 12 hours after the diagnosis of the septic syndrome, if feasible, should be considered [83].

Although source control is reported as a modifiable predictor of mortality in sepsis and septic shock [83], the data particularly from KPC-KP infections are scarce. In a two-match case–control study including 99 patients in each arm comparing patients with KPC-KP and carbapenem-susceptible *K. pneumoniae*, removal of focus of infection was independently associated with patient survival [84]. In a prospective observational cohort study encompassing 53 patients with BSI caused by KPC-KP, prior surgery and therapeutic interventions targeting the removal of the site of infection were strongly correlated with survival [85]. Similar conclusions were reported by Falcone et al. [86] in a retrospective analysis with 111 intensive care unit patients with KPC-KP and septic shock in 21.6% of cases. Source control process was accomplished in 95.2% of patients who survived in comparison to 31.2% who died. Cox regression analyses revealed that control of removable source of infection was associated with favourable outcome (hazard ratio, 0.14; $p < 0.001$). In a retrospective study including 48 BSI due to KPC-KP, adjunctive source control procedures were associated with clinical response at day 7 (odds ratio, 12.2; 95% confidence interval, 1.4–110; p 0.025) [87].

What is the optimal duration of treatment for KPC-KP infections?

Optimal treatment duration for KPC-KP infections is unclear. In retrospective studies, a mean duration of 2 weeks of treatment was reported [88]. In VAP, robust data support a reduced 8-day antibiotics course in patients receiving appropriate initial empirical therapy [89–91]. This strategy was associated with significantly more antibiotic-free days without negative impact on mortality and reduced resistance selection. Higher relapse rates in patients with nonfermenting Gram-negative bacilli were initially reported, suggesting longer treatments when these pathogens were responsible for VAP [89]. An updated meta-analysis of VAP caused by non-fermenters, however, supported a reduced length of treatment (e.g. 7 days), which is currently recommended by guidelines [75].

As far as bacteraemia is concerned, the evidence is even less clear. Havey et al. [92], in a large systematic review and meta-analysis encompassing 24 trials, showed that patients receiving short treatment (5–7 days) versus those receiving long treatment (7–21 days) for non–*Staphylococcus aureus* bacteraemias had no significant differences in mortality, microbiologic eradication or clinical cure. Randomized controlled trials to assess the optimal duration of bacteraemia in the context of multidrug-resistant and KPC producers are awaited and may provide baseline evidence that long treatments may not be necessary. In another meta-analysis, antibiotic algorithms guided by procalcitonin levels were found to safely guide reduced treatment duration without any negative impact on survival [93]. These findings suggest that a holistic approach combining adequate sterilization of septic foci (microbiologic eradication), optimization of antibiotic exposure in critically ill patients and use of biomarkers enabling monitoring of the effectiveness of administered treatment may allow for shorter treatment durations even in the presence of KPC producers.

Can KPC-KP infections be prevented? How?

The ESCMID recently released guidelines aimed to decrease the transmission of multidrug-resistant Gram-negative pathogens [94,95]. The most robust measure to prevent interpatient transmission of KPC-KP appeared to be hand hygiene [96]. In a study showing 30% reduction of KPC-KP transmission rate, this achievement was possible in an 8- to 12-week time frame with active surveillance, contact precautions and isolation or cohorting, but only if at least 60% compliance with hand hygiene compliance was reached.

Additional measures include minimizing use of invasive devices, promotion of antimicrobial stewardship, a standardized approach for active surveillance of at risk populations and protocols for discontinuation of carrier status.

Routine rectal swab surveillance of KPC-KP contacts is an important measure to enhance identification and isolation of carriers, but such surveillance should not be used as an single infection control measure to prevent KPC-KP dissemination [94,97–99]. In this regard, multifaceted interventions are more likely to be successful. For example, the combination of daily baths with 2% chlorhexidine–impregnated wipes, point prevalence surveillance with swabs, isolation of colonized or infected patients, cohorting of medical personnel, enhanced environmental surveillance and repetitive educational campaigns successfully controlled the further horizontal spread of a monoclonal KPC-KP strain [100]. In another study, transmission through contaminated sinks has been suggested as the major responsible for a long-term, low-frequency hospital outbreak of KPC-KP infections, further confirming the need for accurate environmental surveillance and disinfection [101]. In a study from Israel, a significant decline of the nosocomial CPE

Table 3
Summary of studies reporting decolonization strategies as means of eradicating KPC-KP carriage

Study	Design and population	Intervention	Main outcome	Comment
Zuckerman 2011 [116]	• Pilot study in haemato-oncology and bone marrow transplant unit (15 patients). • Goal was to eradicate CRKP from rectal carriage.	• Oral gentamicin at dose of 80 mg q.i.d. was administered to all identified carriers until eradication. • Median duration of therapy, 27 days (range, 7–90 days).	• Eradication rate 66% (10/15) and lasted for median of 9 months (range, 2–10 months). • Discontinuation of persistent bacteraemia occurred in 62.5% (5/8), and nosocomial spread of CRKP carrier state ceased.	• No gentamicin resistance was detected in blood isolates during oral gentamicin treatment. • Administration of intensive chemotherapy and SCT was feasible.
Saidel-Odes 2012 [117]	• Randomized, double-blind, placebo-controlled trial in 1000-bed tertiary-care university hospital	• Forty adults with CRKP-positive rectal swab cultures. • SDD arm received oral gentamicin and polymyxin E gel (0.5 g 4 times per day) and oral solutions of gentamicin (80 mg 4 times per day) and polymyxin E (1×10^6 units 4 times per day for 7 days).	• Positivity for CRKP rectal cultures was significantly reduced by 2 weeks. • 16.1% in placebo arm and 61.1% in SDD arm were negative (OR, 0.13; 95% CI, 0.02–0.74; $p < 0.0016$). Difference between 2 arms was still maintained at 6 weeks (33.3% vs. 58.5%). • No evidence of increase in either gentamicin or polymyxin E MIC among CRKP isolates.	• SDD was effective as decolonization strategy for selected patients colonized with CRKP, such as transplant recipients or immunocompromised patients pending chemotherapy and candidates for major intestinal or oropharyngeal surgery.
Lübbert 2013 [118]	• Single-centre outbreak of KPC-2, affecting 90 patients hospitalized over 28 months. • Retrospective analysis of patients who received SDD compared to remaining patients harbouring KPC-2-KP.	• 14 consecutive patients were treated with short course (7 days) of SDD regimen consisting of colistin (1 million units q.i.d.) and gentamicin (80 mg q.i.d.) as oral solutions, and colistin/gentamicin gel (0.5 g) to oral cavity.	• Decolonization of KPC-2-KP was achieved in 6 (43%) of 14 patients after mean (range) of 21 (12–40) days, but was also observed in 23 (30%) of 76. • Secondary resistance to colistin (by 19%) and gentamicin (by 45%) was observed in SDD group but not in comparative group of non-SDD controls (p 0.102).	• SDD approach was not sufficiently effective for decolonization and was associated with high rates of resistance in subsequent cultures.
Tascini 2014 [119]	• Pilot nonblinded, prospective study in 3 Italian hospitals to assess feasibility of administering oral gentamicin for KPC-KP. • Gut decontamination. • Patients enrolled had gut colonization by gentamicin-susceptible KPC-KP and were candidates for planned surgery, major medical intervention or patient transfer.	• Oral gentamicin, 80 mg 4 times daily, was administered to 50 consecutive patients over 8-month period. • Separate analysis was performed with 23 patients receiving oral gentamicin alone and 27 patients who received CSAT. • Oral gentamicin provided for median (IQR) 16 (10–27) days.	• KPC-KP infections documented in 5 (15%) of 34 successfully decontaminated patients compared to 12 (73%) of 16 persistent carriers ($p < 0.001$). • Decontamination rate was 96% (22/23) in patients receiving oral gentamicin only compared to 44% (12/27) treated with oral gentamicin and CSAT ($p < 0.001$). • Gentamicin-resistant KPC-KP strains were isolated from stools of 4 of 16 persistent carriers	• Useful for gut decontamination and prevention of infection due to KPC-KP, especially in patients not receiving CSAT. • No difference in overall mortality was observed between decontaminated and persistently colonized patients.
Oren 2013 [120]	• Semirandomized prospective controlled trial was conducted to eradicate CRE colonization using oral nonabsorbable antibiotics.	• 152 patients were included; 50 patients received 1 of 3 drug regimens: gentamicin, 26; colistin, 16; both drugs, 8, followed for median duration of 33 days; 102 were followed for spontaneous eradication for median duration of 140 days (controls). • Antibiotic selection was based on isolate's *in vitro* susceptibility.	• Eradication rates in 3 treatment groups were 42%, 50%, and 37.5%, each significantly higher than 7% spontaneous eradication rate in control group ($p < 0.001$, <0.001, and 0.004) with no difference between regimens. • No significant adverse effects were observed.	• Administration of oral nonabsorbable antibiotics was effective and safe for eradication of CRE colonization and thus may reduce patient-to-patient transmission and incidence of clinical infection. • Trend towards lower mortality among patients who experienced eradication while receiving treatment (2/22, 9%) compared to those who did not experience eradication (9/28, 32%) was observed (p 0.052).
Tascini 2015 [121]	• 1:1 case–control study exploring prevention of KPC-KP gut colonization in patients who undergo hepatectomy with oral gentamicin in endemic setting.	• All 31 consecutive patients who underwent liver resections in last year treated were orally with gentamicin; controls comprised 31 patients who underwent surgery in same ward in previous year without gentamicin prophylaxis.	• Overall gut colonization rate in intervention group was 3% (1/31) vs. 29% (9/31) in control group (p 0.016). • Only KPC-KP strain isolated in gentamicin-treated group retained susceptibility to gentamicin.	• Oral administration of gentamicin might be effective to avoid KPC-KP gut colonization without adverse events.
Machuca 2016 [122]	• Retrospective cohort study of patients colonized by. • KPC-KP in 2 hospitals during outbreak with colistin-resistant KPC-KP strain, exploring whether decolonization therapy with aminoglycosides had protective effect in selected patients.	• 77 patients at high risk (neutropenia, major surgery, multiple comorbidities) with rectal colonization by colistin-resistant KPC-KP were followed for 180 days. • Oral aminoglycosides (gentamicin or combination of neomycin/streptomycin) were administered to 44 patients.	• At 180 days of follow-up, decolonization was associated with lower risk of mortality in multivariate analyses (HR 0.18; 95% CI 0.06–0.55) and lower risk of KPC-KP infections (HR 0.14; 95% CI 0.02–0.83) and increased microbiologic success (HR 4.06; 95% CI 1.06–15.6). Beneficial effects were more favourable with gentamicin.	• Intestinal decolonization with aminoglycosides is associated with reduction in crude mortality and KPC-KP infections.

CI, confidence interval; CRE, carbapenem-resistant *Enterobacteriaceae*; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; CSAT, concomitant systemic antibiotic treatment; HR, hazard ratio; IQR, interquartile range; KPC, *Klebsiella pneumoniae* carbapenemase; KPC-KP, *Klebsiella pneumoniae* carbapenemase–producing *K. pneumoniae*; MIC, minimum inhibitory concentration; OR, odds ratio; SCT, stem cell transplantation; SDD, selective digestive decontamination.

Table 4
New antimicrobials with potential activity against KPC-producing *Enterobacteriaceae*

Antibiotic	Antibiotic class	Resistant phenotypes	Status of development	Company	Comments
Ceftazidime/avibactam	β-Lactam/β-lactam inhibitor	• Activity against *Enterobacteriaceae*-producing KPCs, ESBLs, OXA, AmpC enzymes. • No activity against class B β-lactamases (MBL, VIM, NDM). • Avibactam offers no enhanced activity against *Pseudomonas aeruginosa* and *Acinetobacter baumannii.*	• Noninferiority vs. imipenem and meropenem in phase 2 clinical trials for treatment of cUTIs and cIAIs, respectively. • Licensed in USA and EU for cUTIs, cIAIs and HAP/VAP. • Phase 3 study in VAP completed. • Phase 1 study on pharmacokinetics of critically ill patients planned.	USA, Allergan; EU and rest of the world: Pfizer	Ceftazidime/avibactam was recently licensed for treatment HAP/VAP, cUTIs, cIAIs in USA and Europe and for the treatment of infections due to aerobic Gram-negative organisms in adult patients when other treatments might not work [123] (https://clinicaltrials.gov/ct2/results?term=ceftazidime+avibactam&Search=Search); registration trials, however, did not include CRE isolates.
Ceftaroline/avibactam	β-Lactam/β-lactam inhibitor	• ESBL- and KPC-producing *Enterobacteriaceae*. Avibactam effectively inhibits Ambler class A (e.g. ESBL and KPC), C (AmpC), and some D (OXA-like) enzymes. • No activity against *A. baumannii* or *P. aeruginosa.* • No activity against class B enzymes (MBL).	• Completed phase 1 trials and 1 phase 2 trial in cUTI. • Completed phase 2 trial in cUTIs vs. doripenem, and 3 phase 1 trials awaiting results.	Pfizer Laboratories	Ceftaroline/avibactam has promising *in vitro* spectrum; results from clinical trials are pending [123] (https://clinicaltrials.gov/ct2/results?term=ceftaroline+avibactam&Search=Search).
Imipenem/relebactam	Carbapenem/β-lactamase inhibitor (diazabicyclooctane)	• Class A and C β-lactamases, porin mutations, class D (OXA-48 not consistently). • No activity against MBL.	• Completed phase 2 trial in cUTI; currently in phase 3 trials vs. colistin against imipenem-resistant pathogens and vs. piperacillin/tazobactam in bacterial pneumonia.	Merck	Relebactam is under investigation in combination with imipenem/cilastatin with phase 3 trials underway vs. colistin for imipenem-resistant pathogens and vs. piperacillin/tazobactam in bacterial pneumonia [62,123] (https://clinicaltrials.gov/ct2/results?term=imipenem+relebactam&Search=Search).
Meropenem/vaborbactam (RPX 7009)	Carbapenem/boronic acid—based β-lactamase inhibitor	• Class A β-lactamases (KPC and most AmpC). • No activity against MBL and class D OXA-48.	◦ Completed phase 3 trial in cUTI. ◦ Completed phase 3 trial in various infections caused by carbapenemresistant bacteria and approved by FDA. ◦ Planned phase 3 trial in VAP.	Medicines Company	Boronic-based β-lactamase inhibitor vaborbactam combined with meropenem (Carbavance) currently in phase 3 trials [62] (https://clinicaltrials.gov/ct2/results?term=carbavance&Search=Search).
Plazomicin	New aminoglycoside (neoglycoside)	• Various Gram-positive and Gram-negative organisms. • Not active against bacteria harbouring ribosomal methyltransferases (mostly NDM-1 strains).	◦ Completed 2 phase 3 trials (UTIs and serious infections by CRE). ◦ Approved by FDA on September 2017.	Achaogen	New parenteral hemisynthetic aminoglycoside with favourable pharmacokinetics and safety profile, plazomicin, holds also promise against KPC producers [62,123]. Its efficacy against carbapenem-producing bacteria has been recently demonstrated in serious infections including BSI, HAT/VAP and cUTI (https://static1.squarespace.com/static/51199d96e4b084d1d0b105c3/t/58fb6714b8a79b0b91ba96a6/1492870939778/ECCMID+17-EPIC_Final.pdf; https://www.escmid.org/escmid_publications/escmid_elibrary/material/?mid=52433).
Cefiderocol, S-649266	Siderophore cephalosporin	• ESBL, class A (KPC) and class B (NDM-1) carbapenemases and OXA-type enzymes, broad range of pathogens including *A. baumannii, P. aeruginosa, Stenotrophomonas maltophilia* and *Enterobacteriaceae* (CRE).	• Completed phase 2 trial in UTI; currently in phase 3 trials for severe infections by CRE. • Phase 3 trial in nosocomial pneumonia scheduled.	Shionogi	Cefiderocol (formerly S-649266) is promising siderophore cephalosporin, showing high activity against carbapenem-resistant Gram-negative bacteria, and it is currently in phase 3 trial [62,123,124].

(*continued on next page*)

Table 4 (*continued*)

Antibiotic	Antibiotic class	Resistant phenotypes	Status of development	Company	Comments
Eravacycline	Tetracycline	• ESBL-, KPC-, NDM- and OXA-producing *Escherichia coli* and *K. pneumoniae*. • Active against *A. baumannii* and *S. maltophilia*. • Not active against *P. aeruginosa*.	• Completed phase 2 trials in cIAI. • Currently in phase 3 trials in cIAI (vs. meropenem) and in cUTI (vs. ertapenem/levofloxacin).	Tetraphase Pharmaceuticals	Eravacycline is novel fluorocycline with *in vitro* activity against *Enterobacteriaceae* harbouring variety of resistance genes (ESBLs or carbapenemases), potential activity against *A. baumannii*, but not against *P. aeruginosa* [62,123,125] (https://clinicaltrials.gov/ct2/results?term=eravacycline&Search=Search). Compared to tigecycline, it is more potent *in vitro* 2- to 8-fold against Gram-negative bacilli and exhibits 1-fold higher C_{max} and AUC_{0-12} in epithelial lining fluid [126,127]. Noninferiority was demonstrated in phase 3 study evaluating safety and efficacy of eravacycline vs. ertapenem in IAI [128], but not in trial of cUTIs compared to levofloxacin (http://ir.tphase.com/releasedetail.cfm?releaseid=930613).

AUC, area under the plasma concentration vs. time curve; BSI, bloodstream infection; cIAI, complicated intra-abdominal infection; CRE, carbapenem-resistant *Enterobacteriaceae*; cUTI, complicated urinary tract infection; EMA, European Medicines Agency; ESBL, extended-spectrum β-lactamase; FDA, Food and Drug Administration; HAT, ventilator-associated tracheobronchitis; KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-β-lactamase; NDM, New Delhi metallo-β-lactamase; VAP, ventilator-associated pneumonia; VIM, Verona integron-encoded metallo-β-lactamase.

acquisition was achieved with a multiple-step strategy, including ward-based mandatory guidelines for carrier isolation, patient and staff cohorting, active surveillance and new rules for microbiology identification, direct officer visits at healthcare facilities and networking [102].

An important factor to consider is the presence of so-called superspreaders (i.e. those carriers who more easily spread KPC-KP in their immediate environment [93]). Superspreaders are characterized by high rectal CPE concentrations and are more frequently admitted for respiratory disease [103]. This effect has similarities with other enteropathogenetic syndromes such as *Clostridium difficile* colitis and candidaemia, at least by the means of exogenous colonization [103,104]. In a multicentre US study, KPC-KP clearance was attributed to a reduction in the use of urinary catheters, a factor that should be considered in the implementation of a bundle procedure [105].

Who among KPC-KP colonized patients is at increased risk of developing KPC-KP infections?

Many studies have focused on the role of KPC-KP colonization in the development of infection in order to guide the selection of appropriate interventions and administration of early appropriate treatment.

In a retrospective study involving five large Italian hospitals, bowel colonization by KPC-KP played a major role in predicting transition from colonization to infection [106]. The overall number of colonized sites represented the most important risk factor for KPC-KP BSI development among rectal carriers in a prospective multicentre study [107,108]. Other risk factors for KPC-KP BSI included intensive care unit admission, abdominal invasive procedures, chemotherapy or radiotherapy, and previous BSI [107,109]. In a study including patients undergoing open heart surgery, colonization was the most important risk factor for KPC-KP infection [110]. In a prospective cohort study of adult patients undergoing liver transplantation, KPC-KP infection rates among patients noncolonized, colonized at liver transplantation and colonized after liver transplantation were 2%, 18.2% and 46.7%, respectively [107]. In settings where colonization with KPC-KP is common among critically ill patients, antibiotic stewardship programs should be undertaken to optimize antimicrobial use, as shown by a study demonstrating high risk of KPC-KP VAP in colonized patients receiving prolonged antimicrobial therapy [111].

Risk analysis of high mortality rates (64%) among oncohaematologic patients undergoing allogenic transplant has highlighted the presence of pretransplantation KPC-KP infection and the absence of active first-line antibiotic treatment, identifying the need for targeted interventions [112]. A subsequent report illustrated the safety and efficacy of allogenic haematopoietic stem cell transplantation in patients colonized by the KPC-KP using the 'Turin bundle': avoidance of levofloxacin prophylaxis, treatment with gentamicin by mouth in the best window of opportunity before transplantation, administration of tigecycline and piperacillin/tazobactam as empiric treatment of febrile neutropenia and administration of combination regimens (e.g. colistin plus tigecycline plus meropenem) in patients with severe sepsis or septic shock [113]. In another study, the cumulative incidence of KPC-KP BSI and septic shock at 1 year after haematopoietic stem cell transplantation was significantly reduced from 62.5% to 16.6% after the introduction of systematic screening with rectal swabs, contact precautions and early targeted treatment in neutropenic patients with fever with at least two antibiotics [114]. Finally, a multifaceted infection control program was able to reduce both BSI due to CPE and CPE colonization, whereas monthly incidence of CPE carriage was predictive of BSI [115].

Is decolonization a useful strategy in KPC-KP colonized patients?

Studies deploying oral decolonization strategies as a mean to eradicate gut carriage of KPC-KP have produced conflicting results, and only one reported a survival benefit (Table 3) [116–122]. With regard to the use of oral gentamicin for decolonization purposes, an indiscriminate use should be avoided. Indeed, this strategy has a high risk of failure and also cannot be separated from the risk of selecting gentamicin resistance (and thus of losing one of the last—if not the very last—therapeutic options) [119,122]. It should therefore be reserved for highly selected special conditions (e.g. very high risk of developing infection because of severe neutropenia or recurrent KPC-KP infections) on a patient-by-patients basis [122].

What's new in KPC-KP treatment options?

A handful of new compounds expected to address the therapeutic problem of KPC-KP in the near future are summarized in Table 4 (reporting molecules in phase 3 of clinical development) [123–128].

Conclusions

The optimal management of KPC-KP infections in critically ill patients relies on a concerted multidisciplinary approach. On a case-by-case basis, efforts should indeed be directed towards preventing colonization, infection and mortality. Each intervention has its peculiar issues to be addressed (preventing colonization in the patient, preventing infection in the colonized patient and colonization of his or her contacts, reducing mortality in the infected patient by rapidly diagnosing the causative agent and promptly adopting the best therapeutic strategy), but all are crucial to ultimately curtail the high mortality of KPC-KP infections. High-level evidence is urgently needed to firmly guide physicians through all these steps.

Transparency declaration

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.cmi.2017.08.030.

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