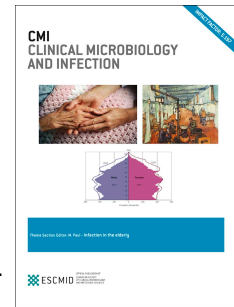


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Management of KPC-Producing *Klebsiella pneumoniae* Infections

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1 **Management of KPC-Producing *Klebsiella pneumoniae* Infections**

2

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30 **Running title:** Management of KPC-KP infections

31

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41

42 **Abstract**

43

44 **Background:** *Klebsiella pneumoniae* carbapenemase (KPC)-producing *K. pneumoniae*
45 (KPC-KP) has become one of the most important contemporary pathogens,
46 especially in endemic areas.

47 **Aims:** our aim was to provide practical suggestion for physicians dealing with the
48 management of KPC-KP infections in critically ill patients, based on expert opinions.

49 **Sources:** PubMed search for relevant publications related to the management of
50 KPC-KP infections.

51 **Contents:** a panel of experts developed a list of 12 questions to be addressed. In
52 view of the current lack of high-level evidence, they were asked to provide answers
53 based on their knowledge and experience in the field. The panel identified several
54 key aspects to be addressed when dealing with KPC-KP in critically-ill patients
55 (preventing colonization in the patient, preventing infection in the colonized patient
56 and colonization of his/her contacts, reducing mortality in the infected patient by
57 rapidly diagnosing the causative agent and promptly adopting the best therapeutic
58 strategy) and provided related suggestions on the basis the available observational
59 literature and the experience of panel members.

60 **Implications:** Diagnostic technologies could speed-up the diagnosis of KPC-KP
61 infections. Combination treatment should be preferred to monotherapy in the case
62 of severe infections. For non-critically-ill patients without severe infections, results
63 from randomized clinical trials are needed for ultimately weighing benefits and costs
64 of using combinations rather than monotherapy. Multifaceted infection-control
65 interventions are needed to decrease the rates of colonization and cross-
66 transmission of KPC-KP.

67

68 Introduction

69 Management of infections caused by multidrug-resistant bacteria impacts
70 considerably on health costs and becomes major modifier of health expenses in the
71 ongoing antibiotic resistance crisis.¹ *Klebsiella pneumoniae* carbapenemase (KPC)-
72 producing *K. pneumoniae* (KPC-KP), has become one of the most important
73 contemporary pathogens, especially in endemic areas.²⁻⁴ KPC-KP optimal treatment,
74 however, is not known and there are currently no published recommendations for
75 the management of infections by KPC-KP. Given the observational nature of the
76 majority of studies on this topic, many of the recommendations listed in this
77 manuscript arise from acquired experience of the invited panel members, and
78 therefore represent expert opinion.

79 Purpose and methods

80 The purpose of this paper was to answer practical questions for physicians dealing
81 with the treatment of KPC-KP infections in critically ill patients, in view of the
82 fragmentation in the observational literature on this topic and the lack of
83 randomized clinical trials.⁵ A panel of 11 experts developed a list of questions to be
84 addressed in the paper; 12 questions were formulated after rounds of discussion
85 between chairs (M. Bassetti, G. Poulakou, C. Viscoli, and H. Giamarellou) and panel
86 members. In view of the lack of high-level evidence, panel members were asked to
87 provide narrative answers on the basis of their knowledge and experience in the
88 field. Finally, provided answers were reviewed and discussed by the panel, until a

89 consensus was reached. The final summary of selected questions and related
90 answers is presented in table 1.

91

92 **Background information for provided answers**

93 **1. How can the laboratory speed-up KPC-KP identification and susceptibility** 94 **testing?**

95 Rapid methods for identification of strains producing KPC and other carbapenemases
96 are important to ensure appropriate and early initiation of specific therapy, as well
97 as the prompt implementation of the most appropriate infection control measures.⁶
98 This is particularly relevant with KPC-KP or other types of carbapenemase-producing
99 Enterobacteriaceae (CPE) infections, since commonly used regimens for empiric
100 antimicrobial chemotherapy do not normally cover for MDR pathogens, except
101 under specific circumstances (e.g., febrile neutropenia in a patient who is known to
102 be colonized by KPC-KP).⁷
103 Several new diagnostic technologies have recently become available to allow
104 increased rapidity of microbiological diagnosis, including Matrix Assisted Laser
105 Desorption Ionization-Time of Flight Mass Spectrometry (MALDI-TOF MS), rapid
106 immunochromatography, rapid enzymatic assays (such as the Carba NP test), single-
107 cell automated time-lapse microscopy and molecular biology-based assays.⁸⁻¹⁰ These
108 new technologies may be very useful to reduce the time for pathogen identification
109 (ID) and antibiotic susceptibility test (AST) .

110 MALDI-TOF MS has proven very successful in rapid bacterial identification
111 from isolated colonies or monomicrobial blood cultures. MALDI-TOF MS can also be

112 used for rapid detection of some resistance determinants, such as beta-lactamases.¹¹
113 A mass spectrometric beta-lactamase (MSBL) assay represents a functional assay
114 based on the direct monitoring of the enzymatic activity of the beta-lactamase and
115 can be performed with bacterial cultures or directly from freshly tagged positive
116 blood cultures, with results available after 1 - 4 hour incubation period.¹¹ Both
117 imipenem and meropenem can be used in these tests, with meropenem being
118 somewhat more efficient.¹²

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

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

133 It should be noted that detection of resistance mechanisms by molecular biology is
134 useful to rapidly predict potential resistance to some agents, but does not provide
135 comprehensive information about the resistance phenotype of the infecting strain,

136 and conventional AST remains the cornerstone for selection of definitive treatment
137 regimens and evaluation of adequate / inadequate antimicrobial chemotherapy.¹⁷
138 However, the rapid detection of some resistance mechanism, and of KPC genes in
139 particular (the presence of which means most of the time resistance to carbapenems
140 and even multiresistance), can be very useful for an earlier revision of empiric
141 regimens, which usually do not cover CPE.

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

152

153 **2. What is currently the best treatment for KPC-KP infections?**

154 A necessary premise is that only low-level evidence with a high risk of bias is
155 available from observational studies regarding the optimal treatment for KPC-KP
156 infections ,thus not allowing for definite conclusions.^{5,18,19} In this light, the following
157 statements are to be weighed cautiously, pending results of randomized clinical trials

158 (NCT01597973 and the AIDA study²⁰ are ongoing or are have been recently
159 completed, respectively).

160 Since monotherapy appeared to be associated with higher mortality rates
161 compared to combination therapy for the targeted treatment of KPC-KP in
162 observational studies, the use of combined regimens should be preferred in patients
163 with severe KPC-KP infections.^{19,21-25} Indeed, the positive impact of combination
164 therapy on survival might be true only in patients with severe infections compared
165 to less severe BSI and in non-bacteraemic intra-abdominal or UTIs, a fact which is
166 also in line with the favourable survival effect of combinations recently observed
167 only in patients with a high INCREMENT-CPE mortality score.^{23,25} In patients at lower
168 risk of mortality, no clear survival benefit of combinations over monotherapy has
169 been demonstrated. In these patients, a conservative combination approach might
170 be used at the beginning, with the option of de-escalating to a simpler regimen in
171 correlation with patient's clinical conditions. However, the risk of inducing further
172 resistance by the use of last-resort antibiotics is a non-negligible risk, and results
173 from randomized clinical trials are needed for ultimately weighing benefits and cost
174 of using combinations in patients with non-severe KPC-Kp infections.

175 **3. What is the role of carbapenems in the treatment of KPC-KP infections?**

176 In combination treatment, meropenem may still be considered as an option
177 for possibly enhancing bacterial killing, provided that: i) the MIC of meropenem is \leq
178 8mg/L and ii) a high-dose and prolonged infusion regimen is administered. With the
179 limitations of the non-randomized design, a survival benefit by using meropenem-
180 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

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

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

208

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

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

219 As maximal antibiotic delivery depends on the type of aerosol generators,
220 novel drug-device combinations stand out as a promising delivery approach in
221 critically ill patients. A randomized trial compared fixed combination of amikacin and
222 fosfomycin (5:2 ratio) or placebo delivered via the investigational eFlow Inline
223 System (PARI GmbH, Germany) as adjunctive treatment to standard iv antibiotics.⁷²
224 Distribution of multidrug-resistant (MDR) and extensively drug-resistant (XDR)
225 isolates did not differ statistically between the two arms (10 and 5 KPC-KP were
226 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., $fT > MIC$) 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 $fT > MIC$ 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

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

252

253 **7. What about source control in patients with KPC-KP infections?**

254 The objective of source control includes the actions to control the foci of infection
255 and to restore optimal function of the site of infection. Source control includes
256 removal of implanted or tunnelled devices, open surgical or percutaneous drainage
257 of infected fluids or abscesses, and surgical resection of infected tissues. Time from
258 hypotension to implementation of source control has been found to be highly
259 correlated with outcome. Therefore interventions to be undertaken for source
260 control within the first 12 hours after the diagnosis of the septic syndrome, if
261 feasible, should be considered.⁸⁴

262 Although source control is reported as a modifiable predictor of mortality in
263 sepsis and septic shock⁸⁴, the data particularly from KPC-KP infections is scarce. In a
264 two-match case control study including 99 patients in each arm comparing patients
265 with KPC-KP and carbapenem susceptible *K. pneumoniae*, removal of focus of
266 infection was independently associated with patient survival.⁸⁵ In a prospective
267 observational cohort study encompassing 53 patients with BSI caused by KPC-KP,
268 prior surgery and therapeutic interventions targeting the removal of the site of
269 infection were strongly correlated with survival.⁸⁶ Similar conclusions were reported
270 by Falcone et al in a retrospective analysis with 111 intensive care unit (ICU) patients
271 with KPC-KP and septic shock in 21.6% cases. Source control process was
272 accomplished in 95.2% of patients who survived in comparison to 31.2% who died.
273 Cox regression analyses revealed that control of removable source of infection was

274 associated with favourable outcome (hazard ratio 0.14, CI 95%, $p < 0.001$).⁸⁷ In a
275 retrospective study including 48 BSI due to KPC-KP, adjunctive source control
276 procedures were associated with clinical response at day 7 (odds ratio 12.2, CI
277 95% 1.4-110, $p = 0.025$).⁸⁸

278

279 **8. What is the optimal duration of treatment for KPC-KP infections?**

280 Optimal treatment duration for KPC-KP infections is unclear. In retrospective studies
281 a mean duration of two weeks of treatment was reported.⁸⁹ In VAP, robust data
282 supports a reduced 8-day antibiotics course in patients receiving appropriate initial
283 empirical therapy.⁹⁰⁻⁹² This strategy was associated with significantly more antibiotic-
284 free days without negative impact on mortality and reduced resistance selection.
285 Higher relapse rates in patients with non-fermenting Gram-negative bacilli were
286 initially reported suggesting longer treatments when these pathogens were
287 responsible for VAP.⁹⁰ An updated meta-analysis of VAP caused by non-fermenters,
288 however, supported a reduced length of treatment (e.g., 7 days) that is currently
289 recommended by guidelines.⁷⁶

290 As far as bacteremia is concerned, the evidence is even less clear. Havey et al
291 in a large systematic review and meta-analysis encompassing 24 trials, showed that
292 patients receiving short treatment (5-7 days) versus those receiving long treatment
293 (7-21 days) for non-*Staphylococcus aureus* bacteremias had no significant differences
294 in mortality, microbiological eradication and clinical cure. Randomized-controlled
295 trials to assess the optimal duration of bacteremia in the context of MDR and KPC-
296 producers are awaited and may provide baseline evidence that long treatments may
297 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,

322 cohorting of medical personnel, enhanced environmental surveillance and repetitive
323 educational campaigns successfully controlled the further horizontal spread of a
324 monoclonal KPC-KP strain.¹⁰¹ In another study, transmission through contaminated
325 sinks has been suggested as the major responsible for a long-term, low-frequency
326 hospital outbreak of KPC-KP infections, further confirming the need for accurate
327 environmental surveillance and disinfection.¹⁰² In a study from Israel, a significant
328 decline of the nosocomial CPE acquisition was achieved with a multiple step
329 strategy, including ward-based mandatory guidelines for carrier isolation, patient
330 and staff cohorting, active surveillance and new rules for microbiology identification,
331 direct officer visits at healthcare facilities and networking.¹⁰³

332 An important factor to consider is the presence of super-spreaders (i.e.,
333 those carriers who more easily spread KPC-KP in their immediate environment⁹⁴).
334 Super-spreaders are characterized by high rectal CPE concentrations and are more
335 frequently admitted for respiratory disease.¹⁰⁴ This effect has similarities with other
336 so called “enteropathogenetic syndromes” such as *Clostridium difficile* colitis and
337 candidemia, at least by the means of exogenous colonization.^{104,105} In a multicentre
338 US study, KPC-KP clearance was attributed to a reduction in the usage of urinary
339 catheters, a factor that should be considered in the implementation of a bundle
340 procedure.¹⁰⁶

341

342 **10. Who among KPC-KP colonized patients is at increased risk of developing KPC-KP**
343 **infections?**

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

347 In a retrospective study involving five large Italian hospitals, bowel
348 colonization by KPC-KP held a major role in predicting transition from colonization to
349 infection.¹⁰⁷ The overall number of colonized sites represented the most important
350 risk factor for KPC-KP BSI development among rectal carriers in a prospective
351 multicentre study.^{108,109} Other risk factors for KPC-KP BSI included ICU admission,
352 abdominal invasive procedures, chemotherapy or radiation therapy, and previous
353 BSI.^{108,110} In a study including patients undergoing open heart surgery, colonization
354 was the most important risk factor for KPC-KP infection.¹¹¹ In a prospective cohort
355 study of adult patients undergoing liver transplant (LT), KPC-KP infection rates
356 among patients non-colonized, colonized at LT, and colonized after LT were 2%,
357 18.2% and 46.7%, respectively.¹⁰⁸ In settings where colonization with KPC-KP is
358 common among critically ill patients, antibiotic stewardship programs should be
359 undertaken to optimize antimicrobial use, as shown by a study demonstrating high
360 risk of KPC-KP VAP in colonized patients receiving prolonged antimicrobial
361 therapy.¹¹²

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

367 bundle”: avoidance of levofloxacin prophylaxis, treatment with gentamicin *per os* in
368 the best window of opportunity pre-transplant, administration of tigecycline and
369 piperacillin/tazobactam as empiric treatment of febrile neutropenia, and
370 administration of combination regimens (e.g., colistin plus tigecycline plus
371 meropenem) in patients with severe sepsis or septic shock.¹¹⁴ In another study, the
372 cumulative incidence of KPC-KP BSI and septic shock at one year after
373 haematopoietic stem cell transplantation was significantly reduced from 62.5% to
374 16.6% after the introduction of systematic screening with rectal swabs, contact
375 precautions, and early targeted treatment in neutropenic patients with fever, with at
376 least two antibiotics.¹¹⁵ Finally, a multifaceted infection control program was able to
377 reduce both BSI due to CPE and CPE colonization, whereas monthly incidence of CPE
378 carriage was predictive of BSI.¹¹⁶

379

380 **11. Is decolonization a useful strategy in KPC-KP colonised patients?**

381 Studies deploying oral decolonization strategies as a mean to eradicate gut
382 carriage of KPC-KP have produced conflicting results and only one reported a survival
383 benefit (Table 3).¹¹⁷⁻¹²³ With regard to the use of oral gentamicin for decolonization
384 purposes, an indiscriminate use should be avoided. Indeed, this strategy has a high
385 risk of failure and also cannot be separated from the risk of selecting gentamicin
386 resistance (and thus of losing one of the last - if not the last - therapeutic
387 options).^{120,123} It should therefore be reserved for very selected special conditions
388 (e.g., very high risk of developing infection because of severe neutropenia or
389 recurrent KPC-KP infections) on a patient-by-patients basis.¹²³

390 12. What is new in KPC-KP treatment options?

391 A handful of new compounds, expected to address the therapeutic problem of KPC-
392 KP in the near future are summarized in Table 4 (reporting molecules in Phase 3 of
393 clinical development).¹²⁴⁻¹³⁷

394 Conclusions

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

404 Conflict of interest

405 MB has received research grants from Merck, Nordic Pharma, Novartis and Pfizer,
406 has received congress lecture fees from Astellas, Angelini ACRAF, AstraZeneca,
407 Basilea, Biologix FZ, Gilead, Merck, Novartis, Pfizer, Tetrphase, Thermofisher, Vifor
408 Pharma; has received consultancy fees from Achaogen, Angelini ACRAF, AstraZeneca,
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436

437 References

- 438 1. Rossolini GM, Arena F, Pecile P, Pollini S. Update on the antibiotic resistance
439 crisis. *Curr Opin Pharmacol* 2014; 18:56-60.
- 440 2. Munoz-Price LS, Poirel L, Bonomo RA, Schwaber MJ, Daikos GL, Cormican M, et
441 al. Clinical epidemiology of the global expansion of *Klebsiella pneumoniae*
442 carbapenemases. *Lancet Infect Dis* 2013; 13:785-96.
- 443 3. Grundmann H, Glasner C, Albiger B, Aanensen DM, Tomlinson CT, Andrasević AT,
444 et al; European Survey of Carbapenemase-Producing Enterobacteriaceae
445 (EuSCAPE) Working Group. Occurrence of carbapenemase-producing *Klebsiella*
446 *pneumoniae* and *Escherichia coli* in the European survey of carbapenemase-
447 producing Enterobacteriaceae (EuSCAPE): a prospective, multinational study.
448 *Lancet Infect Dis* 2017; 17:153-163.
- 449 4. Maltezou HC, Kontopidou F, Dedoukou X, Katerelos P, Gourgoulis GM, Tsonou P,
450 et al. Action Plan to combat infections due to carbapenem-resistant, Gram-
451 negative pathogens in acute-care hospitals in Greece. *J Glob Antimicrob Resist*
452 2014;2:11-16.
- 453 5. Giacobbe DR, Maraolo AE, Viscoli C. Pitfalls of defining combination therapy for
454 carbapenem-resistant Enterobacteriaceae in observational studies. *Eur J Clin*
455 *Microbiol Infect Dis* 2017; doi: 10.1007/s10096-017-3010-z.
- 456 6. Banerjee R, Özenci V, Patel R. Individualized Approaches Are Needed for
457 Optimized Blood Cultures. *Clin Infect Dis* 2016; 63:1332-1339.
- 458 7. Girmenia C, Viscoli C, Picocchi A, Cudillo L, Botti S, Errico A, et al. Management of
459 carbapenem resistant *Klebsiella pneumoniae* infections in stem cell transplant
460 recipients: an Italian multidisciplinary consensus statement. *Haematologica* 2015;
461 100:e373-6.
- 462 8. Patel R. MALDI-TOF MS for the diagnosis of infectious diseases. *Clin Chem* 2015;
463 61:100-11.
- 464 9. Bauer KA, Perez KK, Forrest GN, Goff DA. Review of rapid diagnostic tests used by
465 antimicrobial stewardship programs. *Clin Infect Dis* 2014;59 Suppl 3:S134-45.
- 466 10. Arena F, Viaggi B, Galli L, Rossolini GM. Antibiotic Susceptibility Testing: Present
467 and Future. *Pediatr Infect Dis J* 2015; 34:1128-30.
- 468 11. Kostrzewa M, Sparbier K, Maier T, Schubert S. MALDI-TOF MS: an upcoming tool
469 for rapid detection of antibiotic resistance in microorganisms. *Proteomics Clin*
470 *Appl* 2013; 7:767-78.
- 471 12. Rotova V, Papagiannitsis CC, Skalova A, Chudejova K, Hrabak J. Comparison of
472 imipenem and meropenem antibiotics for the MALDI-TOF MS detection of
473 carbapenemase activity. *J Microbiol Methods* 2017; 137:30-33.
- 474 13. Gaibani P, Galea A, Fagioni M, Ambretti S, Sambri V, Landini MP. Evaluation of
475 Matrix-Assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry for
476 Identification of KPC-Producing *Klebsiella pneumoniae*. *J Clin Microbiol* 2016;
477 54:2609-13.

- 478 14. Hoyos-Mallecot Y, Ouzani S, Dortet L, Fortineau N, Naas T. Performance of the
479 Xpert® Carba-R v2 in the daily workflow of a hygiene unit in a country with a low
480 prevalence of carbapenemase-producing Enterobacteriaceae. *Int J Antimicrob*
481 *Agents*. 2017 Jun;49(6):774-777.
- 482 15. Salimnia H, Fairfax MR, Lephart PR, Schreckenberger P, DesJarlais SM, Johnson
483 JK, *et al.* Evaluation of the FilmArray Blood Culture Identification Panel: Results of
484 a Multicenter Controlled Trial. *J Clin Microbiol* 2016; 54:687-98.
- 485 16. Vincent JL, Brealey D, Libert N, Abidi NE, O'Dwyer M, Zacharowski K, *et al.* Rapid
486 Diagnosis of Infection in the Critically Ill, a Multicenter Study of Molecular
487 Detection in Bloodstream Infections, Pneumonia, and Sterile Site Infections. *Crit*
488 *Care Med* 2015; 43:2283-91.
- 489 17. Arena F, Giani T, Pollini S, Viaggi B, Pecile P, Rossolini GM. Molecular antibiogram
490 in diagnostic clinical microbiology: advantages and challenges. *Future Microbiol*
491 2017; 12:361-364.
- 492 18. Paul M, Carmeli Y, Durante-Mangoni E, Mouton JW, Tacconelli E, Theuretzbacher
493 U, *et al.* Combination therapy for carbapenem-resistant Gram-negative bacteria. *J*
494 *Antimicrob Chemother* 2014; 69:2305–2309.
- 495 19. Zusman O, Altunin S, Koppel F, Dishon Benattar Y, Gedik H, Paul M. Polymyxin
496 monotherapy or in combination against carbapenem-resistant bacteria:
497 systematic review and meta-analysis. *J Antimicrob Chemother* 2017; 72:29-39.
- 498 20. Dickstein Y, Leibovici L, Yahav D, Eliakim-Raz N, Daikos GL, Skiada A, *et al.*
499 Multicentre open-label randomised controlled trial to compare colistin alone
500 with colistin plus meropenem for the treatment of severe infections caused by
501 carbapenem-resistant Gram-negative infections (AIDA): a study protocol. *BMJ*
502 *Open* 2016; 6:e009956.
- 503 21. Tzouveleki LS, Markogiannakis A, Piperaki E, Souli M, Daikos GL. Treating
504 infections caused by carbapenemase-producing Enterobacteriaceae. *Clin Microb*
505 *Infect* 2014; 20:862-72.
- 506 22. Tumbarello M, Viale P, Viscoli C, Trecarichi EM, Tumietto F, Marchese A, *et al.*
507 Predictors of mortality in bloodstream infections caused by *Klebsiella*
508 *pneumoniae* carbapenemase-producing *K. pneumoniae*: importance of
509 combination therapy. *Clin Infect Dis* 2012; 55:943-50.
- 510 23. Tumbarello M, Trecarichi EM, De Rosa FG, Giannella M, Giacobbe DR, Bassetti M,
511 *et al*; on behalf of ISGRI-SITA (Italian Study Group on Resistant Infections of the
512 Societa` Italiana Terapia Antinfettiva). Infections caused by KPC-producing
513 *Klebsiella pneumoniae*: differences in therapy and mortality in a multicentre
514 study. *J Antimicrob Chemother* 2015; 70:2133-43.
- 515 24. Daikos GL, Tsaousi S, Tzouveleki LS, Anyfantis I, Psychogiou M, Argyropoulou A,
516 *et al.* Carbapenemase-producing *Klebsiella pneumoniae* bloodstream infections:
517 lowering mortality by antibiotic combination schemes and the role of
518 carbapenems. *Antimicrob Agents Chemother* 2014;58: 2322-28.
- 519 25. Gutiérrez-Gutiérrez B, Salamanca E, de Cueto M, Hsueh PR, Viale P, Paño-Pardo
520 JR, *et al.* Effect of appropriate combination therapy on mortality of patients with
521 bloodstream infections due to carbapenemase-producing Enterobacteriaceae
522 (INCREMENT): a retrospective cohort study. *Lancet Infect Dis* 2017. pii: S1473-
523 3099(17)30228-1.
- 524 26. Del Bono V, Giacobbe DR, Marchese A, Parisini A, Fucile C, Coppo E, *et al.*
525 Meropenem for treating KPC-producing *Klebsiella pneumoniae* bloodstream

- 526 infections: should we get to the PK/PD root of the paradox? *Virulence* 2017; 8:66-
527 73.
- 528 27. Pea F, Della Siega P, Cojutti P, Sartor A, Crapis M, Scarparo C, et al. Might real-
529 time pharmacokinetic/ pharmacodynamic optimisation of high-dose continuous-
530 infusion meropenem improve clinical cure in infections caused by KPC-producing
531 *Klebsiella pneumoniae*? *Int J Antimicrob Agents* 2017; 49:255-258.
- 532 28. Tenover FC, Kalsi RK, Williams PP, Carey RB, Stocker S, Lonsway D, et al.
533 Carbapenem resistance in *Klebsiella pneumoniae* not detected by automated
534 susceptibility testing. *Emerg Infect Dis* 2006; 12:1209-13.
- 535 29. Clinical and Laboratory Standards Institute (CLSI). 2015. Methods for dilution
536 antimicrobial susceptibility. Tests for bacteria that grow aerobically; approved
537 standards. Tenth edition. CLSI document M07-A10.
- 538 30. Nation RL, Garonzik SM, Thamlikitkul V, Giamarellou H, Bourboulis EJ, Forrest A,
539 Paterson DL, et al. Dosing guidance for intravenous colistin in critically-ill
540 patients. *Clin Infect Dis* 2017;64:565-571.
- 541 31. Capone A, Giannella M, Fortini D, Giordano A, Meledandri M, Ballardini M, et al.
542 SEERBIO-GRAB network. High rate of colistin resistance among patients with
543 carbapenem-resistant *Klebsiella pneumoniae* infection accounts for an excess of
544 mortality. *Clin Microbiol Infect* 2013; 19:E23-30.
- 545 32. Monaco M, Giani T, Raffone M, Arena F, Garcia-Fernandez A, Pollini S, et al.
546 Colistin resistance superimposed to endemic carbapenem-resistant *Klebsiella*
547 *pneumoniae*: a rapidly evolving problem in Italy, November 2013 to April 2014.
548 *Euro Surveill* 2014; 19.pii: 20939.
- 549 33. Giacobbe DR, Bono VD, Trecarichi EM, De Rosa FG, Giannella M, Bassetti M, et al;
550 ISGRI-SITA (Italian Study Group on Resistant Infections of the Società Italiana
551 Terapia Antinfettiva). Risk factors for bloodstream infections due to colistin-
552 resistant KPC-producing *Klebsiella pneumoniae*: results from a multicenter case-
553 control-control study. *Clin Microbiol Infect* 2015; 21:1106.e1-8.
- 554 34. Giamarellou H. Epidemiology of infections caused by polymyxin-resistant
555 pathogens. *Int J Antimicrob Agents*. 2016; 48:614-621.
- 556 35. Spyropoulou A, Papadimitriou-Oliveris M, Bartzavali C, Vamvakopoulou S,
557 Marangos M, Spiliopoulou I, et al. A ten-year surveillance study of
558 carbapenemase-producing *Klebsiella pneumoniae* in a tertiary care Greek
559 university hospital: predominance of KPC- over VIM- or NDM-producing isolates.
560 *J Med Microbiol* 2016;65:240-6.
- 561 36. Meletis G, Oustas E, Botzioti C, Kakasi E, Koteli A. Containment of carbapenem
562 resistance rates of *Klebsiella pneumoniae* and *Acinetobacter baumannii* in a
563 Greek hospital with a concomitant increase in colistin, gentamicin and tigecycline
564 resistance. *New Microbiol* 2015;38:417-21.
- 565 37. Karaikos I, Souli M, Galani I, Giamarellou H. Colistin: still a lifesaver for the 21st
566 century? *Expert Opin Drug Metab Toxicol* 2017; 13:59-71.
- 567 38. Karaikos I, Giamarellou H. Multidrug-resistant and extensively drug-resistant
568 Gram-negative pathogens: current and emerging therapeutic approaches. *Expert*
569 *Opin Pharmacother* 2014; 15:1351-70.
- 570 39. Sorlí L, Luque S, Grau S, Berenguer N, Segura C, Montero MM, et al. Trough
571 colistin plasma level is an independent risk factor for nephrotoxicity: a
572 prospective observational cohort study. *BMC Infect Dis*. 2013; 13:380.

- 573 40. Sandri AM, Landersdorfer CB, Jacob J, Boniatti MM, Dalarosa MG, Falci DR, et al.
574 Population pharmacokinetics of intravenous polymyxin B in critically ill patients:
575 implications for selection of dosage regimens. *Clin Infect Dis* 2013; 57:524-31.
- 576 41. Nation RL, Velkov T, Li J. Colistin and polymyxin B: peas in a pod, or chalk and
577 cheese? *Clin Infect Dis* 2014; 59:88-94.
- 578 42. Gonzalez-Padilla M, Torre-Cisneros J, Rivera-Espinar F, Pontes-Moreno A, López-
579 Cerero L, Pascual A, et al. Gentamicin therapy for sepsis due to carbapenem-
580 resistant and colistin-resistant *Klebsiella pneumoniae*. *J Antimicrob Chemother*
581 2015; 70:905-13.
- 582 43. Machuca I, Gutiérrez-Gutiérrez B, Gracia-Ahufinger I, Rivera Espinar F, Cano Á,
583 Guzmán-Puche J, et al. Mortality associated with bacteremia due to colistin-
584 resistant *Klebsiella pneumoniae* with high-level meropenem resistance:
585 importance of combination therapy without colistin and carbapenems.
586 *Antimicrob Agents Chemother* 2017. pii: AAC.00406-17. doi: 10.1128/AAC.00406-
587 17.
- 588 44. Stankowicz MS, Ibrahim J, Brown DL. Once-daily aminoglycoside dosing: An
589 update on current literature. *Am J Health Syst Pharm* 2015; 72:1357-64.
- 590 45. Decker BS, Molitoris BA. Manifestations of and risk factors for aminoglycoside
591 nephrotoxicity. *UptoDate* Nov 2016 (updated on May 21, 2015).
- 592 46. Poulakou G, Bassetti M, Righi E, Dimopoulos G. Current and future treatment
593 options for infections caused by multidrug-resistant Gram-negative pathogens.
594 *Future Microbiol* 2014; 9:1053-69.
- 595 47. Bassetti M, Eckmann C, Bodmann KF, Dupont H, Heizmann WR, Montravers P, et
596 al. Prescription behaviours for tigecycline in real-life clinical practice from five
597 European observational studies. *J Antimicrob Chemother* 2013; 68 Suppl 2:5–14.
- 598 48. Montravers P, Dupont H, Bedos JP, Bret P. Tigecycline Group. Tigecycline use in
599 critically ill patients: a multicentre prospective observational study in the
600 intensive care setting. *Intensive Care Med* 2014; 40:988-97.
- 601 49. Bassetti M, Poulakou G, Giamarellou H. Is there a future for Tigecycline?
602 *Intensive Care Med* 2014; 40:1039-45.
- 603 50. Ramirez J, Dartois N, Gandjini H, Yan JL, Korth-Bradley J, McGovern PC.
604 Randomized phase 2 trial to evaluate the clinical efficacy of two high-dosage
605 tigecycline regimens versus imipenem-cilastatin for treatment of hospital-
606 acquired pneumonia. *Antimicrob Agents Chemother* 2013; 57:1756-62.
- 607 51. Wiskirchen DE, Koomanachai P, Nicasio AM, Nicolau DP, Kuti JL. In vitro
608 pharmacodynamics of simulated pulmonary exposures of tigecycline alone and in
609 combination against *Klebsiella pneumoniae* isolates producing a KPC
610 carbapenemase. *Antimicrob Agents Chemother* 2011; 55:1420-7.
- 611 52. Giamarellou H, Poulakou G. Pharmacokinetic and pharmacodynamic evaluation
612 of tigecycline. *Expert Opin Drug Metab Toxicol* 2011;7:1459-70.
- 613 53. Pontikis K, Karaiskos I, Bastani S, Dimopoulos G, Kalogirou M, Katsiari M, et al.
614 Outcomes of critically ill intensive care unit patients treated with fosfomycin for
615 infections due to pandrug-resistant and extensively drug-resistant
616 carbapenemase-producing Gram-negative bacteria. *Int J Antimicrob Agents* 2014;
617 43:52-9.
- 618 54. Parker SL, Frantzeskaki F, Wallis SC, Diakaki C, Giamarellou H, Koulenti D, et al.
619 Population Pharmacokinetics of Fosfomycin in Critically Ill Patients. *Antimicrob*
620 *Agents Chemother* 2015; 59:6471-6.

- 621 55. Albiero J, Sy SK, Mazucheli J, Caparroz-Assef SM, Costa BB, Alves JL, et al.
622 Pharmacodynamic Evaluation of the Potential Clinical Utility of Fosfomycin and
623 Meropenem in Combination Therapy against KPC-2-Producing *Klebsiella*
624 *pneumoniae*. *Antimicrob Agents Chemother* 2016; 60:4128-39.
- 625 56. Lepak AJ, Zhao M, VanScoy B, Taylor DS, Ellis-Grosse E, Ambrose PG, et al. In Vivo
626 Pharmacokinetics and Pharmacodynamics of ZTI-01 (Fosfomycin for Injection) in
627 the Neutropenic Murine Thigh Infection Model against *Escherichia coli*, *Klebsiella*
628 *pneumoniae*, and *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother* 2017;
629 61. pii: e00476-17. doi: 10.1128/AAC.00476-17
- 630 57. Docobo-Pérez F, Drusano GL, Johnson A, Goodwin J, Whalley S, Ramos-Martín V,
631 et al. Pharmacodynamics of fosfomycin: insights into clinical use for antimicrobial
632 resistance. *Antimicrob Agents Chemother* 2015;59:5602-10.
- 633 58. Grabein B, Graninger W, Rodríguez Baño J, Dinh A, Liesenfeld DB. Intravenous
634 fosfomycin-back to the future. Systematic review and meta-analysis of the clinical
635 literature. *Clin Microbiol Infect* 2017; 23:363-372.
- 636 59. Shields RK, Potoski BA, Haidar G, Hao B, Doi Y, Chen L, et al. Clinical Outcomes,
637 Drug Toxicity, and Emergence of Ceftazidime-Avibactam Resistance Among
638 Patients Treated for Carbapenem-Resistant Enterobacteriaceae Infections. *Clin*
639 *Infect Dis* 2016; 63:1615-18.
- 640 60. Temkin E, Torre-Cisneros J, Beovic B, Benito N, Giannella M, Gilarranz R, et al.
641 Ceftazidime-Avibactam as Salvage Therapy for Infections Caused by Carbapenem-
642 Resistant Organisms. *Antimicrob Agents Chemother* 2017;61: pii: e01964-16.
- 643 61. Shields RK, Nguyen MH, Chen L, Press EG, Potoski BA, Marini RV, et al.
644 Ceftazidime-avibactam is superior to other treatment regimens against
645 carbapenem-resistant *Klebsiella pneumoniae* bacteremia. *Antimicrob Agents*
646 *Chemother* 2017. pii: AAC.00883-17. doi: 10.1128/AAC.00883-17.
- 647 62. Shields RK, Chen L, Cheng S, Chavda KD, Press EG, Snyder A, et al. Emergence of
648 Ceftazidime-Avibactam Resistance Due to Plasmid-Borne blaKPC-3 Mutations
649 during Treatment of Carbapenem-Resistant *Klebsiella pneumoniae* Infections.
650 *Antimicrob Agents Chemother* 2017; 61. pii: e02097-16.
- 651 63. Perez F, El Chakhtoura NG, Papp-Wallace KM, Wilson BM5, Bonomo RA.
652 Treatment options for infections caused by carbapenem-resistant
653 Enterobacteriaceae: can we apply "precision medicine" to antimicrobial
654 chemotherapy? *Expert Opin Pharmacother* 2016; 17:761-81.
- 655 64. Bulik CC, Nicolau DP. Double-carbapenem therapy for carbapenemase-producing
656 *Klebsiella pneumoniae*. *Antimicrob Agents Chemother* 2011; 55:3002-4.
- 657 65. Giamarellou H, Galani L, Baziaka F, Karaikos I. Effectiveness of a double-
658 carbapenem regimen for infections in humans due to carbapenemase-producing
659 pandrug-resistant *Klebsiella pneumoniae*. *Antimicrob Agents Chemother* 2013;
660 57: 2388-90.
- 661 66. Souli M, Karaikos I, Masgala A, Galani L, Barmpouti E, Giamarellou H. Double-
662 Carbapenem Combination as Salvage Therapy for Untreatable Infections by KPC-
663 2-Producing *Klebsiella pneumoniae*. *Eur J Clin Microbiol* 2017. doi:
664 10.1007/s10096-017-2936-5.
- 665 67. Oliva A, Scorzolini L, Castaldi D, Gizzi F, De Angelis M, Storto M, et al. Double-
666 carbapenem regimen, alone or in combination with colistin, in the treatment of
667 infections caused by carbapenem-resistant *Klebsiella pneumoniae* (CR-Kp). *J*
668 *Infect* 2017; 74:103-6.

- 669 68. Cprek JB, Gallagher JC. Ertapenem-Containing Double-Carbapenem Therapy for
670 Treatment of Infections Caused by Carbapenem-Resistant *Klebsiella pneumoniae*.
671 *Antimicrob Agents Chemother* 2015; 60:669-73.
- 672 69. Poulakou G, Siakallis G, Tsiodras S, Arfaras-Melainis A, Dimopoulos G. Nebulized
673 antibiotics in mechanically ventilated patients: roadmap and challenges. *Expert*
674 *Rev Anti Infect Ther* 2017; 15:211-229.
- 675 70. Lu Q, Girardi C, Zhang M, Bouhemad B, Louchahi K, Petitjean O, *et al.* Nebulized
676 and intravenous colistin in experimental pneumonia caused by *Pseudomonas*
677 *aeruginosa*. *Intensive Care Med* 2010;36:1147-55.
- 678 71. Karvouniaris M, Makris D, Zygoulis P, Triantaris A, Xitsas S, Mantzarlis K, *et al.*
679 Nebulised colistin for ventilator-associated pneumonia prevention. *Eur Respir J*
680 2015; 46:1732-9.
- 681 72. Kollef MH, Ricard JD, Roux D, Francois B, Ischaki E, Rozgonyi Z, *et al.* A
682 randomized trial of the amikacin fosfomycin inhalation system for the adjunctive
683 therapy of Gram-negative ventilator-associated pneumonia: IASIS Trial. *Chest*
684 2016. pii: S0012-3692(16)62463-7.
- 685 73. Rello J, Solé-Lleonart C, Rouby JJ, Chastre J, Blot S, Poulakou G, *et al.* Use of
686 Nebulized Antimicrobials for the Treatment of Respiratory Infections in Invasively
687 Mechanically Ventilated Adults: A Position Paper from the European Society of
688 Clinical Microbiology and Infectious Diseases. *Clin Microbiol Infect.* 2017. pii:
689 S1198-743X(17)30219-7.
- 690 74. Solé-Lleonart C, Rouby JJ, Blot S, Chastre J, Blot S, Poulakou G, *et al.* Nebulization
691 of Antiinfective Agents in Invasively Mechanically Ventilated Adults: A Systematic
692 Review and Meta-analysis. *Anesthesiology.* 2017. pii: S1198-743X(17)30219-7.
- 693 75. Palmer LB, Smaldone GC. Reduction of bacterial resistance with inhaled
694 antibiotics in the intensive care unit. *Am J Respir Crit Care Med* 2014; 189:1225-
695 33.
- 696 76. Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, *et al.*
697 Management of adults with hospital-acquired and ventilator-associated
698 pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of
699 America and the American Thoracic Society. *Clin Infect Dis* 2016; 1:575-82.
- 700 77. Monogue ML, Kuti JL, Nicolau DP. Optimizing Antibiotic Dosing Strategies for the
701 Treatment of Gram-negative Infections in the Era of Resistance. *Expert Review of*
702 *Clinical Pharmacology* 2016; 9:459-76.
- 703 78. Berthoin K, Le Duff CS, Marchand-Brynaert J, Carryn S, Tulkens PM. Stability of
704 meropenem and doripenem solutions for administration by continuous infusion.
705 *J Antimicrob Chemother* 2010; 65:1073-5.
- 706 79. Pea F, Viale P, Cojutti P, Furlanut M. Dosing nomograms for attaining optimum
707 concentrations of meropenem by continuous infusion in critically ill patients with
708 severe gram-negative infections: a pharmacokinetics/pharmacodynamics-based
709 approach. *Antimicrob Agents Chemother* 2012; 56:6343-8.
- 710 80. Lorente L, Lorenzo L, Martín MM, Jiménez A, Mora ML. Meropenem by
711 continuous versus intermittent infusion in ventilator-associated pneumonia due
712 to gram-negative bacilli. *Ann Pharmacother* 2006; 40:219-23.
- 713 81. Ho VP, Jenkins SG, Afaneh G, Turbendian HK, Nicolau DP, Barie PS. Use of
714 Meropenem by Continuous Infusion to Treat a Blakpc-2-Positive *Klebsiella*
715 *pneumoniae* Blood Stream Infection. *Surgical Infections* 2011; 12:325-7.

- 716 82. Kim MK, Capitano B, Mattoes HM, Xuan D, Quintiliani R, Nightingale CH, *et al.*
717 Pharmacokinetic and Pharmacodynamic Evaluation of Piperacillin/Tazobactam
718 4.5 G Q8H and 3.375 G Q6H. *Pharmacotherapy* 2002; 22:569-77.
- 719 83. Keel RA, Kuti JL, Sahm DF, Nicolau DP. Pharmacodynamic Evaluation of
720 Commonly Prescribed Antibiotics against *Pseudomonas aeruginosa* Isolated from
721 United States Hospitals. *American Journal Health-System Pharmacy* 2011;
722 68:1619-25.
- 723 84. Martínez ML, Ferrer R, Torrents E, Guillaumat-Prats R, Gomà G, Suárez D, *et al.*
724 Edusepsis Study Group. Impact of Source Control in Patients With Severe Sepsis
725 and Septic Shock. *Crit Care Med* 2017; 45:11-19.
- 726 85. Patel G, Huprikar S, Factor SH, Jenkins SG, Calfee DP. Outcomes of carbapenem-
727 resistant *Klebsiella pneumoniae* infection and the impact of antimicrobial and
728 adjunctive therapies. *Infect Control Hosp Epidemiol* 2008; 29:1099-106.
- 729 86. Zarkotou O, Pournaras S, Tselioti P, Dragoumanos V, Pitiriga V, Ranellou K, *et al.*
730 Predictors of mortality in patients with bloodstream infections caused by KPC-
731 producing *Klebsiella pneumoniae* and impact of appropriate antimicrobial
732 treatment. *Clin Microbiol Infect* 2011; 17:1798-803.
- 733 87. Falcone M, Russo A, Iacovelli A, Restuccia G, Ceccarelli G, Giordano A, *et al.*
734 Predictors of outcome in ICU patients with septic shock caused by *Klebsiella*
735 *pneumoniae* carbapenemase-producing *K. pneumoniae*. *Clin Microbiol Infect*
736 2016; 22:444-50.
- 737 88. Nguyen M, Eschenauer GA, Bryan M, O'Neil K, Furuya EY, Della-Latta P, *et al.*
738 Carbapenem-resistant *Klebsiella pneumoniae* bacteremia: factors correlated with
739 clinical and microbiologic outcomes. *Diagn Microbiol Infect Dis* 2010; 67:180-4.
- 740 89. de Oliveira MS, de Assis DB, Freire MP, Boas do Prado GV, Machado AS, Abdala
741 E, *et al.* Treatment of KPC-producing Enterobacteriaceae: suboptimal efficacy of
742 polymyxins. *Clin Microb Infect* 2015; 21:179.e1–179.e7.
- 743 90. Dimopoulos G, Matthaiou DK. Duration of therapy of ventilator-associated
744 pneumonia. *Curr Opin Infect Dis* 2016; 29:218-22.
- 745 91. Chastre J, Wolff M, Fagon JY, Chevret S, Thomas F, Wermert D, *et al.* Pneuma
746 Trial Group. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-
747 associated pneumonia in adults: a randomized trial. *JAMA* 2003; 290:2588–2598.
- 748 92. Capellier G, Mockly H, Charpentier C, Annane D, Blasco G, Desmettre T, *et al.*
749 Early-onset ventilator-associated pneumonia in adults randomized clinical trial:
750 comparison of 8 versus 15 days of antibiotic treatment. *PLoS One* 2012;
751 7:e41290.
- 752 93. Havey TC, Fowler RA, Daneman N. Duration of antibiotic therapy for bacteremia:
753 a systematic review and meta-analysis. *Crit Care* 2011; 15:R267.
- 754 94. Matthaiou DK, Ntani G, Kontogiorgi M, Poulakou G, Armaganidis A, Dimopoulos
755 G. An ESICM systematic review and meta-analysis of procalcitonin-guided
756 antibiotic therapy algorithms in adult critically ill patients. *Intensive Care Med*
757 2012; 38:940–9.
- 758 95. Tacconelli E, Cataldo MA, Dancer SJ, De Angelis G, Falcone M, Frank U, *et al.*
759 ESCMID guidelines for the management of the infection control measures to
760 reduce transmission of multidrug-resistant Gram-negative bacteria in
761 hospitalized patients. *Clin Microbiol Infect* 2014; 20 Suppl 1:1-55.

- 762 96. De Rosa FG, Corcione S, Cavallo R, Di Perri G, Bassetti M. Critical issues for
763 *Klebsiella pneumoniae* KPC-carbapenemase producing *K. pneumoniae* infections:
764 a critical agenda. *Future Microbiol* 2015; 10:283-94.
- 765 97. Sypsa V, Psychogiou M, Bouzala GA, Hadjihannas L, Hatzakis A, Daikos GL.
766 Transmission dynamics of carbapenemase-producing *Klebsiella pneumoniae* and
767 anticipated impact of infection control strategies in a surgical unit. *PLoS One*
768 2012; 7:e41068.
- 769 98. Gagliotti C, Ciccarese V, Sarti M, Giordani S, Barozzi A, Braglia C, et al. Active
770 surveillance for asymptomatic carriers of carbapenemase-producing *Klebsiella*
771 *pneumoniae* in a hospital setting. *J Hosp Infect* 2013; 83:330-2.
- 772 99. Lin MY, Lyles-Banks RD, Lolans K, Hines DW, Spear JB, Petrak R, et al. The
773 importance of long-term acute care hospitals in the regional epidemiology of
774 *Klebsiella pneumoniae* carbapenemase-producing Enterobacteriaceae. *Clin Infect*
775 *Dis* 2013; 57:1246-52.
- 776 100. Giacobbe DR, Del Bono V, Marchese A, Viscoli C. Early carbapenem-resistant
777 *Klebsiella pneumoniae* bacteraemia: should we expand the screening? *Clin*
778 *Microbiol Infect*. 2014; 20:O1157-8.
- 779 101. Munoz-Price LS, De La Cuesta C, Adams S, Wyckoff M, Cleary T, McCurdy SP,
780 et al. Successful eradication of a monoclonal strain of *Klebsiella pneumoniae*
781 during a *K. pneumoniae* carbapenemase-producing *K. pneumoniae* outbreak in a
782 surgical intensive care unit in Miami, Florida. *Infect Control Hosp Epidemiol* 2010;
783 31:1074-7.
- 784 102. Tofteland S, Naseer U, Lislevand JH, Sundsfjord A, Samuelsen O. A long-term
785 low-frequency hospital outbreak of KPC-producing *Klebsiella pneumoniae*
786 involving Intergenous plasmid diffusion and a persisting environmental reservoir.
787 *PLoS One* 2013; 8:e59015.
- 788 103. Schwaber MJ, Carmeli Y. An ongoing national intervention to contain the
789 spread of carbapenem-resistant enterobacteriaceae. *Clin Infect Dis* 2014; 58:697-
790 703 .
- 791 104. Lerner A, Adler A, Abu-Hanna J, Cohen Percia S, Kazma Matalon M, Carmeli
792 Y. Spread of KPC-producing carbapenem-resistant Enterobacteriaceae: the
793 importance of super-spreaders and rectal KPC concentration. *Clin Microbiol*
794 *Infect* 2015; 21:470.e1-7.
- 795 105. De Rosa FG, Corcione S, Raviolo S, Montrucchio C, Aldieri C, Pagani N, et al.
796 Candidemia, and infections by *Clostridium difficile* and carbapenemase-
797 producing Enterobacteriaceae: new enteropathogenetic opportunistic
798 syndromes? *Infez Med* 2015; 23:105-16.
- 799 106. Abdallah M, Olafisoye O, Cortes C, Urban C, Landman D, Ghitan M, et al. Rise
800 and fall of KPC-producing *Klebsiella pneumoniae* in New York City. *J Antimicrob*
801 *Chemother* 2016; 71:2945-8.
- 802 107. Tumbarello M, Trearichi EM, Tumietto F, Del Bono V, De Rosa FG, Bassetti
803 M, et al. Predictive models for identification of hospitalized patients harboring
804 KPC-producing *Klebsiella pneumoniae*. *Antimicrob Agents Chemother* 2014;
805 58:3514-20.
- 806 108. Giannella M, Bartoletti M, Morelli MC, Tedeschi S, Cristini F, Tumietto F, et
807 al. Risk factors for infection with carbapenem-resistant *Klebsiella pneumoniae*
808 after liver transplantation: the importance of pre- and posttransplant
809 colonization. *Am J Transplant* 2015; 15:1708-15.

- 810 109. Giannella M, Trecarichi EM, De Rosa FG, Del Bono V, Bassetti M, Lewis RE, et
811 al. Risk factors for carbapenem-resistant *Klebsiella pneumoniae* bloodstream
812 infection among rectal carriers: a prospective observational multicentre study.
813 Clin Microbiol Infect 2014; 20:1357-62.
- 814 110. Giacobbe DR, Del Bono V, Bruzzi P, Corcione S, Giannella M, Marchese A, et
815 al; ISGRI-SITA (Italian Study Group on Resistant Infections of the Società Italiana
816 Terapia Antinfettiva). Previous bloodstream infections due to other pathogens as
817 predictors of carbapenem-resistant *Klebsiella pneumoniae* bacteraemia in
818 colonized patients: results from a retrospective multicentre study. Eur J Clin
819 Microbiol Infect Dis 2017; 36:663-669.
- 820 111. Salsano A, Giacobbe DR, Sportelli E, Olivieri GM, Brega C, Di Biase C, et al.
821 Risk factors for infections due to carbapenem-resistant *Klebsiella pneumoniae*
822 after open heart surgery. Interact Cardiovasc Thorac Surg 2016; 23:762-8.
- 823 112. Sbrana F, Malacarne P, Bassetti M, Tascini C, Vegnuti L, Della Siega P, et al.
824 Risk factors for ventilator associated pneumonia due to carbapenemase-
825 producing *Klebsiella pneumoniae* in mechanically ventilated patients with
826 tracheal and rectal colonization. Minerva Anestesiol 2016; 82:635-40.
- 827 113. Girmenia C, Rossolini GM, Picocchi A, Bertaina A, Pisapia G, Pastore D, et al;
828 Gruppo Italiano Trapianto Midollo Osseo (GITMO). Infections by carbapenem-
829 resistant *Klebsiella pneumoniae* in SCT recipients: a nationwide retrospective
830 survey from Italy. Bone Marrow Transplant 2015; 50:282-8.
- 831 114. De Rosa FG, Corcione S, Raviolo S, Bruno B, Busca A. Management of
832 Carbapenem-Resistant *K. pneumoniae* in Allogenic Stem Cell Transplant
833 Recipients: The Turin Bundle. *New Microbiologica* 2017. In press.
- 834 115. Forcina A, Baldan R, Marasco V, Cichero P, Bondanza A, Noviello M, et al.
835 Control of infectious mortality due to carbapenemase-producing *Klebsiella*
836 *pneumoniae* in hematopoietic stem cell transplantation. Bone Marrow Transplant
837 2017; 52:114-9.
- 838 116. Viale P, Tumietto F, Giannella M, Bartoletti M, Tedeschi S, Ambretti S, et al.
839 Impact of a hospital-wide multifaceted programme for reducing carbapenem-
840 resistant Enterobacteriaceae infections in a large teaching hospital in northern
841 Italy. Clin Microbiol Infect. 2015; 21:242-7.
- 842 117. Zuckerman T, Benyamini N, Sprecher H, Fineman R, Finkelstein R, Rowe
843 JM, et al. SCT in patients with carbapenem resistant *Klebsiella pneumoniae*: a
844 single center experience with oral gentamicin for the eradication of carrier state.
845 Bone Marrow Transplant 2011; 46: 1226–30.
- 846 118. Saidel-Odes L, Polachek H, Peled N, Riesenberk K, Schlaeffer F, Trabelsi Y, et
847 al. A randomized, double-blind, placebo-controlled trial of selective digestive
848 decontamination using oral gentamicin and oral polymyxin E for eradication of
849 carbapenem resistant *Klebsiella pneumoniae* carriage. Infect Control Hosp
850 Epidemiol. 2012; 33: 14–9.
- 851 119. Lübbert C, Fauchoux S, Becker-Rux D, Laudi S, Dürrbeck A, Busch T, et al.
852 Rapid emergence of secondary resistance to gentamicin and colistin following
853 selective digestive decontamination in patients with KPC-2-producing *Klebsiella*
854 *pneumoniae*: a single-centre experience. Int J Antimicrob Agents. 2013;42:565-
855 70.
- 856 120. Tascini C, Sbrana F, Flammini S, Tagliaferri E, Arena F, Leonildi A, et al. Oral
857 gentamicin gut decontamination for prevention of KPC-producing *Klebsiella*

- 858 *pneumoniae* infections: relevance of concomitant systemic antibiotic therapy.
859 Antimicrob Agents Chemother. 2014; 58: 1972–6.
- 860 121. Oren I, Sprecher H, Finkelstein R, Hadad S, Neuberger A, Hussein K, et al.
861 Eradication of carbapenem resistant Enterobacteriaceae gastrointestinal
862 colonization with nonabsorbable oral antibiotic treatment: a prospective
863 controlled trial. Am J Infect Control. 2013; 41: 1167–72.
- 864 122. Tascini C, Urbani L, Sbrana F, Forfori F, Licitra G, Leoni C, et al. Oral
865 administration of gentamicin for prophylaxis of KPC-producing *Klebsiella*
866 *pneumoniae* gut colonization in patients treated with a novel parenchymal-
867 sparing liver surgery: the GEN Gut study. Intensive Care Med. 2016;42:124-5.
- 868 123. Machuca I, Gutiérrez-Gutiérrez B, Pérez Cortés S, Gracia-Ahufinger I, Serrano
869 J, Madrigal MD, et al. Oral decontamination with aminoglycosides is associated
870 with lower risk of mortality and infections in high-risk patients colonized with
871 colistin-resistant, KPC-producing *Klebsiella pneumoniae*. J Antimicrob Chemother.
872 2016;71:3242-9.
- 873 124. Bassetti M, Righi E. New antibiotics and antimicrobial combination therapy
874 for the treatment of gram-negative bacterial infections. Curr Opin Crit Care 2015;
875 21:402-11
- 876 125. <https://clinicaltrials.gov/ct2/results?term=ceftazidime+avibactam&Search=Search>
877 earch
878 a. assessed 28.02.2017
- 879 126. <https://clinicaltrials.gov/ct2/results?term=ceftaroline+avibactam&Search=Search>
880 earch
881 a. assessed 28.02.2017
- 882 127. <https://clinicaltrials.gov/ct2/results?term=imipenem+relebactam&Search=Search>
883 earch
- 884 128. <https://clinicaltrials.gov/ct2/results?term=carbavance&Search=Search>
- 885 129. Cloutier DJ, Miller LG, Komirenko AS, Cebrik DS, Krause KM, Keepers TR, et
886 al. Plazomicin versus Meropenem for the Treatment of Complicated Urinary Tract
887 infection (cUTI) and Acute Pyelonephritis (AP): Results of the EPIC Study.
888 Presented at: 27th European Congress of Clinical Microbiology and Infectious
889 Diseases (ECCMID), Vienna, Austria, April 22-25, 2017.
- 890 130. Connolly LE, Jubb AM, O’Keeffe B, Serio AW, Smith A, Gall J, et al. Plazomicin
891 Is Associated With Improved Survival and Safety Compared With Colistin in the
892 Treatment of Serious Infections Due to Carbapenem-resistant
893 Enterobacteriaceae: Results of the CARE Study. Presented at: 27th European
894 Congress of Clinical Microbiology and Infectious Diseases (ECCMID), Vienna,
895 Austria, April 22-25, 2017.
- 896 131. Falagas ME, Skolidis T, Vardakas KZ, Legakis NJ. Hellenic Cefiderocol Study
897 Group. Activity of cefiderocol (S-649266) against carbapenem-resistant Gram-
898 negative bacteria collected from inpatients in Greek hospitals. J Antimicrob
899 Chemother 2017; 72:1704-1708.
- 900 132. <https://clinicaltrials.gov/ct2/results?term=eravacycline&Search=Search>
- 901 133. Sutcliffe JA, O'Brien W, Fyfe C, Grossman TH. Antibacterial activity of
902 eravacycline (TP-434), a novel fluorocycline, against hospital and community
903 pathogens. Antimicrob Agents Chemother 2013; 57:5548-5558.
- 904 134. Connors KP, Housman ST, Pope JS, Russomanno J, Salerno E, Shore E, et al.
905 Phase I, open-label, safety and pharmacokinetic study to assess

- 906 bronchopulmonary disposition of intravenous eravacycline in healthy men and
907 women. *Antimicrob Agents Chemother* 2014; 58:2113-2118.
- 908 135. Zhang Y, Lin X, Bush K. In vitro susceptibility of β -lactamase-producing
909 carbapenem-resistant Enterobacteriaceae (CRE) to eravacycline. *J Antibiot*
910 (Tokyo) 2016; 69:600-4.
- 911 136. Solomkin J, Evans D, Slepavicius A, Lee P, Marsh A, Tsai L, et al. Assessing the
912 Efficacy and Safety of Eravacycline vs Ertapenem in Complicated Intra-abdominal
913 Infections in the Investigating Gram-Negative Infections Treated With
914 Eravacycline (IGNITE 1) Trial: A Randomized Clinical Trial. *JAMA Surg* 2017;
915 152:224-232.
- 916 137. TETRAPHASE ANNOUNCES TOP-LINE RESULTS FROM IGNITE2 PHASE 3
917 CLINICAL TRIAL OF ERAVACYCLINE IN CUTI. TETRAPHASE PHARMACEUTICALS,
918 2015. Available at: <http://ir.tphase.com/releasedetail.cfm?releaseid=930613>
919
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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.

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 <i>et al.</i> 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 <i>in vitro</i> against <i>Enterobacteriaceae</i> producing ESBLs, AmpC, KPC and OXA-48. Clinical experience for carbapenem-resistant <i>Enterobacteriaceae</i> 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 <i>Klebsiella pneumoniae</i> (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.

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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 <i>Pseudomonas aeruginosa</i> and <i>Acinetobacter</i> <i>baumannii</i>	-Non-inferiority versus imipenem and meropenem in Phase 2 clinical trials for the treatment of cUTIs and cIAls respectively -Licensed in US, and EU for cUTIs and cIAls -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 cIAls 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 <i>A.</i> <i>baumannii</i> or <i>P.</i> <i>aeruginosa</i> 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 <i>Escherichia coli</i> and <i>K. pneumoniae</i> . Active against <i>A. baumannii</i> and <i>S. maltophilia</i> . Not active against <i>P. aeruginosa</i>	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 <i>A. baumannii</i> , but not against <i>P. aeruginosa</i> . ^{63,124,,132,133} Compared to tigecycline, it is more potent <i>in vitro</i> 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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