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

UNIVERSITÀ DEGLI STUDI DI TORINO

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[1]. Enterobacteriacee 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.[2]

Klebsiella pneumoniae is the most common producer of carbapenemases (KPC), a class of bacterial enzymes capable of inactivating carbapenems.[3] 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.[4]

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.[5] So far, combination regimens with at least two antibiotics with *in vitro* activity

against KPC-Kp have been shown to be more effective than appropriate monotherapy.[6-8] Adequate programs of infection control prevention are needed in the healthcare settings and should include surveillance programs for early detection and isolation of colonized patients.[2] In 2010 and 2012, a pro-active strategy (combating the problem before it is established) was suggested as a tool to reduce the spread of carbapenemase-producing bacteria, assuming that allocating resources up front will allow earlier detection and containment, largely because of the logarithmic escalation of such an outbreak.[2,9]

In 2014, we aim to review clinical data on KPC-Kp 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.

Epidemiology of KPC-Kp infections

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

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

A countrywide cross-sectional survey was carried out from 15 May to 30 June 2011 in Italy to investigate the diffusion of carbapenem-resistant Enterobacteriaceae (CRE) and to characterise the most prevalent resistance mechanisms and their dissemination patterns.[8] Twenty-five large clinical microbiology laboratories, distributed across the national territory, participated in the study. There were 270 (2.0%) consecutive *non-replicate* clinical isolates of Enterobacteriaceae confirmed as CRE, highlighting an increase proportion of CRE among isolates from inpatients (3.5%). KPC-Kp was the most represented species (globally: 11.9%) and contributed to the majority of CRE (234 of 270, 86.7%).[11]

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

Risk Factors

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

which was associated with confirmed KPC-Kp infection and severe sepsis or septic shock, amongst other factors typical of ICU risk factors.[14]

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

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

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

Infection control

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

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

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

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

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

bundle of interventions was able to successfully control the further horizontal spread of this organism.[21]

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

Treatment

KPC enzymes confer broad-spectrum resistance to β-lactams including carbapenems. Furthermore, KPC-Kp producers frequently carry additional genetic determinants, which confer resistance to other antibiotics, such as fluoroquinolones, aminoglycosides and cotrimoxazole. Few options may be available, depending on local epidemiology, for infected patients : tigecycline, polymyxins (colistin and polymyxin B), gentamicin and new carbapenems, or their combination.[3,5] Most of available reports highlighted the effectiveness of combination antibiotic treatment with colistin, tigecycline gentamycin and meropenem.

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

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

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

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

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

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

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

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

However, there are methodological flaws that should be cited as the absence of well-established evidence to support combination treatment, including colistin-carbapnem combination therapy, with infections caused by carbapenemases producing bacteria. [25]

The issue of tigecycline treatment

Tigecycline is a new glycylcyline drug with a very broad spectrum of activity against bacteria, including Gram-positive and anaerobes. Tigecycline was also used, mostly as combination therapy but with standard dosages, for patients with nosocomial infections by different MDR bacteria, including KPC-Kp.[27]

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

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

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

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

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

The issue of dual carbapenem

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 for infections caused by KPC-producing isolates, particularly when the MIC is low.[34-35] Ceccarelli et al. reported a successful ertapenem-doripenem combination treatment of a 65-year-old male with bacteremic ventilator-associated pneumonia due to colistin-resistant KPC-Kp, after failures of multiple antibiotic regimens. Alter starting combined therapy with ertapenem 500 mg q 24 h plus doripenem 250 mg q8h based on renal function, fever disappeared on the fourth day and the bacteremia was cleared after 8 days. The patient completed a 4-week dual-carbapenem treatment course and no relapse was observed after 1 further month of follow-up.[36]

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

hour after being treated with ertapenem and some Auhtors criticized the flaws with such low inoculum experiments, since carbapenem activity against KPC producers is markedly enhanced by a reduction in inoculum density.[38] A therapeutic advantage of such combination remains elusive and the presumed "suicide substrate" of ertapenem sill needs to be demonstrated.[37,39]

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

Ecology and Digestive tract decontamination

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

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

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

Carbapenem sparing strategies

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

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

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

Solid organ transplants and HSCT

CRE infection is common in transplant recipients and patients with hematologic malignancies and has severe complications; solid organ transplant is an independent predictor of risk for these infections.[48-49] Approximately 3%-10% of solid organ transplant recipients in endemic areas develop an infection caused by CRE and the infection site correlates with the transplanted organ. Mortality rates associated with these infections approach 40% in solid organ transplant recipients and 65% in patients with hematologic malignancies.[49]

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

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

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

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

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

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

Conclusions

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

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

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

Future perspective

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

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

Executive summary

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

- 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

Basic recommendations in endemic situation		
Intervention	***Evidence***	***Recommendation***
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
Basic and additional specific approaches in outbreak situation		
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

Table 3. Diagnostic and therapeutic bundles to be implemented.

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; *in vitro* ration should understood
The role carbapenem-sparing strategies	Strong rational
Reinforcing the colonization-resistance mechanism for enteric bacteria, including *C. difficile* and *Candida* 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

References

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

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

615 29. Daly MW, Riddle DJ, Ledeboer 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)

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

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

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