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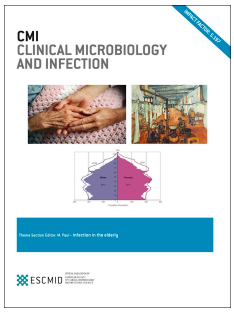

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Management of KPC-Producing Klebsiella pneumoniae Infections

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Running title: Management of KPC-KP 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: our aim was 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 based on 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/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 on the basis 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 the case of severe infections. For non-critically-ill patients without severe infections, results from randomized clinical trials are needed for ultimately 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.

Introduction

Management of infections caused by multidrug-resistant bacteria impacts considerably on health costs and becomes 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] KPC-KP optimal treatment, however, is not known and there are currently no published recommendations for the management of infections by KPC-KP. Given the observational nature of the majority of studies on this topic, many of the recommendations listed in this manuscript arise from acquired experience of the invited panel members, and therefore represent expert opinion.

Purpose and methods

The purpose of this paper was 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 in the paper; 12 questions were formulated after rounds of discussion between chairs (M. Bassetti, G. Poulakou, C. Viscoli, and H. Giamarellou) 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

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

Several new diagnostic technologies have recently become available to allow increased rapidity of microbiological diagnosis, including Matrix Assisted Laser 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 very useful to reduce the time for pathogen identification (ID) and antibiotic susceptibility test (AST) .

MALDI-TOF MS has proven very 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 beta-lactamases.[11] A mass spectrometric beta-lactamase (MSBL) assay represents a functional assay based on the direct monitoring of the enzymatic activity of the beta-lactamase and can be performed with bacterial cultures or directly from freshly tagged positive blood cultures, with results available after 1 - 4 hour incubation period.[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 beta-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 one hour compared to conventional microbiological 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 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 does not provide comprehensive information about the resistance phenotype of the infecting strain,

and conventional AST remains the cornerstone for selection of definitive treatment regimens and evaluation of adequate / 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 very 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 that 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 AST 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

2. 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 for definite conclusions. [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 ongoing or are have been recently completed, respectively).

Since 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 non-bacteraemic intra-abdominal or UTIs, 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 non-negligible risk, and results from randomized clinical trials are needed for ultimately weighing benefits and cost of using combinations in patients with non-severe KPC-Kp infections.

3. 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: i) the MIC of meropenem is ≤ 8mg/L and ii) a high-dose and prolonged infusion regimen is administered. With the limitations of the non-randomized design, a survival benefit by using meropenem-based regimens has indeed been argued in many observational studies, with

181 published data mostly referring to meropenem-including combinations for treating
182 KPC-KP bloodstream infections (BSI). In large multicentre studies conducted in Italy
183 and Greece an increased survival by using combinations of meropenem was
184 observed when KPC-KP exhibited MIC ≤ 8 mg/L.[23,24] Smaller cases series also
185 suggested that increasing carbapenem dosage, use of prolonged infusion, and
186 therapeutic drug monitoring (TDM) might be helpful for treating KPC-producing
187 organisms with meropenem MICs up to 32-64 mg/L.[26,27] However, clinical evidence
188 supporting this possibility is preliminary,[26,27] and the combination of two other
189 agents showing *in vitro* activity against the given KPC-KP isolate should be
190 considered as a reasonable alternative to carbapenem-including regimens. The
191 administration of carbapenem-based regimens when facing meropenem MICs > 8
192 mg/L might be considered for MICs up to 32-64 mg/L, provided that TDM is
193 available to monitor optimal drug exposure, in view of the risk of futility and
194 perpetuation of resistance selection.

195 Since carbapenem MICs are important for including or not meropenem in
196 combination antimicrobial regimens against KPC-KP and other CPE, the accurate
197 measurement of carbapenem MICs of KPC-KP is a clinically relevant issue.
198 Unfortunately, automated systems and gradient diffusion tests (which are commonly
199 used for AST in diagnostic microbiology) may be inaccurate for measurement of
200 carbapenem MICs with KPC-KP and other CPE.[28] Therefore, we recommend that
201 carbapenem MICs of KPC-KP be determined using the reference broth microdilution
202 methodology,[29] covering meropenem concentrations up to at least 32-64 mg/L.
203

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

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

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

Inadequate penetration of iv antibiotics that may be used against KPC-KP (including colistin, aminoglycosides, and tigecycline) to the epithelial lining fluid (ELF) have prompted the administration of aerosolized antibiotic therapy in patients with VAP.[69] Clinical outcomes were usually non-comparable between clinical studies due to heterogeneity in regimens, indications (i.e., VAP, VAT, colonization), therapeutic approaches (iv antibiotic and/or nebulized) and different nebulizing devices used.[70-71] Data on KPC-producers is overall scarce.

As 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, Germany) as adjunctive treatment to standard iv antibiotics.[72] Distribution of multidrug-resistant (MDR) and extensively drug-resistant (XDR) isolates did not differ statistically between the two arms (10 and 5 KPC-KP were identified in target and control arms, respectively). Although clinical benefit was not

227 demonstrated, resistance selection was prevented and eradication of pathogens was
228 higher in the nebulised arm.

229 Several studies along with a rigorous meta-analysis performed by the European
230 Society of Clinical Microbiology and Infectious diseases (ESCMID) critically ill patients
231 study group (ESGCIP)[73,74] argue for an unclear clinical benefit of inhaled antibiotic in
232 VAP due to KPC-producers.[69] A potential impact on resistance, however, needs to be
233 further investigated.[69,75] Recently published guidelines recommend the add-on use
234 of inhaled colistin in patients with VAP due to carbapenem-resistant pathogens that
235 are susceptible only to colistin.[76] The recommendation was based on a meta-analysis
236 of four studies reporting that add-on nebulized colistin was associated with
237 improved clinical cure. Non-responding VAP is another indication for add-on
238 nebulized colistin.[74]

239

240 **6. Is prolonged infusion of beta-lactams preferable for KPC-KP?**

241 Prolonged β-lactam infusions is intended to enhance the potency (i.e., *f*T>MIC) of
242 these agents against pathogens with elevated MICs.[77] Since KPC-KP is intrinsically
243 resistant to carbapenems, the use of a pharmacodynamically optimized regimen that
244 utilizes an increased dose and infusion time has been advocated as a technique to
245 maximize *in vivo* exposures. [78,79] Enhancement of *f*T>MIC can be achieved using
246 either continuous (total daily dose infused over a 24 hr period) or prolonged
247 infusions (conventional 0.5 hr infusion prolonged up to 6 hours[80,81]). Carbapenem
248 reduced stability at room temperature, requires frequent replacements of the
249 antimicrobial at each dosing interval[82,83] but provides pharmacodynamic

optimization and more flexibility for the nursing staff in the patient receiving polypharmacy and limited intravenous access.

7. 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.[84]

Although source control is reported as a modifiable predictor of mortality in sepsis and septic shock [84], the data particularly from KPC-KP infections is 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.[85] 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.[86] Similar conclusions were reported by Falcone et al in a retrospective analysis with 111 intensive care unit (ICU) patients with KPC-KP and septic shock in 21.6% 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, CI 95%, p<0.001).[87] 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, CI 95%1.4-110, p=0.025).[88]

8. 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 two weeks of treatment was reported.[89] In VAP, robust data supports a reduced 8-day antibiotics course in patients receiving appropriate initial empirical therapy.[90-92] 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 non-fermenting Gram-negative bacilli were initially reported suggesting longer treatments when these pathogens were responsible for VAP.[90] An updated meta-analysis of VAP caused by non-fermenters, however, supported a reduced length of treatment (e.g., 7 days) that is currently recommended by guidelines.[76]

As far as bacteremia is concerned, the evidence is even less clear. Havey et al 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* bacteremias had no significant differences in mortality, microbiological eradication and clinical cure. Randomized-controlled trials to assess the optimal duration of bacteremia in the context of MDR and KPC-producers are awaited and may provide baseline evidence that long treatments may not be necessary.[93] In another meta-analysis, antibiotic algorithms guided by

298 procalcitonin levels were found to safely guide reduced treatment duration without
299 any negative impact on survival.[94] These findings, suggest that a holistic approach
300 combining adequate sterilization of septic foci (microbiological eradication),
301 optimization of antibiotic exposure in critically ill patients, and the usage of
302 biomarkers enabling monitoring of the effectiveness of administered treatment may
303 allow for shorter treatment durations even in the presence KPC-producers.

304

305 **9. Can KPC-KP infections be prevented? And how?**

306 The ESCMID recently released guidelines aimed to decrease the transmission of MDR
307 Gram-negative pathogens.[95,96] The most robust measure to prevent inter-patient
308 transmission of KPC-KP appeared to be hand hygiene.[97] In a study showing 30%
309 reduction of KPC-KP transmission rate, this achievement was possible in a 8 to 12
310 week timeframe with active surveillance, contact precautions and isolation or
311 cohorting, but only if at least 60% compliance with hand- hygiene compliance was
312 reached.

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

316 Routine rectal swab surveillance of KPC-KP contacts is an important measure
317 to enhance identification and isolation of carriers, but should not be used as an
318 single infection-control measure to prevent KPC-KP dissemination. [95,98-100] In this
319 regard, multifaceted interventions are more likely to be successful. For example, the
320 combination of daily baths with 2% chlorhexidine impregnated wipes, point-
321 prevalence surveillance with swabs, isolation of colonized/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.[101] 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.[102] In a study from Israel, a significant decline of the nosocomial CPE 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.[103]

An important factor to consider is the presence of super-spreaders (i.e., those carriers who more easily spread KPC-KP in their immediate environment[94]). Super-spreaders are characterized by high rectal CPE concentrations and are more frequently admitted for respiratory disease.[104] This effect has similarities with other so called "enteropathogenetic syndromes" such as *Clostridium difficile* colitis and candidemia, at least by the means of exogenous colonization.[104,105] In a multicentre US study, KPC-KP clearance was attributed to a reduction in the usage of urinary catheters, a factor that should be considered in the implementation of a bundle procedure.[106]

10. 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 held a major role in predicting transition from colonization to infection.[107] 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.[108,109] Other risk factors for KPC-KP BSI included ICU admission, abdominal invasive procedures, chemotherapy or radiation therapy, and previous BSI.[108,110] In a study including patients undergoing open heart surgery, colonization was the most important risk factor for KPC-KP infection.[111] In a prospective cohort study of adult patients undergoing liver transplant (LT), KPC-KP infection rates among patients non-colonized, colonized at LT, and colonized after LT were 2%, 18.2% and 46.7%, respectively.[108] 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.[112]

Risk analysis of high mortality rates (64%) among oncohaematological patients undergoing allogenic transplant, highlighted the presence of pre-transplant KPC-KP infection and the absence of active first-line antibiotic treatment, identifying the need for targeted interventions.[113] A subsequent report illustrated the safety and efficacy of allogenic HSCT in patients colonized by the KPC-KP using the “Turin

bundle": avoidance of levofloxacin prophylaxis, treatment with gentamicin *per os* in the best window of opportunity pre-transplant, 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.[114] In another study, the cumulative incidence of KPC-KP BSI and septic shock at one 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.[115] 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.[116]

11. Is decolonization a useful strategy in KPC-KP colonised 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).[117-123] 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 last - therapeutic options).[120,123] It should therefore be reserved for very 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.[123]

12. What is 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).[124-137]

Conclusions

The optimal management of KPC-KP infections in critically ill patients relies on concerted multidisciplinary approach. On a case-by-case basis, efforts should indeed be directed towards preventing colonization, infection, or 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/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.

Conflict of interest

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956 **Table 1. Clinical question defined by the panel and related answers based on**
957 **expert opinion**

Question 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 patients' outcome. However, whether or not they should be introduced into the laboratory workflow remain a choice to be carefully balanced locally, according to the available resources and personnel in every single hospital.*
Question 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 infections, results from randomized clinical trials are needed for ultimately weighing the related benefits and costs, also in terms of induction of resistance.*
Question 3	What is the role of carbapenems in the treatment of KPC-KP infections? *Administration of high-dose (e.g., 2 grams q 8 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 TDM is available to monitor optimal drug exposure.*
Question 4	What molecules can be used in the treatment of KPC-KP infections? *Various molecules can be used in combination treatment against KPC-KP, including aminoglycosides, polymyxins, tigecycline, fosfomycin, and carbapenems in selected cases (see table 2 for details).*
Question 5	What is the role of nebulized antibiotics in the treatment of ventilator-associated pneumonia (VAP) and ventilator-associated tracheobronchitis (VAT) by KPC-KP? *The use of nebulised 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).*
Question 6	Is prolonged infusion of beta-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.
Question 7	What about source control in patients with KPC-KP infections? *Although data among patients with KPC-KP infections is limited, source control in this population has been associated with favourable outcomes and should be performed promptly whenever possible.*
Question 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 microbiological eradication, use of biomarkers and optimization of antibiotic exposure could be used to reduce treatment duration*
Question 9	Can KPC-KP infections be prevented? And how? *Multifaceted infection control components are needed to decrease the rates of colonization and cross transmission of KPC-Kp.*
Question 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.*
Question 11	Is decolonization a useful strategy in KPC-KP colonised patients? *Decolonization of KPC-Kp carriers is currently not supported by large studies and may be considered only in selected cases.*
Question 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.*

958 KPC-KP, *Klebsiella pneumoniae* carbapenemase-producing *Klebsiella pneumoniae*.

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961 **Table 2. Antimicrobial agents Against *Klebsiella pneumoniae* carbapenemase-producing *Klebsiella pneumoniae* (KPC-KP).**

Drug	Loading dose	Daily dose for normal renal function	Comments
Polymyxins [ref. 30-41]			
Colistin[a]	9 million IU	4.5 million IU IV q 12h. Intrathecal/intraventricular: 125.000-250.000 IU Inhaled: 1 to 3 million IU q 8h	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 refer to nation R *et al.*[29]
Polymyxin B[b]	Not required	7500–12500 IU/Kg q 12 h q 12 h Intrathecal/intraventricular: 50000 IU q 24 h	No dose adjustment for renal failure.
Aminoglycosides [ref. 42-45]			
Gentamicin	Not required when administered in pulse dosing schemes	5 to 7 mg/kg infused over 1 h	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]
Amikacin	Not required when administered in	15 to 20 mg/kg infused over 1 h	

	pulse dosing schemes		
Tigecycline [ref. 21,22,46-52]	100-200 mg	50-100 mg q 12 h 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 q 12 h), preferably in combination with another agent. Not to be used in urinary tract infections, no concentrations in urine.
Fosfomycin [ref. 38,53-58]	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 8g every 8 hours. Resistance can occur during treatment and should be monitored. The potential of fosfomycin to select resistant mutants precludes its use as a single agent.
Ceftazidime/ avibactam [ref. 59-63]	Not required	2.5g q 8 h IV infused over 2 h	Approved for complicated urinary tract and intra-abdominal infections; active *in vitro* against *Enterobacteriaceae* producing ESBLs, AmpC, KPC and OXA-48. Clinical experience for carbapenem-resistant *Enterobacteriaceae* is currently limited to case series.[56-59] 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 [ref. 23-29,64-68]	1-2 g	2 g q 8 h IV infused over 3-6 h	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 two carbapenems, e.g. ertapenem plus either meropenem or doripenem can be considered when other options are not suitable or available.

962 a. 1 mg of colistin base activity is contained in 2.4 mg colistimethate which is equivalent to 30,000 IU.

963 b. 1 mg of polymyxin B is equivalent to 10,000 IU

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966 **Table 3. Summary of studies reporting decolonisation strategies as a means of eradicating KPC-KP carriage**

Study	Design-Population	Intervention	Main outcome	Comment
Zuckerman T et al, 2011 [ref. 117]	Pilot study in haemato-oncology and Bone Marrow Transplant unit (15 patients) Goal: To eradicate carbapenem resistant Klebsiella pneumoniae (CRKP) from rectal carriage	Oral gentamicin at a dose of 80 mg q.i.d. was administered to all identified carriers until eradication [median duration of 27 days (range: 7–90)].	Eradication rate achieved was 66% (10/15) and lasted for a median of 9 months (range: 2–10); discontinuation of persistent bacteremia 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 L, et al, 2012 [ref. 118]	A randomized, double-blind, placebo-controlled trial in a 1,000-bed tertiary-care university hospital.	Forty adults with CRKP-positive rectal swab cultures. The 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 (1X 10^6 units 4 times per day for 7 days).	Positive for CRKP rectal cultures were significantly reduced by 2 weeks [16.1% in the placebo arm and 61.1% in the SDD arm were negative (odds ratio, 0.13; 95% confidence interval, 0.02–0.74; P <0 .0016)]. Difference between the 2 arms was still maintained at 6 weeks (33.3% vs 58.5%). There was no evidence of an 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 C et al, 2015 [ref. 119]	A single centre outbreak of KPC-2 , affecting 90 patients hospitalized over 28 months. Retrospective analysis, of patients who received selective digestive decontamination (SDD) compared with the remaining patients harbouring KPC-2-KP.	14 consecutive patients were treated with a short course (7days) 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 (0.5g) to the oral cavity.	Decolonisation of KPC-2-KP was achieved in 6/14 patients (43%) after a mean of 21days (range12–40 days), but was also observed in 23/76 (30%). Secondary resistance to colistin(by 19%) and gentamicin (by 45%) was observed in SDD group but not in the comparative group. of thenon-SDD controls (P = 0.102).	The SDD approach was not sufficiently effective for decolonization and was associated with high rates of resistance in subsequent cultures.
Tascini C, et al, 2014 [ref. 120]	A pilot non-blinded, prospective study in three Italian hospitals to assess the 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 need for patient transfer.	Oral gentamicin, 80 mg four times daily, was administered to 50 consecutive patients over an 8 month period. A separate analysis was performed with the 23 patients receiving oral gentamicin alone and with the 27 patients who received Concomitant Systemic Antibiotic Treatment (CSAT). Oral gentamicin was given for a median of 16 days (interquartile range, 10 to 27 days).	KPC-Kp infections were documented in 5/34 (15%) successfully decontaminated patients compared to 12/16 (73%) persistent carriers (P<0.001). The decontamination rate was 96% (22/23) in patients receiving oral gentamicin only, compared to 44% (12/27) of those treated with oral gentamicin and CSAT (P<0.001). Gentamicin-resistant KPC-Kp strains were isolated from stools of 4/16 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 I, et al, 2013 [ref. 121]	A semi-randomized, prospective, controlled trial was conducted to eradicate	152 patients were included; 50 patients received 1 of the 3 drug regimens: gentamicin, 26; colistin, 16; both drugs,	Eradication rates in the 3 treatment groups were 42%, 50%, and 37.5%, respectively, each significantly higher than the 7%	Administration of oral nonabsorbable antibiotics was an effective and safe strategy for eradication of CRE colonization and, thereby, may reduce patient-to-

	CRE colonization using oral nonabsorbable antibiotics.	8, followed for a median duration of 33 days and 102 were followed for spontaneous eradication for a median duration of 140 days (controls). Antibiotic selection was based on isolate's in vitro susceptibility.	spontaneous eradication rate in the control group (P < .001, P < .001, and P = .004, respectively) with no difference between the regimens. No significant adverse effects were observed.	patient transmission and incidence of clinical infection. A trend towards lower mortality among patients who succeeded eradication on treatment (2/22, 9%), compared with those who failed eradication on treatment (9/28, 32%) was observed (p=0.052)
Tascini C et al, 2015 [ref. 122]	A 1:1 case control study exploring prevention of KPC-Kp gut colonization in patients that undergo hepatectomy with oral gentamicin in an endemic setting	All 31 consecutive patients who underwent liver resections in the last year treated orally with gentamicin; controls were 31 patients who underwent surgery in the same ward in the previous year without gentamicin prophylaxis.	The overall gut colonization rate in the intervention group was 3 % (1/31) versus 29 % (9/31) in the control group (p = 0.016). The only KPC-Kp strain isolated in the gentamicin-treated group retained susceptibility to gentamicin	Oral administration of gentamicin might be effective to avoid KPC-Kp gut colonization without adverse events.
Machuca I et al, 2016 [ref.123]	A retrospective cohort study of patients colonized by KPCKP in two hospitals during an outbreak with colistin-resistant KPCKP strain, exploring whether decolonization therapy (DT) with aminoglycosides had a protective effect in selected	77 patients at high risk [(a) neutropenia (b) major surgery; (c) multiple comorbidities], with rectal colonization by colistin-resistant KPCKP were followed for 180 days. Oral aminoglycosides (gentamicin or combination of neomycin/streptomycin) were administered in 44 patients.	At 180 days of follow-up, decolonization was associated with a lower risk of mortality in multivariate analyses (HR 0.18; 95% CI 0.06–0.55) and a lower risk of KPCKP infections (HR 0.14; 95% CI 0.02–0.83) and increased microbiological success (HR 4.06; 95%CI 1.06–15.6). Beneficial effects were more favorable with gentamicin.	Intestinal decolonization with aminoglycosides is associated with a reduction in crude mortality and KPCKP infections.

patients.

983 **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 beta-lactamases (MBL, VIM, NDM). Avibactam offers no enhanced activity against *Pseudomonas aeruginosa* and *Acinetobacter baumannii*	-Non-inferiority versus imipenem and meropenem in Phase 2 clinical trials for the treatment of cUTIs and cIAIs respectively -Licensed in US, and EU for cUTIs and cIAIs -Awaiting results of Phase 3 trial in VAP Phase 1 study on PKs of critically ill patients planned	US: Allergan Inc. EU: Astra Zeneca	Ceftazidime-avibactam was recently licensed for the treatment of cUTIs and cIAIs in US and Europe.[124,125] The 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 one phase 2 trial in cUTIs -Completed a Phase 2 trial in cUTIs versus doripenem, and three Phase 1 trials awaiting results	Forest Laboratories	Ceftaroline–avibactam has a promising in vitro spectrum; results from clinical trials are pending.[124,126]
Imipenem/	carbapenem/ β-	Class A and C β-	Completed phase 2 trial in	Merck	Relebactam is under investigation in

relebactam	lactamase inhibitor (diazabicyclooctane)	lactamases, porin mutations, Class D (OXA-48 not consistently) No activity against MBL	cUTI, currently in Phase 3 trials versus colistin against imipenem resistant pathogens and versus piperacillin tazobactam in bacterial pneumonia		combination with imipenem/cilastatin with Phase 3 trials underway versus colistin for imipenem-resistant pathogens and versus piperacillin/tazobactam in bacterial pneumonia.[124,63,127]
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, -Ongoing Phase 3 trial in various infections caused by carbapenem resistant bacteria, -Planned Phase 3 trial in VAP	The Medicines company	The boronic-based beta-lactamase inhibitor vaborbactam combined with meropenem (Carbavance) is currently in Phase 3 trials.[63,128]
Plazomicin	New aminoglycoside (neoglycoside)	Various Gram-positive and Gram-negative organisms Not active against bacteria harboring ribosomal methyltransferases (mostly NDM-1 strains)	Completed two phase 3 trials (cUTIs and serious infections by CRE) Submission for FDA approval in 2017 and EMA in 2018	Achaogen	A new parenteral hemisynthetic aminoglycoside with favourable pharmacokinetics and safety profile, plazomicin, holds also promise against KPC-producers.[63,124] Its efficacy against carbapenem-producing bacteria has been recently demonstrated in serious infections including BSI, HAP/VAP, and cUTI.[129,130]
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.*	Completed phase 2 trial in UTI, currently in Phase 3 trials for severe infections by CRE. Phase 3 in nosocomial	Shionogi	Cefiderocol (formerly S-649266) is a promising siderophore cephalosporin, showing high activity against carbapenem-resistant Gram-negative bacteria, and it is currently in Phase 3 trial.[63,124,131]

		baumannii, P. aeruginosa, S. maltophilia, and Enterobacteriaceae (CRE)	pneumonia scheduled		
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 (versus meropenem) and in cUTI (versus ertapenem/levofloxacin)	Tetraphase Pharmaceuticals Inc	Eravacycline is a novel fluorocycline with in vitro activity against Enterobacteriaceae harbouring a variety of resistance genes (ESBLs or carbapenemases), potential activity against *A. baumannii*, but not against *P. aeruginosa.*[63,124,,132,133] Compared to tigecycline, it is more potent *in vitro* two- to eightfold against Gram-negative bacilli and exhibits 1-fold higher C_{max} and AUC_{0-12} in ELF.[134,135] Non-inferiority was demonstrated in a Phase 3 study evaluating the safety and efficacy of eravacycline versus ertapenem in cIAI,[136] but not in the trial of cUTIs compared to levofloxacin.[137]

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