

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

**Critical issues for *Klebsiella pneumoniae* KPC-carbapenemase producing *K. pneumoniae* infections: a critical agenda.**

**This is the author's manuscript**

*Original Citation:*

*Availability:*

This version is available <http://hdl.handle.net/2318/157819> since

*Published version:*

DOI:10.2217/fmb.14.121

*Terms of use:*

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)



# UNIVERSITÀ DEGLI STUDI DI TORINO

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14

***This is an author version of the contribution published on:***

*Future Microbiol. 2015 Feb;10:283-94. doi: 10.2217/fmb.14.121.*

*Critical issues for Klebsiella pneumoniae KPC-carbapenemase producing K. pneumoniae infections: a critical agenda.*

*De Rosa FG(1), Corcione S, Cavallo R, Di Perri G, Bassetti M.*

***The definitive version is available at:***

*La versione definitiva è disponibile alla URL:*

*[http://www.futuremedicine.com/doi/abs/10.2217/fmb.14.121?url\\_ver=Z39.88-2003&rfr\\_id=ori:rid:crossref.org&rfr\\_dat=cr\\_pub%3dpubmed](http://www.futuremedicine.com/doi/abs/10.2217/fmb.14.121?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed)*

## Critical issues for *Klebsiella pneumoniae* KPC-carbapenemase producing *K. pneumoniae* infections: a critical agenda

### Abstract

The wide dissemination of carbapenemase producing *K. pneumoniae* (KPC-Kp) has caused a public health crisis of global dimensions, due to the serious infections in hospitalized patients associated with high mortality. In 2014, we aim to review clinical data on KPC-Kp at a time when a pro-active strategy (combating the problem before it is established) is no longer useful, focusing on epidemiology, patient risk profile, infection control, digestive tract colonization and treatment issues such as the role of carbapenems or carbapenem sparing strategies, colistin and resistance, dual carbapenem administration and the role of tigecycline. All these issues are illustrated prospectively to provide a forum for a Consensus strategy when not only ICUs but also medical and surgical wards are affected by the epidemics.

**Key words:** KPC, treatment, infection control, mortality, therapy, tigecycline, colistin, epidemiology, KPC-Kp, *Klebsiella pneumoniae*

### Introduction

The prevalence of multidrug-resistant (MDR) pathogens, has increased and represents a great concern for medical and scientific community<sup>1</sup>. Enterobacteriaceae such as *K. pneumoniae* are significantly contributing to the wide dissemination of carbapenemase-producing Gram-negatives (CPGNs), generating a global public health crisis with epidemiological, microbiological, clinical and infection control issues. Cross-transmission is common in the healthcare setting, with possible severe infections and associated high mortality rate, with few therapeutic options.<sup>2</sup>

*Klebsiella pneumoniae* is the most common producer of carbapenemases (KPC), a class of bacterial enzymes capable of inactivating carbapenems.<sup>3</sup> KPC carbapenemase-producing clones of *K. pneumoniae* (KPC-Kp) have been observed in the United States, Greece, Italy and Israel, and similar strains are now spreading worldwide: these strains are difficult to detect routinely in the clinical microbiology laboratory.<sup>4</sup>

Moreover, the shortage of new antimicrobial agents suggests that enhanced adherence to infection prevention procedures and antimicrobial stewardship programs are needed to curb patient-to-patient transmission and to reduce the selection of multidrug-resistant bacteria.<sup>5</sup> So far, combination regimens with at least two antibiotics with *in vitro* activity

49 against KPC-Kp have been shown to be more effective than appropriate monotherapy.<sup>6-8</sup>  
50 Adequate programs of infection control prevention are needed in the healthcare settings  
51 and should include surveillance programs for early detection and isolation of colonized  
52 patients.<sup>2</sup> In 2010 and 2012, a pro-active strategy (combating the problem before it is  
53 established) was suggested as a tool to reduce the spread of carbapenemase-producing  
54 bacteria, assuming that allocating resources up front will allow earlier detection and  
55 containment, largely because of the logarithmic escalation of such an outbreak.<sup>2,9</sup>  
56 In 2014, we aim to review clinical data on KPC-Kp focusing on epidemiology, patient risk  
57 profile, infection control, digestive tract colonization and treatment issues such as the role  
58 of carbapenems or carbapenem sparing strategies, colistin and resistance, dual  
59 carbapenem administration and the role of tigecycline. All these issues are illustrated  
60 prospectively to provide a forum for a Consensus strategy when not only ICUs but also  
61 medical and surgical wards are affected by the epidemics.

62

### 63 **Epidemiology of KPC-Kp infections**

64 Carbapenem resistance due to KPC has evolved rapidly since 2001 and the distribution of  
65 KPC-Kp is a public health concern of increasing importance worldwide; in Europe  
66 determinants now vary substantially by geography.<sup>3</sup> According to the Global Report on  
67 surveillance 2014 of WHO, KPC-Kp is globally low, but alarming rates – exceeding 50% –  
68 have been reported in some Countries such as Iran and Greece.<sup>10</sup>

69 According to European Antimicrobial Resistance Surveillance Network (EARS-Net), the  
70 European population-weighted mean percentage for carbapenem resistance was 6.2% in  
71 2012. Italy is at second place after Greece in term of resistance (28,8%), much higher than  
72 other European Countries. It is noteworthy that in Italy the KPC-Kp resistance grew rapidly  
73 in only three years (from 1% in 2009 to near 19% in 2012).<sup>4</sup>

74 A countrywide cross-sectional survey was carried out from 15 May to 30 June 2011 in Italy  
75 to investigate the diffusion of carbapenem-resistant Enterobacteriaceae (CRE) and to  
76 characterise the most prevalent resistance mechanisms and their dissemination patterns.<sup>8</sup>

77 Twenty-five large clinical microbiology laboratories, distributed across the national territory,  
78 participated in the study. There were 270 (2.0%) consecutive *non-replicate* clinical isolates  
79 of Enterobacteriaceae confirmed as CRE, highlighting an increase proportion of CRE  
80 among isolates from inpatients (3.5%). KPC-Kp was the most represented species  
81 (globally: 11.9%) and contributed to the majority of CRE (234 of 270, 86.7%).<sup>11</sup>

82 A regional surveillance program 2012 for KPC-Kp in Piedmont region, North-west of Italy,  
83 involving 28 regional Public Health Infection Control Units covering all the area (4,374,000  
84 inhabitants) investigated the epidemiology in this region. During the year 2012, 8,179  
85 *Klebsiella pneumoniae* strains were reported, of which 17.5% were KPC-Kp. The  
86 incidence of KPC-Kp was 1.9/1,000 patients admitted to hospital; KPC-Kp was more  
87 frequently isolated in tertiary care referral hospitals and from urine samples (50%). Even if  
88 there was a decreasing trend in KPC-Kp spread at local level due to the implementation of  
89 infection control measures in 2012 if compared to 2011, as many as 31% of KPC-Kp were  
90 identified in patients admitted to medical wards, followed by ICUs (15%), surgical wards  
91 (13%) and emergency department (14%).<sup>12</sup> This report highlighted possible epidemiology  
92 changes, with more medical wards affected than ICUs when the KPC-Kp diffusion is no  
93 longer restricted to major hospitals but also challenges tertiary care hospitals and their  
94 infection control strategies.

95

## 96 Risk Factors

97 Some studies investigated risk factors for infection and/or colonization by KPC-Kp (2,14).  
98 Papadimitriou et al. evaluated KPC-Kp enteric colonization in the ICU setting. In the first  
99 prospective observational study, they tried to identify risk factors for KPC-Kp colonization  
100 at ICU admission in 405 patients during a 22 month period, through the analysis of rectal  
101 samples taken from each patient within 12–48 h of admission. Upon ICU admission,  
102 52/405 (12.8%) samples were positive and colonization was associated with previous ICU  
103 stay, chronic obstructive pulmonary disease, duration of previous hospitalization, previous  
104 use of carbapenems and use of beta-lactams/beta-lactamase inhibitors. For patients  
105 previously hospitalized on peripheral wards the following risk factors were identified:  
106 duration of hospitalization prior to ICU admission, number of comorbidities and number of  
107 antimicrobials administered.<sup>13</sup> The second prospective observational study, conducted on  
108 226 ICU patients, aimed to evaluate the risk factors of KPC-Kp enteric colonization  
109 acquired during ICU stay and their impact on mortality. As many as 72.6% of the patients  
110 were colonized during ICU stay and the study highlighted that, in addition to common ICU  
111 factors such as tracheotomy, number of invasive catheters and antibiotics given, issues  
112 related to infection control were also important, such as prior bed occupants and patients  
113 in nearby beds colonized with with KPC-Kp. In that study there was a 35.4% ICU mortality,

114 which was associated with confirmed KPC-Kp infection and severe sepsis or septic shock,  
115 amongst other factors typical of ICU risk factors.<sup>14</sup>

116 A case-control study evaluated the risk factors for KPC-Kp bacteremia in 85 hospitalized  
117 patients: 18 (21.2%) were KPC-producers and 67 (78.8%) were non-KPC. At the  
118 multivariate analysis age ( $p = 0.004$ ), mechanical ventilation ( $p = 0.007$ ) and  
119 fluoroquinolone exposure during hospitalization ( $p = 0.02$ ) were independent risk factors  
120 for KPC in patients with *K. pneumoniae* bacteremia.<sup>15</sup>

121 Gut colonization represents the main human reservoir for epidemic dissemination in  
122 hospitals. A study examined the duration of KPC-Kp carriage following hospital discharge  
123 and the risk factors for persistent carriage in a cohort of 125 carriers (mean age 67.5  
124 years; 49.6% male) followed monthly for between 3 and 6 months after discharge from an  
125 acute-care hospital. Analyses were separated for recent (<4 months) (REC, 75 patients)  
126 and remote ( $\geq 4$  months) (REM, 50 patients) acquisition groups. A significant risk factor for  
127 persistent carriage identified in both the groups was the presence of any catheter ( $p <$   
128  $0.05$ ). Unique risk factor groups included long-term care facility residence ( $p < 0.01$ ) and a  
129 low functional status ( $p < 0.05$ ).<sup>16</sup>

130 Tumbarello et al. recently proposed predictive models for identification of hospitalized  
131 patients harboring KPC-Kp. This was a retrospective multicentre case-control study in five  
132 Italian hospitals where 657 adult inpatients (426 infected) with at least one isolation of a  
133 KPC-Kp strain were compared with patients without any isolation of such strains. The  
134 Authors found several risk factors associated with isolation or infection, including  
135 respectively, recent admission to an ICU, invasive catheterization and/or surgical drain,  $\geq 2$   
136 recent hospitalizations, hematological cancer and recent treatment with a fluoroquinolone  
137 and/or carbapenem, or a Charlson index of  $\geq 3$ , indwelling CVC, recent surgery,  
138 neutropenia,  $\geq 2$  recent hospitalizations and recent fluoroquinolone and/or carbapenem  
139 therapy.<sup>17</sup>

140

#### 141 **Infection control**

142 The spread of KPC-Kp is a challenging public health threat<sup>18</sup> and the application of  
143 infection prevention and control measures that have been applied in hospitals for MDR  
144 Gram-negative pathogens, which were variable in different countries. So far there is no  
145 consensus as to the most effective interventions or the best combination of interventions to  
146 reduce transmission of MDR Gram-negative pathogens in hospitalized patients. Evidence-

147 based guidelines on infection prevention and control interventions for reducing the  
148 transmission of MDR Gram-negative pathogens have been recently published by ESCMID  
149 (European Society of Clinical Microbiology and Infectious Diseases); the recommendations  
150 are stratified by type of infection prevention and control intervention and species of MDR  
151 Gram-negative pathogens<sup>19</sup>. The level of evidence and the strength of each  
152 recommendation were defined according to the GRADE approach. In Table 1 the main  
153 recommendations for endemic situation (defined as setting where there are frequent  
154 admissions of patients colonized or infected with MDR Gram-negative bacteria) and  
155 suggestion regarding approaches in outbreak situation (defined as settings where there is  
156 an unusual or unexpected increase of cases) are reported.<sup>19</sup>

157 According to the recent ESCMID Guidelines, the probable inter-patients main route of  
158 transmission is via the hands of healthcare workers. As a reference the Guidelines cited a  
159 Greek prospective observational study in a surgical unit where 18 out of 850 patients were  
160 colonized by KPC-Kp at admission and 51 were colonized during hospital stay. By  
161 surveillance cultures and Ross-Macdonald model, it was shown that the minimum hand  
162 hygiene compliance level necessary to control transmission was 50%. The Authors also  
163 demonstrated that a 30% reduction rate of the colonized patients on admission within 8-12  
164 weeks is possible with the available methods (active surveillance, contact precautions and  
165 isolation or cohorting), if coupled with at least a 60% compliance with hands hygiene.  
166 Moreover, the Authors highlighted that reduction in antibiotics use did not have a  
167 substantial benefit when an aggressive control strategy was implemented.<sup>20</sup>

168 In most of papers, successful infection control measures during outbreaks included early  
169 identification and isolation of infected patients. The study by Gagliotti et al. evaluated a  
170 KPC-Kp screening strategy in a tertiary Italian hospital, where 65 out of 1687 patients  
171 (3.9%) screened by rectal swabs during the five-month study period were positive for KPC-  
172 Kp, with only 5.1% of case contacts tested positive. Screening case contacts appears to  
173 be the essential surveillance component for detecting asymptomatic carriers of KPC-Kp.<sup>18</sup>

174 Following a KPC-Kp outbreak in a surgical ICU in Miami, Florida, where 9 patients were  
175 colonized or infected with a monoclonal strain), investigation and control measures were  
176 implemented: daily baths with 2% chlorhexidine impregnated wipes, point-prevalence  
177 surveillance with swabs, isolation of colonized/infected patients, medical personnel  
178 cohorted during their shifts and on a rotating basis, environmental culture and UV light  
179 surveillance, environmental cleaning, educational campaigns. The implementation of a

180 bundle of interventions was able to successfully control the further horizontal spread of this  
181 organism.<sup>21</sup>

182 Finally, Schwaber et al. recently reported a nationwide intervention implemented in 2007  
183 by the Israel Ministry of Health, based on ward-based mandatory guidelines for carrier  
184 isolation, patient and staff cohorting, active surveillance and other interventions including  
185 rules for microbiology identification, direct site visits at healthcare facilities and  
186 communications networking. There was a decline of the nosocomial CRE acquisition from  
187 a monthly rate of 55.5 to an annual low of 4.8 cases per 100,000 patient-days ( $P < .001$ ).<sup>22</sup>  
188 These studies showed that multiple interventions should be employed to successfully  
189 control KPC-Kp epidemics, also including simultaneous interventions in different hospitals,  
190 regional or national levels.

191

## 192 **Treatment**

193 KPC enzymes confer broad-spectrum resistance to  $\beta$ -lactams including carbapenems.  
194 Furthermore, KPC-Kp producers frequently carry additional genetic determinants, which  
195 confer resistance to other antibiotics, such as fluoroquinolones, aminoglycosides and  
196 cotrimoxazole. Few options may be available, depending on local epidemiology, for  
197 infected patients : tigecycline, polymyxins (colistin and polymyxin B), gentamicin and new  
198 carbapenems, or their combination.<sup>3,5</sup> Most of available reports highlighted the  
199 effectiveness of combination antibiotic treatment with colistin, tigecycline gentamycin and  
200 meropenem.

201 Zarkhotou et al. evaluated outcomes, risk factors for mortality and impact of appropriate  
202 antimicrobial treatment in 53 consecutive patients enrolled between May 2008 and May  
203 2010 with bloodstream infections caused by molecularly confirmed KPC-Kp. Globally, the  
204 mortality rate was 52.8% and infection mortality was 34%; the mortality was 20% when an  
205 appropriate antimicrobial therapy was administered (35 patients). All 20 patients treated  
206 with combination schemes had a favourable infection outcome; in contrast, 7 of 15 patients  
207 treated with an appropriate monotherapy died ( $p = 0.001$ ) but drug dosages were not  
208 specified. In univariate analysis, appropriate antimicrobial treatment ( $p = 0.003$ ) and  
209 combinations of antimicrobials active *in vitro* ( $p = 0.001$ ) were significantly associated with  
210 survival.<sup>7</sup>

211 The importance of an appropriate combination therapy was confirmed by an Italian  
212 multicenter retrospective cohort study, which evaluated the outcome of 125 patients with



213 bloodstream infections caused by KPC-Kp diagnosed between January 2010 and June  
214 2011.<sup>6</sup> The overall 30-day mortality rate was 41.6%, with a significantly higher rate in  
215 patients treated with monotherapy (54.3% vs 34.1% in those treated with combined drug  
216 therapy;  $p = 0.02$ ). Besides, this study confirmed that an inadequate initial antimicrobial  
217 therapy is independently associated with 30-day mortality.<sup>6</sup>

218 Also the group of Qureshi reported the superiority of combination antimicrobial regimens in  
219 treating bacteremia due to KPC-Kp, with a 28-day mortality of 13.3% compared with  
220 57.8% in the monotherapy group ( $p = 0.01$ ). The most commonly used combinations were  
221 colistin-polymyxin B or tigecycline combined with a carbapenem: the mortality rate in this  
222 group was 12.5%.<sup>8</sup> Overall, these studies showed that treatment with two or more drugs  
223 with *in vitro* activity is more effective than monotherapy in bloodstream infections due to  
224 KPC-Kp. However, as it is detailed in Table 2, there may be a series of bias in these  
225 studies which still needs to be addressed in the future: selection of patients for  
226 monotherapy or combination treatment, severity of disease, drug dosages (for example of  
227 tigecycline), the diagnostic and therapeutic delay related to strategies or early detection of  
228 colonized patients, when adopted.

229 Lee et al. performed a systematic review of published studies and reports (38 selected  
230 with 105 cases) of treatment outcomes of KPC infections using MEDLINE (2001–2011).  
231 The majority of infections were due to *K. pneumoniae* (89%). The most common site of  
232 infection was the bloodstream (52%), followed by the respiratory tract (30%). Forty-nine  
233 cases (47%) received monotherapy and 56 (53%) cases received combination therapy:  
234 significantly more treatment failures were observed in patients treated with monotherapy  
235 compared to those treated with combination therapy (49% vs 25%;  $p = 0.01$ ). Treatment  
236 failure rates were not significantly different in the three most common antibiotic-class  
237 combinations: polymyxin plus carbapenem, polymyxin plus tigecycline, polymyxin plus  
238 aminoglycoside (30%, 29%, and 25% respectively;  $p = 0.6$ ).<sup>23</sup>

239 Whilst monotherapy, especially with colistin, may be late and ineffective due to severe  
240 infections, dosages and side effects, specific considerations should be given to the issue  
241 of meropenem MIC in combination therapy. Tumbarello et al. described that when the  
242 KPC-Kp isolate had a meropenem MIC of  $\leq 4$  mg/L, inclusion of this drug in a combined-  
243 drug regimen was associated with a higher survival rate of (86.6%), whilst when  
244 meropenem MICs  $\geq 16$  mg/L there was a lower survival rate (64.7%).<sup>6</sup>

245 Daikos et al. found that if the isolate had a carbapenem MIC of  $\leq 4$  mg/L, combined therapy  
246 with a carbapenem plus one other active drug (an aminoglycoside or colistin or tigecycline)  
247 was associated with significantly lower mortality than combinations of non-carbapenem  
248 drugs with *in vitro* activity<sup>24</sup>. The issue of carbapenem MIC when deciding the possible  
249 addition to other antibiotics still needs to be defined as well as the mechanism that confers  
250 therapeutic activity to meropenem or imipenem when the MIC is well above the sensitivity  
251 breakpoint, lacking randomized controlled trials allowing definite conclusion.<sup>25</sup>

252 A recent study evaluated the effectiveness of the antibiotic treatment administered for  
253 infections caused by CRE (predominantly *Klebsiella* spp.) in 10 non-randomized studies  
254 enrolling 692 patients. Based on clinical data, and due to the fact that mortality rates were  
255 generally higher in patients treated with a monotherapy respect to those treated with a  
256 combination therapy, the Authors concluded that combination antibiotic treatment may be  
257 considered the optimal option for severely ill patients with severe infections.<sup>26</sup>

258 However, there are methodological flaws that should be cited as the absence of well-  
259 established evidence to support combination treatment, including colistin-carbapnem  
260 combination therapy, with infections caused by carbapenemases producing bacteria.<sup>25</sup>

261

### 262 **The issue of tigecycline treatment**

263 Tigecycline is a new glycylycline drug with a very broad spectrum of activity against  
264 bacteria, including Gram-positive and anaerobes. Tigecycline was also used, mostly as  
265 combination therapy but with standard dosages, for patients with nosocomial infections by  
266 different MDR bacteria, including KPC-Kp.<sup>27</sup>

267 Tigecycline was used in a total of seven patients with a 71% success rate (5/7 patients).  
268 Of the five patients with clinical success, two were treated for pneumonia, one for clinically  
269 significant tracheobronchitis, one for urosepsis and one for shunt-related meningitis  
270 (combined with gentamicin given intravenously and intrathecally).<sup>28-29</sup>

271 Di Carlo et al. described two cases of monomicrobial intraabdominal abscesses due to  
272 KPC-Kp ST258 clone successfully treated with a long term combined treatment of  
273 intravenous colistin 5 mg/kg/day divided in 3 equal doses and tigecycline at standard  
274 dosage (100 mg initially, followed by 50 mg every *bid*), associated to percutaneous  
275 drainage.<sup>30</sup>

276 The same group evaluated risk factors for mortality and the impact of a combination  
277 therapy of colistin plus standard tigecycline dosage or higher dosage (200 mg initially, the

278 100 mg *bid*, n = 12) of tigecycline (according to intra-abdominal abscess severity and  
279 MICs for tigecycline) of 30 ICU patients who underwent abdominal surgery with severe  
280 infections caused by KPC-Kp (15 intra-abdominal abscess, 8 anastomotic leakage, 4  
281 surgical site infection and 3 peritonitis). The average duration of treatment with a  
282 combination of tigecycline and intravenous colistin was  $18 \pm 6.5$  days and the overall crude  
283 ICU mortality rate was 40% (12 out of 30 patients). A significantly lower mortality rate was  
284 observed in patients treated with the higher dosage, without significantly higher rate of  
285 adverse effects. This study highlights that timely microbiological diagnosis and high  
286 dosages are essential to prevent worse outcomes.<sup>31</sup>

287 Finally, a very recent retrospective observational study assessed the efficacy of tigecycline  
288 in the treatment of 16 severe infections (pneumonia 31%; urinary tract infection 31%;  
289 peritonitis 20%), due to KPC-Kp in 15 critically ill patients, with high dosage administered  
290 in 10 patients. The overall 30-day mortality rate was 25% and the univariate analysis  
291 showed that mortality was not significantly associated with the tigecycline dose.<sup>32</sup>  
292 Notwithstanding the multiple critics to the use of tigecycline in patients with severe  
293 infections as highlighted by guidelines, metanalysis, FDA and EMEA warnings, there are  
294 indications of efficacy in patients with infections by KPC-Kp mostly as part of a  
295 combination treatment, with high daily dosages.<sup>33</sup>

296

### 297 **The issue of dual carbapenem**

298 *In vitro* and *in vivo* studies showed that dual carbapenem regimens may have enhanced  
299 efficacy over either agent alone and may represent a promising option for infections  
300 caused by KPC-producing isolates, particularly when the MIC is low.<sup>34-35</sup> Ceccarelli et al.  
301 reported a successful ertapenem-doripenem combination treatment of a 65-year-old male  
302 with bacteremic ventilator-associated pneumonia due to colistin-resistant KPC-Kp, after  
303 failures of multiple antibiotic regimens. After starting combined therapy with ertapenem 500  
304 mg q 24 h plus doripenem 250 mg q8h based on renal function, fever disappeared on the  
305 fourth day and the bacteremia was cleared after 8 days. The patient completed a 4-week  
306 dual-carbapenem treatment course and no relapse was observed after 1 further month of  
307 follow-up.<sup>36</sup>

308 However, criticism and experimental concerns were raised on the timing of administration  
309 of ertapenem and doripenem with two models: an *in vitro* chemostat model and an *in vivo*  
310 immunocompetent murine thigh infection model.<sup>35,37</sup> The mice were given doripenem one

311 hour after being treated with ertapenem and some Auhtors criticized the flaws with such  
312 low inoculum experiments, since carbapenem activity against KPC producers is markedly  
313 enhanced by a reduction in inoculum density.<sup>38</sup> A therapeutic advantage of such  
314 combination remains elusive and the presumed “suicide substrate” of ertapenem sill needs  
315 to be demonstrated.<sup>37,39</sup>

316 Lee et al demonstrated a synergistic effect and a rapid bactericidal activity, as early as 4  
317 hours, with a combination of colistin sulphate plus doripenem or polymyxin B with  
318 doripenem against clinical isolates of colistin-resistant KPC-Kp.<sup>40</sup> The clinical efficacy of  
319 polymyxin B and doripenem was also reported in two case reports of an 87-year-old man  
320 nursing-home resident and a 66-year-old man treated with doripenem plus polymyxin B: in  
321 both cases, soon after this antibiotic combination was started, fever and leukocytosis  
322 resolved and blood cultures became negative.<sup>41</sup>

323

### 324 **Ecology and Digestive tract decontamination**

325 Other than active surveillance for prompt carrier identification and infection control  
326 measures (isolation or cohorting with dedicated staff), digestive tract decontamination of  
327 patients colonized by KPC-Kp with nonabsorbed antibiotics has been suggested to reduce  
328 transmission and preventing subsequent infectious episodes in colonized patients. One of  
329 the most used regimen for digestive tract decontamination in this setting is oral gentamicin  
330 or combination of gentamicin plus polymyxin E.<sup>42-44</sup>

331 Tascini et al. evaluated the microbiological and clinical outcome of gut decontamination  
332 with oral gentamicin 80 mg four times daily in 50 consecutive patients colonized by  
333 gentamicin-susceptible KPC-Kp, with or without concomitant systemic antibiotic therapy.  
334 The overall decontamination rate was 68% (34/50): 96% in patients receiving oral  
335 gentamicin only, compared to 44% of those treated with oral gentamicin and concomitant  
336 systemic antibiotic therapy ( $p < 0.001$ ). At the six months follow-up, a KPC-Kp infection  
337 was observed in 15% of successfully decontaminated patients compared to 73% of  
338 persistent carriers ( $P < 0.001$ ). Besides, KPC-Kp infections were documented in 9% of  
339 patients treated with oral gentamicin only and in 56% of those also receiving systemic  
340 antibiotic therapy ( $p = 0.003$ ). The univariate analysis identified systemic antibiotic therapy,  
341 KPC-Kp infection and ICU stay as significant variables associated with gut  
342 decontamination, and the multivariate analysis confirmed systemic antibiotic therapy and  
343 KPC-Kp infection.<sup>45</sup>

344 A problem to be considered is the risk of emergence of gentamicin-resistant KPC-Kp  
345 following gut decontamination with oral gentamicin. In the previous study, gentamicin-  
346 resistant gut decontamination with oral gentamicin strains were isolated from stools of 4/16  
347 persistent carriers.<sup>44</sup> Lubbert et al. evaluated 90 patients hospitalised between July 2010  
348 and October 2012 to Leipzig University Hospital and affected by an outbreak due to a  
349 KPC-Kp. In order to eliminate KPC-Kp from their digestive tracts, 14 consecutive patients  
350 (16%) were treated with 7 days of gut decontamination with combination of colistin and  
351 oral gentamicin (80 mg qid), and applying colistin/gentamicin gel (0.5 g) to the oral cavity;  
352 this group was compared with the remaining 76 patients harbouring KPC-Kp. Even if  
353 decolonisation of KPC-Kp was achieved in 43% of patients treated with the antibiotics,  
354 30% of untreated controls reached the same result ( $p = 0.102$ ). On the other side,  
355 decontamination treatment caused the development of secondary resistance to colistin  
356 (19% increase in resistance rate) and gentamicin (45% increase) in post-treatment isolates,  
357 while in the control group, no secondary resistance occurred.<sup>46</sup> These results shows that  
358 oral topic antibiotic therapy can be useful but could favour the emergence of resistant  
359 KPC-Kp, especially in patients who failed to respond to gut decontamination regimens,  
360 and that the risk should be considered before starting decontamination.

361

### 362 ***Carbapenem sparing strategies***

363 Due to the spread of KPC-Kp strains, some Authors suggested carbapenem sparing  
364 strategies and rotation of antibiotics, in order to reduce the selective pressure of antibiotics  
365 on patients endogenous microflora.

366 Sbrana et al. evaluated the effectiveness of carbapenem sparing combination regimens for  
367 treating 26 KPC-Kp infections (ventilator acquired pneumonia = 16; bloodstream infections  
368 = 7; urinary tract infections = 2 patients; peritonitis = 1) in 22 ICU patients with relatively  
369 good health conditions, representd by polytrauma without other substantial comorbidities  
370 or immunosuppression. High dose tigecycline was used in 25 of 26 infections as the  
371 “backbone” drug (intravenous 100 mg every 12 hours), in combination with iv gentamicin in  
372 19 episodes or iv colistin in 12 episodes; iv fosfomycin was used as a third drug in 13 of 26  
373 infectious episodes. Antibiotic regimens were selected primarily on the basis of specific  
374 patient clinical risk factors, site of infection, and MIC results assessed by the attending  
375 physicians. In this series, a carbapenem-sparing regimen of tigecycline plus gentamicin or  
376 colistin was effective for treating 24 of 26 (92%) KPC-Kp infectious episodes.

377 Treatment responses to the carbapenem sparing combinations were similar for patients  
378 with bacteremic vs nonbacteremic VAP, as well as for patients with central venous  
379 catheter (CVC)–related vs non-CVC-related bacteremia and the 30-day crude mortality  
380 rate was 14%. This study is important to demonstrate that in low risk patients a  
381 carbapenem- sparing strategy may be safely employed, with high-dose tigecycline.<sup>47</sup>

382

### 383 **Solid organ transplants and HSCT**

384 CRE infection is common in transplant recipients and patients with hematologic  
385 malignancies and has severe complications; solid organ transplant is an independent  
386 predictor of risk for these infections.<sup>48-49</sup> Approximately 3%-10% of solid organ transplant  
387 recipients in endemic areas develop an infection caused by CRE and the infection site  
388 correlates with the transplanted organ. Mortality rates associated with these infections  
389 approach 40% in solid organ transplant recipients and 65% in patients with hematologic  
390 malignancies.<sup>49</sup>

391 Due to the limited antimicrobial armamentarium for the management of CRE infections, a  
392 multifaceted approach for decreasing nosocomial transmission and preventing further  
393 outbreaks: active surveillance in immunocompromised hosts with identification of  
394 colonized patients, contact precautions and antimicrobial stewardship.<sup>49</sup> Furthermore,  
395 clinicians urgently need better data to guide use of existing antibiotics, including optimal  
396 dose regimen, duration of treatment and use of combination therapy, as well as a robust  
397 pipeline of new agents to treat these infections.<sup>48</sup>

398 Some clinical experiences pointed out the problem of KPC-Kp infections in transplant  
399 recipients. In one report by Bergamasco et al., 12 solid organ transplant recipients were  
400 described during an outbreak, with different infections including urinary tract, bloodstream,  
401 surgical site infections and pneumonia. Amikacin and gentamicin were always effective,  
402 the mortality was 42% and patients were treated with a variety of combination regimens,  
403 such as tigecycline plus polymyxin B, polymyxin B plus carbapenem, polymyxin B alone,  
404 or tigecycline plus imipenem. Notably, two deaths were reported and both were treated  
405 with only a carbapenem before the cultures were available.<sup>50</sup>

406 Another potential risk in transplant recipients is the transmission of pathogens from donor  
407 to recipient. A study evaluated the clinical course and outcomes of 4 transplant recipients  
408 who received tissues from a donor with multi-organ infection with KPC-Kp. The 4 patients  
409 underwent simultaneous liver and kidney transplantation (1 case), living-donor liver

410 transplantation (1 case), kidney transplantation (1 case) and heart transplantation (1 case);  
411 all of them received an adequate perioperative antibiotic prophylaxis with tigecycline  
412 (associated to amikacin in one case). The antibiotic prophylaxis was able to prevent the  
413 develop of infections due to KPC-Kp in 3 out of 4 cases; the only case with a postoperative  
414 KPC-Kp infection (infected hematoma and peritonitis) was treated with a prolonged course  
415 of tigecycline, amikacin, and meropenem, in conjunction with surgical evacuation and  
416 percutaneous drainage of the infected fluid collections.<sup>51</sup>

417 Finally, a very recent retrospective observational case-control single-center study  
418 evaluated if colonization of liver transplant recipients with KPC-Kp was associated with  
419 high infection rates and excess mortality. In the center there was a large outbreak of KPC-  
420 Kp infections involving a total of 103 patients. Nine patients with orthotopic liver  
421 transplantation and confirmed evidence of colonization with KPC-2-KP were matched to 18  
422 cases of orthotopic liver transplantation without carbapenem-resistant pathogens. Eight  
423 out of 9 patients (89%) progressed to infection due to KPC-Kp; five of them (56%) had a  
424 confirmed bloodstream infection. Matched-pair analysis of the two groups showed a  
425 significantly increased relative risk of 7.0 for fatal infection with KPC-Kp after  
426 transplantation, with a mortality rate of 78 % (vs. 11%,  $p = 0.001$ ).<sup>52</sup>

427 These studies highlight the importance of a multidisciplinary cooperation to ensure the  
428 successful management of transplant recipients.

429

### 430 **Conclusions**

431 The epidemics by KPC-Kp is challenging the health-care system on diagnostic and  
432 therapeutic issues in different settings since it is no more limited to the ICUs but has  
433 extended to internal medicine and surgical wards. There are a number of critical issues  
434 that have to be recognized instead of limiting our observation to the results of retrospective  
435 studies with a variety of combination treatments, often including carbapenems. The exact  
436 upper limit of carbapanems MIC that is useful in combination treatments should be studied  
437 and closely monitored within the local epidemiology.

438 The rate of colistin resistance is growing and caution should be used when choosing  
439 colistin-based combination antimicrobial treatments. So far, there is an enormous need for  
440 clinical and microbiological criteria that balance efficacy with toxicity. Similarly, the reversal  
441 of colistin resistance with doripenem combination treatment and the value of rifampin-  
442 colistin regimens need to be fully explored and validated.

443 Special considerations should be done for tigecycline in the current years, since extended  
444 use in the setting of nosocomial infections caused by MDR bacteria has generated  
445 controversies in understanding the clinical and microbiological outcome of severely ill  
446 patients treated with a variety of combination treatments in off-label indications. Special  
447 efforts should be made to understand the efficacy of higher dosages, the upper MIC limit  
448 which still confers a clinical advantage, the type of combination drug as well as the utility in  
449 patients with bloodstream infections and the special role in carbapenem-sparing strategies.  
450 The early detection of gastrointestinal colonization is desirable by an infection control  
451 point of view as well as for early empiric treatment of patients with suspected infection.  
452 Wide studies of gastrointestinal colonization, at admission or perhaps weekly in high-risk  
453 patients may support the use of different therapeutic strategies in patients with possible,  
454 probable or proven infection, which have to be characterized and defined. Similarly to what  
455 has been proposed in neutropenic patients, escalation and de-escalation regimens should  
456 be defined, melting together the issues of colistin-resistance and carbapenem sparing  
457 strategies. Such actions may be urgent in the setting of a growing epidemics, affecting  
458 nowadays also medical and surgical wards.

459

#### 460 **Future perspective**

461 The future agenda for KPC-Kp infections is compelling and should be based on the special  
462 need to restore the integrity of the gut, protecting it from a heavy colonization by a bacteria  
463 which is very well adapted to the bowel (Table 3). Programs of antibacterial and antifungal  
464 stewardship should be implemented, increasing the specificity of diagnosis and limiting the  
465 duration of treatments.

466 A “save the bowel” strategy may be the correct strategy in response to the KPC-KP  
467 epidemic.

468

#### 469 **Executive summary**

- 470 • The wide dissemination of carbapenemase-producing *K. pneumoniae* has caused  
471 serious infections in hospitalized patients associated with high mortality.
- 472 • The shortage of new antimicrobial agents suggests that enhanced adherence to  
473 infection prevention procedures and antimicrobial stewardship programs are  
474 needed.
- 475 • Some studies investigated risk factors for infection and/or colonization by KPC-Kp.



- 476
- 477
- 478
- 479
- 480
- 481
- 482
- 483
- 484
- 485
- 486
- 487
- 488
- 489
- 490
- 491
- 492
- 493
- 494
- 495
- 496
- 497
- 498
- 499
- 500
- 501
- 502
- 503
- 504
- 505
- So far there is no consensus as to the most effective interventions combination to reduce transmission of MDR Gram-negative pathogens in hospitalized patients.
  - Few treatment options are available for KPC-Kp infections: tigecycline, polymyxins, gentamicin and carbapenems. Most of available reports highlighted the effectiveness of combination antibiotic treatment with colistin, tigecycline gentamycin and meropenem.
  - *In vitro* and *in vivo* studies showed that dual carbapenem regimens may have enhanced efficacy over either agent alone and may represent a promising option if MIC is low.
  - Digestive tract decontamination of patients colonized by KPC-Kp has been suggested to reduce transmission and preventing subsequent infectious episodes in colonized patients. One of the most used regimen in this setting is oral gentamicin or combination of gentamicin plus polymyxin E
  - Some Authors suggested carbapenem sparing strategies and rotation of antibiotics, in order to reduce the selective pressure of antibiotics on patients endogenous microflora.
  - A multifaceted approach for decreasing nosocomial transmission and preventing further outbreaks is particularly important in immunocompromised hosts, with identification of colonized patients, contact precautions and antimicrobial stewardship
  - The future agenda for KPC-Kp infections should be based on the special need to restore the integrity of the gut, programs of antibacterial and antifungal stewardship and increasing the specificity of diagnosis and limiting the duration of treatments.

506 **Table 1. ESCMID recommendations for KPC-Kp (mod. from 19)**

507

<b>Basic recommendations in endemic situation</b>		
<b><i>Intervention</i></b>	<b><i>Evidence</i></b>	<b><i>Recommendation</i></b>
Hand hygiene	Moderate	Strong
Contact precautions	Moderate	Strong
Alert code (previous positive) and pre-emptive CP	Moderate	Conditional
Isolation room	Moderate	Strong
Education	Moderate	Conditional
Environmental cleaning	Moderate	Conditional
Antimicrobial stewardship	Moderate	Conditional
Infection prevention and control infrastructure	NA	No evidence available
<b><i>Basic and additional specific approaches in outbreak situation</i></b>		
Hand hygiene	Very low	Strong
Active screening cultures	Moderate	Strong
Contact precautions	Moderate	Strong
Alert code (previous positive) and pre-emptive Contact precautions	Moderate	Strong
Cohort patients	Moderate	Conditional
Cohort staff	Moderate	Strong
Isolation room	Moderate	Strong
Education	Moderate	Conditional
Environmental cleaning	Moderate	Conditional
Environmental screening	Low	Conditional
Antimicrobial stewardship	Very low	Conditional
Healthcare workers screening	NA	
Chlorhexidine gluconate for patient bathing	Low	Conditional
Infection prevention and control infrastructure	Moderate	Conditional

508

509 **Table 2. Summary of bias to be addressed in future studies on KPC-Kp infections**

- Screening of at-risk patients
- Selection of patients and type of infection
- Severity of disease
- Timing of appropriate treatment
- Monotherapy or combination treatment
- Drug dosages
- Escalation versus de-escalation strategies
- De-colonization of patients
- Toxicity of combination regimens

510  
511  
512  
513  
514  
515  
516  
517  
518  
519  
520  
521  
522  
523  
524  
525  
526  
527  
528  
529

530 **Table 3. Diagnostic and therapeutic bundles to be implemented.**

531

Critical Issue	Critical Agenda
Infection control strategies: isolation	Strategies for swabbing of low and high risk patients
Strategies of decontamination	Selection of patients, dosage and duration of treatment, in case of failure is possible to try again?
Definition of the highest MIC for imipenem and meropenem possibly associated with clinical success with combination treatment	Accuracy of Laboratory to define the precise MIC for carbapenem
Definition of disease	Critically ill patients Vs Medical/Surgical/Trauma patients; site of infections (blood, respiratory, urinary, cSSSI)
Utility of dual carbapenem treatment	Case series and prospective data needed; <i>in vitro</i> ration should understood
The role carbapenem-sparing strategies	Strong rational
Reinforcing the colonization-resistance mechanism for enteric bacteria, including <i>C. difficile</i> and <i>Candida</i> spp.	Reduction of antibiotic and antifungal selective pressure to restore the role of the gut
Treatment	Clinical and microbiological failure should be clearly defined Toxicity should be evaluated in monotherapy and combination treatment

532

533

534

535

536 **References**

537

- 538 1. Carvalhaes CG, Cayô R, Gales AC: Klebsiella pneumoniae carbapenemase-producing Klebsiella  
539 pneumoniae in the intensive care unit: a real challenge to physicians, scientific community, and  
540 society. *Shock*. May 39 (Suppl 1), 32-7 (2013)
- 541 2. Akova M, Daikos GL, Tzouveleakis L, Carmeli Y: Interventional strategies and current clinical  
542 experience with carbapenemase-producing Gram-negative bacteria. *Clin Microbiol Infect*. May; 18(5),  
543 439-48 (2012)
- 544 3. Chen LF, Anderson DJ, Paterson DL: Overview of the epidemiology and the threat of Klebsiella  
545 pneumoniae carbapenemases (KPC) resistance. *Infection and Drug Resistance* 5, 133–141 (2012)
- 546 4. European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in  
547 Europe 2012. Annual Report of the European Antimicrobial Resistance Surveillance Network  
548 (EARS-Net). Stockholm: ECDC (2013)
- 549 5. Rapp RP, Urban C: Klebsiella pneumoniae carbapenemases in Enterobacteriaceae: history,  
550 evolution, and microbiology concerns. *Pharmacotherapy*. May; 32 (5), 399-407 (2012)
- 551 6. \*\*Tumbarello M, Viale P, Viscoli C, et al.: Predictors of mortality in bloodstream infections caused by  
552 Klebsiella pneumoniae carbapenemase-producing K. pneumoniae: importance of combination  
553 therapy. *Clin Infect Dis*. Oct; 55 (7), 943-50 (2012).
- 554 7. \*\*Zarkotou O, Pournaras S, Tselioti P, et al.: Predictors of mortality in patients with bloodstream  
555 infections caused by KPC-producing Klebsiella pneumoniae and impact of appropriate antimicrobial  
556 treatment. *Clin Microbiol Infect*. Dec; 17 (12), 1798-803 (2011)
- 557 8. \*\*Qureshi ZA, Paterson DL, Potoski BA, et al.: Treatment outcome of bacteremia due to KPC-  
558 producing Klebsiella pneumoniae: superiority of combination antimicrobial regimens. *Antimicrob*  
559 *Agents Chemother*. Apr; 56 (4), 2108-13 (2012)
- 560 9. Bilavsky E, Schwaber MJ, Carmeli Y: How to stem the tide of carbapenemase-producing  
561 enterobacteriaceae? Proactive versus reactive strategies. *Curr Opin Infect Dis*. 23, 327–331 (2010)
- 562 10. Antimicrobial resistance: global report on surveillance. World Health Organization 2014
- 563 11. Giani T, Pini B, Arena F, et al.: Epidemic diffusion of KPC carbapenemase-producing Klebsiella  
564 pneumoniae in Italy: results of the first countrywide survey, 15 May to 30 June 2011. *Euro Surveill* 18  
565 (22), pii=20489 (2013)
- 566 12. Rocchetti A, Zotti CM, Argentero PA, et al.: Epidemiology of carbapenemase-producing Klebsiella  
567 pneumoniae in a North-West Italian Region: Report from the regional surveillance system. *ECCMID*  
568 2014
- 569 13. Papadimitriou-Olivgeris M, Marangos M, Fligou F et al.: Risk factors for KPC-producing Klebsiella  
570 pneumoniae enteric colonization upon ICU admission. *J Antimicrob Chemother* 67, 2976–2981  
571 (2012)
- 572 14. Papadimitriou-Olivgeris M, Marangos M, Fligou F, et al.: KPC-producing Klebsiella pneumoniae  
573 enteric colonization acquired during intensive care unit stay: the significance of risk factors for its  
574 development and its impact on mortality. *Diagnostic Microbiology and Infectious Disease* 77, 169–  
575 173 (2013)

- 576 15. Tuon FF, Rocha JL, Toledo P, et al.: Risk factors for KPC-producing *Klebsiella pneumoniae*  
577 bacteremia. *Braz J Infect Dis*. Sep-Oct; 16 (5), 416-9 (2012)
- 578 16. Feldman N, Adler A, Molshatzki N, et al.: Gastrointestinal colonization by KPC-producing *Klebsiella*  
579 *pneumoniae* following hospital discharge: duration of carriage and risk factors for persistent carriage.  
580 *Clin Microbiol Infect*. Apr; 19 (4), E190-6 (2013)
- 581 17. Tumbarello M, Trecarichi EM, Tumietto F, et al.: Predictive Models for Identification of Hospitalized  
582 Patients Harboring KPC-Producing *Klebsiella pneumoniae*. *Antimicrob Agents Chemother*. Jun; 58  
583 (6), 3514-3520 (2014)
- 584 18. Gagliotti C, Ciccarese V, Sarti M, et al.: Active surveillance for asymptomatic carriers of  
585 carbapenemase-producing *Klebsiella pneumoniae* in a hospital setting. *J Hosp Infect*. Apr; 83 (4),  
586 330-2 (2013)
- 587 19. Tacconelli E, Cataldo MA, Dancer SJ, et al.: ESCMID guidelines for the management of the infection  
588 control measures to reduce transmission of multidrug-resistant Gram-negative bacteria in  
589 hospitalized patients. *Clin Microbiol Infect*. Jan; 20 (Suppl 1), 1-55 (2014)
- 590 20. Sypsa V, Psychogiou M, Bouzala GA, Hadjihannas L, Hatzakis A, Daikos GL. Transmission  
591 dynamics of carbapenemase-producing *Klebsiella pneumoniae* and anticipated impact of infection  
592 control strategies in a surgical unit. *PLoS One* 7 (7), e41068 (2012)
- 593 21. Munoz-Price LS, De La Cuesta C, Adams S, et al.: Successful eradication of a monoclonal strain of  
594 *Klebsiella pneumoniae* during a *K. pneumoniae* carbapenemase-producing *K. pneumoniae* outbreak  
595 in a surgical intensive care unit in Miami, Florida. *Infect Control Hosp Epidemiol*.; 31 (10), 1074-7  
596 (2010)
- 597 22. Schwaber MJ, Carmeli Y: An ongoing national intervention to contain the spread of carbapenem-  
598 resistant enterobacteriaceae. *Clin Infect Dis*.; 58 (5), 697-703 (2014)
- 599 23. Lee GC, Burgess DS: Treatment of *Klebsiella pneumoniae* carbapenemase (KPC) infections: a  
600 review of published case series and case reports. *Ann Clin Microbiol Antimicrob*. ; 11, 32 (2012)
- 601 24. \*\*Daikos GL, Tsaousi S, Tzouvelekis LS, et al.: Carbapenemase-producing *Klebsiella pneumoniae*  
602 bloodstream infections: lowering mortality by antibiotic combination schemes and the role of  
603 carbapenems. *Antimicrob Agents Chemother*; 58(4): 2322-8 (2014)
- 604 25. \*\*Paul M, Carmeli Y, Durante-Mangoni E et al.: Combination therapy for carbapenem-resistant Gram-  
605 negative bacteria. *J Antimicrob Chemother*; 69(9):2305-9 (2014).
- 606 26. Falagas ME, Lourida P, Poulidakos P, Rafailidis PI, Tansarli GS: Antibiotic treatment of infections  
607 due to carbapenem-resistant Enterobacteriaceae: systematic evaluation of the available evidence.  
608 *Antimicrob Agents Chemother* ; 58 (2), 654-63 (2014)
- 609 27. Reygaert WC. Antibiotic optimization in the difficult-to-treat patient with complicated intra-abdominal  
610 or complicated skin and skin structure infections: focus on tigecycline. *Therapeutics and Clinical Risk*  
611 *Management* 6, 419–430 (2010)
- 612 28. Weisenberg SA, Morgan DJ, Espinal-Witter R. (2009) Clinical outcomes of patients with *Klebsiella*  
613 *pneumoniae* carbapenemase-producing *K. pneumoniae* after treatment with imipenem or  
614 meropenem. *Diagn Microbiol Infect Dis*; 64: 233–5

- 615 29. Daly MW, Riddle DJ, Ledebner NA: Tigecycline for treatment of pneumonia and empyema caused  
616 by carbapenemase-producing *Klebsiella pneumoniae*. *Pharmacotherapy* 27, 1052–7 (2007)
- 617 30. Di Carlo P, Pantuso G, Cusimano A, et al.: Two cases of monomicrobial intraabdominal abscesses  
618 due to KPC - 3 *Klebsiella pneumoniae* ST258 clone. *BMC Gastroenterology* 11, 103 (2011)
- 619 31. Di Carlo P, Gulotta G, Casuccio A, et al.: KPC - 3 *Klebsiella pneumoniae* ST258 clone infection in  
620 postoperative abdominal surgery patients in an intensive care setting: analysis of a case series of 30  
621 patients. *BMC Anesthesiol.* Jul 3; 13 (1), 13 (2013)
- 622 32. Balandin Moreno B, Fernández Simón I, Pintado García V, et al.: Tigecycline therapy for infections  
623 due to carbapenemase-producing *Klebsiella pneumoniae* in critically ill patients. *Scand J Infect Dis.*  
624 Mar ;46 (3), 175-80 (2014)
- 625 33. Bassetti M, Poulakou G, Giamarellou H: Is there a future for tigecycline? *Intensive Care Med* DOI  
626 10.1007/s00134-014-3343-3 (2014)
- 627 34. Wiskirchen DE, Crandon JL, Nicolau DP: Impact of various conditions on the efficacy of dual  
628 carbapenem therapy against KPC-producing *Klebsiella pneumoniae*. *Int J Antimicrob Agents.* Jun;  
629 41 (6), 582-5 (2013)
- 630 35. Bulik CC, Nicolau DP: Double-carbapenem therapy for carbapenemase-producing *Klebsiella*  
631 *pneumoniae*. *Antimicrob Agents Chemother.* Jun; 55 (6), 3002-4 (2011)
- 632 36. Ceccarelli G, Falcone M, Giordano A, et al.: Successful ertapenem-doripenem combination  
633 treatment of bacteremic ventilator-associated pneumonia due to colistin-resistant KPC-producing  
634 *Klebsiella pneumoniae*. *Antimicrob Agents Chemother.* Jun; 57 (6), 2900-1 (2013)
- 635 37. Thomson KS: Double-carbapenem therapy not proven to be more active than carbapenem  
636 monotherapy against KPC-positive *Klebsiella pneumoniae*. *Antimicrob Agents Chemother* 56 (7),  
637 4037 (2012)
- 638 38. Bratu S, Mooty M, Nichani S, et al.: Emergence of KPC-possessing *Klebsiella pneumoniae* in  
639 Brooklyn, New York: epidemiology and recommendations for detection. *Antimicrob. Agents*  
640 *Chemother* 49, 3018–3020 (2005)
- 641 39. Anderson KF, Lonsway DR, Rasheed JK, et al.: Evaluation of methods to identify the *Klebsiella*  
642 *pneumoniae* carbapenemase in Enterobacteriaceae. *J. Clin. Microbiol* 45, 2723–2725 (2007)
- 643 40. Lee GC, Burgess DS: Polymyxins and Doripenem Combination Against KPC-Producing *Klebsiella*  
644 *pneumoniae*. *J Clin Med Res.* Apr; 5 (2), 97-100 (2013)
- 645 41. Gomez E, Sanchez M, Gul Z, et al.: Polymyxin Combination Therapy and the Use of Serum  
646 Bactericidal Titers in the Management of KPC-Producing *Klebsiella pneumoniae* Infections: A Report  
647 of 3 Cases. *Case Rep Med.* 2011, 659769 (2011)
- 648 42. Zuckerman T, Benyamini N, Sprecher H, et al.: SCT in patients with carbapenem resistant *Klebsiella*  
649 *pneumoniae*: a single center experience with oral gentamicin for the eradication of carrier state.  
650 *Bone Marrow Transpl* 46, 1226–1230 (2011)
- 651 43. Oren I, Sprecher H, Finkelstein R, et al.: Eradication of carbapenem-resistant Enterobacteriaceae  
652 gastrointestinal colonization with nonabsorbable oral antibiotic treatment: a prospective controlled  
653 trial. *Am. J. Infect. Control* 41, 1167–1172 (2013)

- 654 44. Saidel-Odes L, Polachek H, Peled N, et al.: A randomized, double-blind, placebo-controlled trial of  
655 selective digestive decontamination using oral gentamicin and oral polymyxin E for eradication of  
656 carbapenem-resistant *Klebsiella pneumoniae* carriage. *Infect. Control Hosp. Epidemiol* 33, 14–19  
657 (2012)
- 658 45. Tascini C, Sbrana F, Flammini S, et al.: Oral gentamicin gut decontamination for prevention of KPC-  
659 producing *Klebsiella pneumoniae* infections: relevance of concomitant systemic antibiotic therapy.  
660 *Antimicrob Agents Chemother.* Apr; 58 (4), 1972-6 (2014)
- 661 46. Lübbert C, Fauchoux S, Becker-Rux D, et al.: Rapid emergence of secondary resistance to  
662 gentamicin and colistin following selective digestive decontamination in patients with KPC-2-  
663 producing *Klebsiella pneumoniae*: a single-centre experience. *Int J Antimicrob Agents.* Dec; 42 (6),  
664 565-70 (2013)
- 665 47. Sbrana F, Malacarne P, Viaggi B, et al.: Carbapenem-sparing antibiotic regimens for infections  
666 caused by *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* in intensive care unit.  
667 *Clin Infect Dis.* Mar; 56 (5), 697-700 (2013)
- 668 48. Johnson K, Boucher HW: Editorial commentary: imminent challenges: carbapenem-resistant  
669 enterobacteriaceae in transplant recipients and patients with hematologic malignancy. *Clin Infect Dis.*  
670 May; 58 (9), 1284-6 (2014)
- 671 49. Satlin MJ, Jenkins SG, Walsh TJ: The global challenge of carbapenem-resistant Enterobacteriaceae  
672 in transplant recipients and patients with hematologic malignancies. *Clin Infect Dis.* May; 58 (9),  
673 1274-8 (2014)
- 674 50. Bergamasco MD, Barroso Barbosa M, de Oliveira Garcia D, et al.: Infection with *Klebsiella*  
675 *pneumoniae* carbapenemase (KPC)-producing *K. pneumoniae* in solid organ transplantation.  
676 *Transpl Infect Dis.* Apr; 14 (2), 198-205 (2012)
- 677 51. Ariza-Heredia EJ, Patel R, Blumberg EA, et al.: Outcomes of transplantation using organs from a  
678 donor infected with *Klebsiella pneumoniae* carbapenemase (KPC)-producing *K. pneumoniae*.  
679 *Transpl Infect Dis.* Jun; 14 (3): 229-36 (2012)
- 680 52. Lübbert C, Becker-Rux D, Rodloff AC, et al.: Colonization of liver transplant recipients with KPC-  
681 producing *Klebsiella pneumoniae* is associated with high infection rates and excess mortality: a  
682 case-control analysis. *Infection.* Apr; 42 (2), 309-16 (2014)

683

684 \*\* References 6-8;24: main important retrospective studies regarding therapy and outcomes for KP-KPC  
685 infections.

686 \*\* References 26: In this paper the issue of lack of randomized clinical trials is well highlighted.