First documented outbreak of KPC-2-producing Klebsiella pneumoniae *in Switzerland: infection control measures and clinical management*

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Infection
A Journal of Infectious Disease

ISSN 0300-8126
Volume 42
Number 3

Infection (2014) 42:529-534
DOI 10.1007/s15010-013-0578-9

Springer

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BRIEF REPORT

First documented outbreak of KPC-2-producing *Klebsiella pneumoniae* in Switzerland: infection control measures and clinical management

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Received: 5 September 2013 / Accepted: 20 December 2013 / Published online: 30 January 2014

Abstract We report the epidemiological and clinical features of the first outbreak of *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* (KPC-KP) type 2 in Switzerland. The outbreak took place in the medical intensive care unit (MICU) of our tertiary care hospital and affected three severely ill patients. After the implementation of strict infection control measures, no further patients colonised with KPC-KP could be detected by the screening of exposed patients. Successful treatment of patients infected with KPC-KP consisted of a combination therapy of meropenem, colistin and tigecycline.

Keywords Carbapenem-resistant Enterobacteriaceae (CRE) · KPC · *Klebsiella pneumoniae* · Outbreak · Switzerland · Infection control

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Introduction

Within the last decade, carbapenem-resistant Enterobacteriaceae (CRE) have become a major global threat [1, 2]. One of the most common CRE, *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* (KPC-KP), was first described 1996 in eastern USA and has since spread globally [2, 3]. The prevalence of KPC-KP in Europe is increasing, although the rates vary considerably between countries [1]. A north–south gradient can be seen with endemic KPC-KP in Italy, Greece and Israel [1]. A recent survey from Italy reported several hospital outbreaks and countrywide dissemination of KPC-KP [4, 5]. In many European countries with low KPC prevalence, outbreaks have been linked to patients transferred from endemic regions [1, 6].

In Switzerland, the prevalence of KPC-KP is unknown, as data are only available on the number of isolates with elevated minimal inhibitory concentrations (MICs) for carbapenems [7]. The first description of a KPC producer was a KPC-2 *K. pneumoniae* isolate in the urine and sputum samples of a patient transferred from Sicily (Italy) to Neuchâtel (Switzerland) in 2011 [8]. Subsequently, four unrelated cases of KPC-2 and KPC-3 *K. pneumoniae* were reported from the University Hospital of Basel. All four cases were related to endemic countries [9].

We report the first outbreak of KPC-KP in Switzerland, its epidemiological and clinical features, as well as the infection control measures implemented during the outbreak period.

Methods

Setting

Our institution is a 700-bed tertiary care hospital in eastern Switzerland, treating approximately 33,000 inpatients

annually. The supposed transmission of KPC-KP took place in the 12-bed medical intensive care unit (MICU) between February and April 2013. In 2012, a total of 2,108 patients were hospitalised on the ward, accounting for 5,870 patient-, 1,610 ventilation- and 257 dialysis-days. At the time of the outbreak, MRSA screening was performed at admission for patients at risk [10].

Microbiology

Aerobic and anaerobic blood cultures were incubated using the Bactec™ FX system (BD Biosciences, San Jose, CA), according to the manufacturer's instructions. Positive blood cultures and samples of the lower respiratory tract were processed according to standard procedures [11, 12].

Since selective culture media for KPC-KP were not available in our laboratory during the outbreak, screening was done according to the following procedure. Nasal, pharyngeal, rectal, axillary and inguinal screening swabs (Copan, Brescia, Italy) were inoculated on MacConkey agar plates (BD Biosciences) for 24 and 48 h. Growing colonies of different morphotypes were identified by MALDI-TOF (Bruker Daltonik, Bremen, Germany) and susceptibility testing was performed with the BD Phoenix™ 100 system (BD Biosciences) according to Clinical and Laboratory Standards Institute (CLSI) guidelines [13]. Multi-resistant *K. pneumoniae* with elevated MICs for carbapenems were further tested with the Etest® (bioMérieux, Marcy l'Etoile, France) containing imipenem (with and without EDTA), the double-disk synergy test with boronic acid, as well as with the modified Hodge test [9, 13]. The MICs of colistin and tigecycline were determined with the Etest®. KPC-specific conventional polymerase chain reaction (PCR) was followed by direct sequencing, as previously described [9]. Molecular typing of KPC-KP was done using pulsed-field gel electrophoresis (PFGE) using restriction endonuclease *Xba*I according to the procedure described by Babouee et al. [14], with the exception that the percentage of similarities were calculated based on the Pearson rather than the Dice coefficient. PFGE patterns were analysed using the software package GelCompar II, version 5.10 (Applied Maths NV, Sint-Martens-Latem, Belgium).

Results

Outbreak description and epidemiological investigation

In case 1, KPC-KP was detected in a blood culture on March 17th. On that same day, case 2 yielded a KPC-KP-positive bronchial secretion. Therefore, an outbreak investigation according to international guidelines was initiated [15].

As cases 1 and 2 were room-mates in the MICU from March 7th to March 11th, this ward was identified as the putative place of transmission and the screening of patients at risk was performed. Active screening revealed a third patient (case 3) on March 21st with KPC-KP-positive screening samples (Fig. 1).

All patients hospitalised for more than three days in the MICU between the period from February 19th to April 23rd were scheduled to undergo screening. Screening was repeated every 7 days for patients in the MICU. If patients were discharged from the MICU, two additional screenings 7 days apart were planned.

Case 1 was also hospitalised on the haemato-oncology ward during the outbreak period. However, no further screening was deemed necessary in this ward, since the patient was in a single room at all times and hand hygiene adherence was over 80 % throughout the last 3 years (own data).

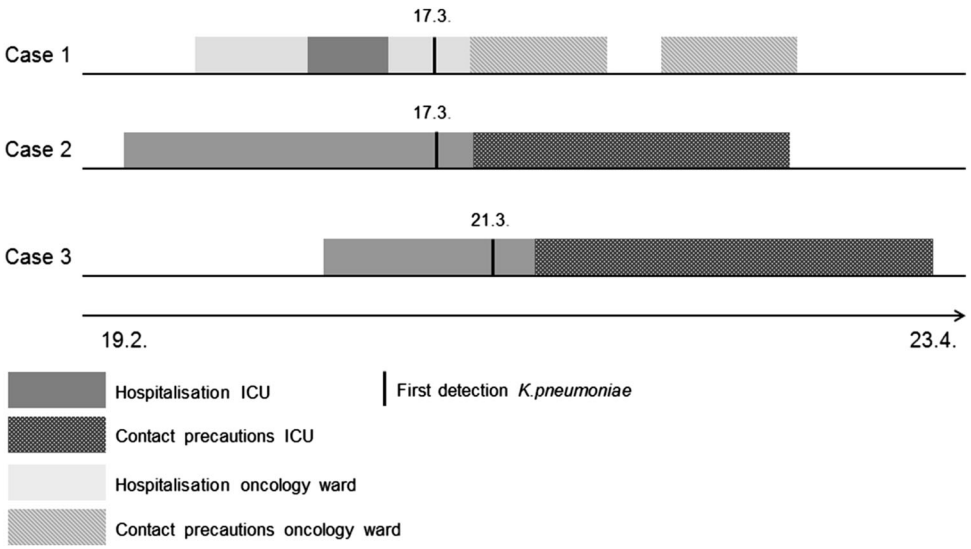

Fig. 1 Timeline of the outbreak

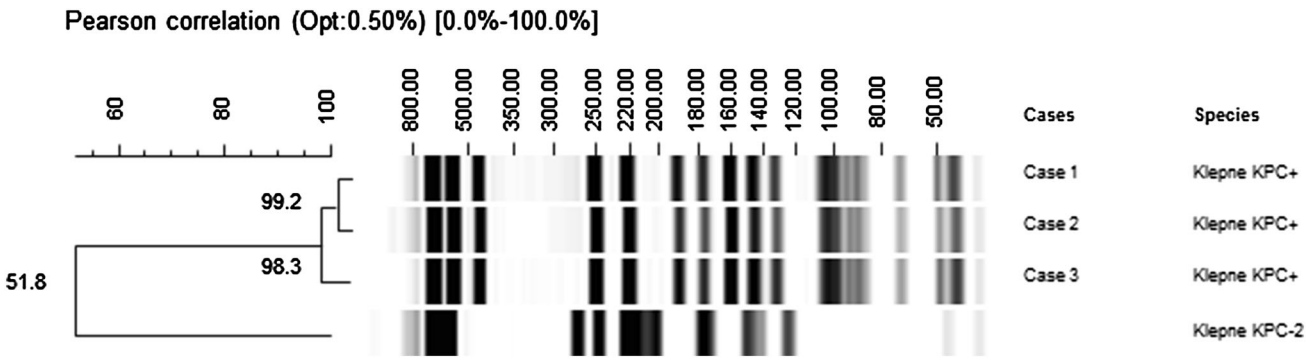

Fig. 2 Pulsed-field gel electrophoresis (PFGE) using *Xba*I of the three KPC-2 *K. pneumoniae* isolates compared with an unrelated KPC-2 *K. pneumoniae* strain

Thus, 36 patients were scheduled to undergo screening. Twenty-one completed the screening with at least two negative results (one patient with six screenings, six patients with three screenings and 14 patients with two screenings). Thirteen patients had incomplete screenings, with seven patients having only one negative screening and six patients having been discharged from our institution before screening began. Patients with incomplete screening were labelled in our electronic alert system to ensure screening at re-hospitalisation. For at-risk patients having been discharged, health care workers involved in subsequent patient care were informed. Two patients died. One passed away after unsuccessful resuscitation following cardiac arrest on day 3 of the hospitalisation. The second patient was discharged from the MICU to a rehabilitation centre after treatment of cardiogenic shock. He was readmitted to another hospital because of haematothorax and died of bronchopneumonia 44 days after discharge from the MICU. Neither of the two patients was screened. Therefore, colonisation or infection with KPC-KP cannot be excluded in either of the two patients.

Infection control measures and interventions

Contact precautions were put in place for the identified cases and patient cohorting was initiated. Staff cohorting was arranged but could not be strictly maintained. At the time of outbreak detection, all rooms, surfaces and devices were disinfected with a quaternary ammonium-based formulation. This procedure was repeated 3 weeks following outbreak detection. Disinfection was additionally repeated each time an isolated patient was discharged from the MICU. Hand hygiene adherence and hygiene behaviour was observed by infection control specialists and direct feedback was given to the health care workers. During the outbreak, hand hygiene adherence according to the World Health Organization (WHO) guidelines [16] was 82 % (243 opportunities observed).

Patients transferred to other units in our institution were not pre-emptively put in contact isolation, but health care workers, patients and family members were reminded to strictly adhere to standard precautions, especially hand hygiene procedures.

Microbiological investigations

The isolated strains from cases 1, 2 and 3 were sent to the reference laboratory in Basel, where phenotypic and molecular methods confirmed KPC-KP. Genotyping after sequencing exhibited the beta-lactamase (*bla*) KPC-2 gene. Additionally, PFGE of the three *K. pneumoniae* strains showed very similar fingerprints, indicating clonal identity (Fig. 2).

Description of cases (Table 1)

Case 1

Case 1, a 54-year-old man with multiple myeloma, was hospitalised on February 25th for the administration of high-dose chemotherapy. He was transferred to the MICU on March 7th because of aplasia and bilateral pneumonia with persistent fever spikes. After being treated with piperacillin/tazobactam, he clinically improved and could be transferred back to the haematoncology unit on March 11th. Three days later, the patient re-developed a fever. Blood cultures drawn on March 17th grew KPC-KP and antibiotic therapy was switched to meropenem and tigecycline. Assuming catheter-related bloodstream infection (BSI), the central line was removed and the catheter tip cultured (no growth). The patient subsequently recovered quickly and antibiotic therapy was stopped on the day of hospital discharge on March 29th. On April 4th, however, he had to be re-admitted due to pneumonia. KPC-KP was again isolated from the bronchoalveolar lavage (BAL) and meropenem, tigecycline and colistin were administered for 12 days. The patient was finally discharged on April 16th.

Table 1 Outbreak of KPC-KP, February to April 2013: characteristics of involved patients ($n = 3$), all having been treated with meropenem, colistin and tigecycline

Case	Underlying condition	Reason for MICU admission	Hospitalisation abroad[a]	Device[b]	KPC-KP-positive samples	KPC-KP infection	Duration of antibiotic treatment	Survival[c]
1	Multiple myeloma, high-dose chemotherapy	Aplasia and bilateral pneumonia (no microorganism)	No	CL	Blood, BAL	CRBSI assumed, HAP	12 days	Yes
2	None	Bilateral pneumonia (influenza A)	Italy	ECMO, MV, IVC filter, CL	BAL, CL[d]	VAP assumed	4 weeks	Yes
3	None	Bilateral pneumonia (influenza B, MSSA)	Austria	ECMO, MV, cvvHD, CL	Skin, pharynx, rectum, blood, BAL	VAP with secondary BSI assumed	4 weeks	Yes

MICU medical intensive care unit, *KPC-KP* KPC-producing *Klebsiella pneumoniae*, *CL* central line, *CRBSI* catheter-related bloodstream infection, *HAP* hospital-acquired pneumonia, *BAL* bronchoalveolar lavage, *ECMO* extracorporeal membrane oxygenation, *MV* mechanical ventilation, *IVC* inferior vena cava, *VAP* ventilator-associated pneumonia, *MSSA* methicillin-sensitive *Staphylococcus aureus*, *cvvHDF* continuous veno-venous haemofiltration, *BSI* bloodstream infection

[a] Within 30 days before MICU admission

[b] At the time of KPC-KP detection

[c] At 30 days after KPC-KP detection

[d] I.e. cultured catheter tip

Case 2

Case 2, a 67-year-old Swiss male spending his vacation in Italy, had been hospitalised in Calabria from 17th to 19th of February because of bilateral pneumonia. Antibiotic therapy with ampicillin/sulbactam and levofloxacin was initiated. On February 19th, the patient was transferred to our MICU.

Upon arrival at our hospital, antibiotic therapy was changed to piperacillin/tazobactam and clarithromycin. Due to worsening of the respiratory situation, extracorporeal membrane oxygenation (ECMO) was installed. A multiplex PCR of the BAL was positive for influenza A and therapy with oseltamivir was initiated. The patient was not put under droplet isolation because he was mechanically ventilated at the time. Piperacillin/tazobactam was switched to imipenem. The cardiopulmonary situation slowly improved and the ECMO could be removed on March 14th. Because of an inguinal deep vein thrombosis and simultaneous bleeding complications in the nasopharynx, an inferior vena cava (IVC) filter was installed. Due to recurrent fever, all intravascular catheters were exchanged on March 15th and cultures of the central catheter tip showed KPC-KP. The same microorganism could be detected in a BAL performed on March 17th because of respiratory deterioration. Antibiotic therapy was switched to meropenem, colistin and tigecycline, assuming ventilator-associated pneumonia (VAP). The patient recovered and could finally be extubated on April 7th. After removal of the IVC filter, the patient was transferred to another hospital on April 15th.

Case 3

Case 3, a 39-year-old man, was initially admitted to a hospital in Austria because of sepsis and bilateral pneumonia on March 9th. Due to respiratory deterioration of the intubated patient, ECMO was installed and the patient was transferred to our MICU.

Influenza B and *S. aureus* could be isolated from the patient's sputum and therapy with oseltamivir and amoxicillin/clavulanate was started. In addition, because the *S. aureus* isolate was found to be positive for Panton–Valentine leucocidin (PVL), clindamycin (for 14 days) and intravenous immunoglobulins (for 3 days) were administered. No droplet isolation was put in place because the patient was on mechanical ventilation. The patient remained on ECMO until March 24th. He exhibited multiple complications of sepsis: because of acral necrosis due to microvascular derangements, both feet and nine fingers had to be amputated during the course of hospitalisation. Short-term agranulocytosis was probably related to severe sepsis (including PVL) and/or multiple medications.

Furthermore, the patient developed renal failure and was dependent on renal replacement therapy until transfer. Patient screening on March 21st, including swab samples of the patient's skin, pharynx and rectum, revealed positive results for KPC-KP. Antibiotic therapy was initially switched to meropenem. Tigecycline and colistin were added on March 26th due to VAP with secondary KPC-KP bacteraemia. The patient could finally be extubated and was transferred to another hospital on April 23rd.

Discussion

Outbreak and epidemiology

To the best of our knowledge, this is the first published outbreak with KPC-KP in Switzerland confirmed by PFGE-identical strains.

We postulate that case 2, who was transferred from an Italian hospital, was the index patient of the described outbreak. This hypothesis is corroborated by looking at the epidemiology of KPC-KP in Europe. Italy is one of the few European countries where CRE are considered to be endemic, especially KPC-2- and KPC-3-producing *K. pneumonia* [1, 4, 5]. Many cases and outbreaks of CRE in other countries have been attributed to patient transfers from Italy [6, 9].

Case 3 was hospitalised in Austria, a low prevalence country for KPC-KP, before admission to the ICU and is, therefore, less likely to be the source of the outbreak [1]. Case 1 was not hospitalised abroad within the 12 months preceding the outbreak, which makes it implausible that he is the index patient.

Infection control measures

Since the gastrointestinal tract is the most common human reservoir, KPC-KP acquisition by ingestion is likely [17]. Depending on the gastrointestinal flora and antibiotic consumption, gastrointestinal colonisation is transient or permanent. During the time of gastrointestinal carriage, shedding and transmission to other patients is possible [17]. Even though this mechanism may account for transmission in the community setting, the transmission of KPC-KP in western countries is almost exclusively seen in hospitals [17]. Although never proven in health care settings, transmission is assumed to occur via contact between patients and personnel.

Fortunately, our outbreak was rapidly controlled with rigorous hand hygiene, contact precautions with patient cohorting and surface disinfection. However, the screening of exposed patients was incomplete and follow-up of discharged patients proved difficult. One-sixth of at-risk patients were not screened due to early discharge to another institution. They could potentially serve as a reservoir for KPC-KP and spread the bacteria within the community or, in the event of re-hospitalisation, within health care institutions. Electronic patient labelling may help to identify these patients in case of re-admission to our institution. Admission to other institutions, however, would go undetected because electronic patient systems do not exist in our region outside our tertiary care centre. This case demonstrates the difficulties faced due to the lack of electronic patient systems at a regional level, revealing how complicated it may be to obtain and provide information about outbreaks and local epidemiology on an international level. Therefore, we join the 2010 ESCMID Expert Group on acquired carbapenemases in advocating the need for better regional, national and international collaboration [18].

Given the absence of KPC-KP in our institution prior to this outbreak, our laboratory was not prepared to perform patient screenings for KPC-KP. Therefore, screenings during the outbreak were done without selective culture media for KPC-KP, resulting in a probably lower screening sensitivity. Following control of the outbreak, a screening programme for patients at risk for CRE has been implemented in our institution using selective culture media. As yet, KPC-KP has not been detected in our hospital following the outbreak, in neither clinical nor screening samples.

Clinical aspects

All of our patients exhibited risk factors for the acquisition of *K. pneumoniae*. Case 1 was immunocompromised due to high-dose chemotherapy, while all three patients suffered severe infections and were, therefore, treated with broad-spectrum antimicrobials prior to infection with KPC-KP. Further, cases 2 and 3 had severe sepsis, a state of immunosuppression in itself [19], and both patients had a prolonged stay in the ICU. Moreover, these two patients were on ECMO and mechanical ventilation at the time of KPC-KP isolation, with both factors contributing to the increased susceptibility to nosocomial pathogens [20].

Data on the treatment of CRE are scarce. As has been shown in vitro, carbapenems seem to have a synergistic effect when given together with colistin or tigecycline, despite the presence of a carbapenemase [21, 22]. Our patients were treated with a combination therapy consisting of meropenem, tigecycline and colistin. In a retrospective study analysing 125 cases of BSI with KPC-producing bacteria, this combination therapy was associated with decreased mortality (34 vs. 54 %) compared to patients with monotherapy [23]. Similar results have been published by others [24, 25]. In addition, the development of resistance has been documented under monotherapy, especially for colistin [26]. Combination therapy against KPC-KP should, therefore, be the treatment of choice until

further data based on prospective randomised trials are available.

Conclusion

Our report describes a KPC-2 outbreak in Switzerland following a patient transfer from Italy and its containment by means of rigorous infection control measures. Infections in the three affected individuals were successfully treated with a triple therapy consisting of meropenem, colistin and tigecycline.

Acknowledgements The authors would like to thank Lauren Clack for the language support.

Conflict of interest There was no financial support and the authors have no potential conflicts of interest to declare.

Ethical approval No formal informed consent was obtained from the patients, as this evaluation was considered to be within the context of the overall quality control system instituted at the hospital.

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