Extended measures for controlling an outbreak of VIM-1 producing imipenem-resistant *Klebsiella pneumoniae* in a liver transplant centre in France, 2003–2004

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We report the successful control of an outbreak caused by imipenem-resistant VIM-1-producing *Klebsiella pneumoniae* (IR-Kp) in France. This outbreak occurred in a care centre for abdominal surgery that includes a 15-bed liver intensive care unit and performs more than 130 liver transplantations per year. The index case was a patient with acute liver failure transferred from a hospital in Greece for urgent liver transplantation who was carrying IR-Kp at admission as revealed by routine culture of a rectal swab. Infection control measures were undertaken and included contact isolation and promotion of hand hygiene with alcohol-based hand rub solution. Nevertheless, secondary IR-Kp cases were identified during the six following months from 3 December 2003 to 2 June 2004. From 2 June to 21 October, extended infection control measures were set up, such as cohorting IR-Kp carriers, contact patients and new patients in distinct sections with dedicated staff, limiting ward admission, and strict control of patient transfer. They led to a rapid control of the outbreak. The global attack rate of the IR-Kp outbreak was 2.5%, 13% in liver transplant patients and 0.4% in the other patients in the care centre ($p < 0.005$). Systematic screening for IR-Kp of all patients admitted to the care centre is still maintained to date and no secondary IR-Kp case has been detected since 2 June 2004.

Introduction

Klebsiella pneumoniae has been a prominent cause of nosocomial infections and outbreaks, particularly in intensive care units. Metallo-beta-lactamases (MBLs) hydrolyse all beta-lactam antibiotics including

carbapenems (except aztreonam) and are reported increasingly in *Enterobacteriaceae*. Among MBLs, the first member of the VIM-family of enzymes, VIM-1, was identified in a clinical isolate of *Pseudomonas aeruginosa* in Verona, Italy [1]. During the last decade, VIM-type MBLs have spread in *Enterobacteriaceae* [2–10] and outbreaks of such strains have been reported in Greece [11] and Italy [12]. *Klebsiella pneumoniae* carbapenemase (KPC) is one of the most prevalent carbapenemases in *Enterobacteriaceae* especially in Asia, Israel, southern Europe, the United Kingdom (UK), and the United States (US) [13]. In 2009, a novel MBL named NDM-1 (New Delhi metallo-beta-lactamase) was identified by Yong D *et al.* in *K. pneumoniae* and *Escherichia coli* isolates recovered from a Swedish patient transferred from India to a hospital in Sweden [14]. A recent study reported NDM-1 MBLs in various *Enterobacteriaceae* in the UK [15]. Many of the NDM-1-positive patients had travelled in India or Pakistan in the year preceding their infection or had links with these countries [15]. Population mobility is known to be a major factor in the spread of multidrug-resistant organisms [16]. Prevention of the spread of carbapenemases, especially into northern and western European countries where these enzymes are not yet endemic, is vital. The European Union is facing the threat of multiple outbreaks involving carbapenemase-producing *Enterobacteriaceae* and thus needs to establish guidelines to control such outbreaks rapidly and efficiently.

We report on the first control of an outbreak involving a single strain of VIM-1-producing *K. pneumoniae* that occurred in 2004 at Paul Brousse hospital, a 716-bed

tertiary-care teaching hospital of Assistance Publique–Hôpitaux de Paris (AP-HP), the largest public health institution in France with 23,000 beds. The outbreak occurred in the abdominal surgery care centre that comprises 81 single bedrooms including 15 beds on the first floor dedicated to intensive care and an acute care facility of 66 beds located on the third and fourth floors of the building. The intensive care unit admits more than 800 patients per year. The abdominal surgery care centre performs more than 130 liver transplantations per year, 15% of them in patients from foreign countries, and 200 hepatectomies.

We have previously described the bacteriological characteristics of the strain involved in this outbreak [17].

We describe here the characteristics of the IR-Kp cases and the specific measures that led to the control of the outbreak.

Outbreak description

The index case (Case 1) was a patient with acute fulminant hepatic failure admitted on 2 December 2003 to the intensive care unit for an urgent liver transplantation. He was transferred from Athens, Greece, where he had been hospitalised for an acute hepatitis due to hepatitis B virus infection. It was the first time that an IR-Kp has been identified in our hospital, since systematic screening for extended spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* was introduced in 2002. We learnt later that the Greek hospital this

TABLE 1

Clinical characteristics of patients colonised or infected with imipenem-resistant *Klebsiella pneumoniae* in an abdominal surgery care centre, France, 2003–2004 (n=8)

Case	Age (years)	Date of admission	Clinical events	First isolate: site	Interval between admission and IR-Kp isolation (days)	Antibiotic treatment	Outcome	Suspected place of acquisition
1	in their 20s	December 2003	Liver transplantation	rectal swab	0	No treatment	Discharged	Index case transferred from Greece
2	in their 50s	December 2004	Liver transplantation	blood culture	13	No treatment	Discharged	Acute care facility
3	in their 60s	September 2003	Liver transplantation	tracheal fluid	175	Piperacillin/tazobactam Ciprofloxacin ^a	Deceased (due to IR-Kp infection)	Acute care facility
4	in their 60s	February 2004	Liver transplantation	urine culture	48	No treatment (asymptomatic)	Deceased	Intensive care unit
5	in their 70s	April 2004	Liver cirrhosis	urine culture	31	No treatment (asymptomatic)	Deceased	Intensive care unit
6	in their 50s	January 2004	Liver transplantation	blood culture	173	Colistin	Deceased (due to IR-Kp infection)	Intensive care unit
7	in their 50s	March 2004	Liver transplantation	rectal swab	101	No treatment	Discharged	Intensive care unit
8	in their 40s	January 2004	Liver transplantation	rectal swab	206	No treatment	Discharged	Acute care facility

^a Two antibiotics to which the strain was resistant. IR-Kp was identified post mortem.

TABLE 2

Organisation of distinct sections in intensive care unit and acute care facility during Period 2 of the control measures, abdominal surgery care centre, France, 2 June to 21 October 2004

Separation with plastic wall ↓		
First floor intensive care unit	IR-Kp patients section	IR-Kp-free – long stay intensive care unit section
	IR-Kp patients who stayed in intensive care until discharge Number of beds ^a : 3	Patients requiring intensive care for an expected duration of more than 48 hours Number of beds ^a : 12
Third floor acute care facility	IR-Kp free patients non-intensive care unit section	IR-Kp-free – short stay intensive care unit section
	Patients directly admitted to the acute care facility Number of beds ^a : 25	Patients having major surgery but requiring monitoring for less than 48 hours Number of beds ^a : 5
Fourth floor acute care facility	Contact acute care section	
	Patients hospitalised on the same floor and at the same time as an IR-Kp patient Number of beds ^a : 36	

IR-Kp: imipenem-resistant VIM-1-producing *Klebsiella pneumoniae*.

^a Only single bedrooms.

patient had been transferred from was at that time experiencing an outbreak with IR-Kp [8].

A secondary IR-Kp case was defined as a patient with IR-Kp isolated from any clinical sample (if infected) and/or from a rectal swab (if colonised). In the context of this outbreak, five further cases of IR-Kp infection and two cases of IR-Kp colonisation occurred in our hospital. The characteristics of the IR-Kp cases are listed in

Table 1. Six of the seven secondary cases had a liver transplantation and one had end-stage liver cirrhosis.

The interval between admission and the first IR-Kp-positive specimen ranged between 13 and 206 days (median: 101 days). Considering only the seven cases who acquired IR-Kp in the abdominal surgery care centre (Table 1), patient age ranged between 46 and 69 years (median 62 years).

FIGURE 1
Synoptic curve of imipenem-resistant *Klebsiella pneumoniae* cases (infection and colonisation) in an abdominal surgery care centre, France, December 2003 to October 2004 (n=8)

FIGURE 2
Patients screened in connection with an outbreak of imipenem-resistant *Klebsiella pneumoniae* in an abdominal surgery care centre, France, 2 December 2003 to 21 October 2004

Treatment and outcome

IR-Kp was isolated from a rectal swab of the index case sampled on the day of admission to the intensive care unit. This case did not receive any antibiotic therapy during his stay and remained colonised until he was discharged in January 2004 and returned to Greece.

The five secondary IR-Kp cases (Cases 2 to 6) were treated as follows: Case 2 had a central venous catheter-related bloodstream infection that resolved after removal of the catheter, without antibiotic treatment. Case 3 received piperacillin/tazobactam and ciprofloxacin for bacteraemia (two antibiotics to which the strain was resistant, see chapter on Microbiological diagnostic) and died of Gram-negative septic shock, the IR-Kp having been identified only after the patient's death. Cases 4 and 5 had an asymptomatic urinary tract infection with IR-Kp and did not receive any antibiotic therapy. Case 6 had a liver abscess caused by IR-Kp and was treated with colistin. Four months after an apparent cure, the patient had a relapse and died deceased from IR-Kp bacteraemia associated with end-stage liver failure.

The two secondary cases with IR-Kp colonisation (Cases 7 and 8) were not treated.

Cases 1, 2, 7 and 8 were discharged, while cases 3 to 6 died either in direct relation to their IR-Kp infection (Case 3 and 6) or from other reasons related to pathology. Interestingly, Cases 2 and 7 became IR-Kp-negative 15 months and two months, respectively, after initial diagnosis, whereas Case 8 was still carrying IR-Kp in July 2008, four years after initial diagnosis.

Control measures

Period 1 (2 December 2003 to 2 June 2004)

Immediately after identification of the index case, measures were implemented according to the French recommendations for controlling multidrug-resistant bacteria in hospital [18]: isolation of positive patients in a single bed room, barrier precautions (e.g. gowns and gloves for staff when entering the patient's room), hand disinfection with alcohol-based hand-rub solution before entering and after leaving the room, and environmental disinfection of the room [18]. Training of staff was organised to insure stringent application of these measures. All patients hospitalised in the intensive care unit were screened for IR-Kp once a week. This screening was maintained when these patients were transferred to the acute care facility.

Despite these measures, new IR-Kp carriers were identified in the intensive care unit during this period (see Table 1) which led to the implementation in June 2004 of extended infection control measures to stop cross-transmission.

Period 2 (2 June to 21 October 2004)

The additional control measures were implemented with the help of the central infection control team of AP-HP. Firstly, we defined five distinct sections in the

intensive care unit and acute care facility (Table 2) in order to separate IR-Kp-carrying patients, contact patients and newly admitted patients who were neither IR-Kp-carrying nor contact patients (IR-Kp-free patients). Contact patients were defined as patients who had stayed on the same floor at the same time as an IR-Kp patient (even if this time was less than 24 hours) before the implementation of the reinforced control measures on 2 June 2004.

Secondly, we thoroughly modified the organisation of care in the abdominal surgery care centre. Nursing staff was assigned exclusively to one of the five sections. Admissions of new patients were limited to emergencies and liver transplants. In order to prevent spread of the outbreak to other care centres, transfers were allowed only for IR-Kp-free patients. Transfer of IR-Kp patients within our hospital or to another hospital was allowed only for specific investigations (e.g. computed axial tomography or magnetic resonance imaging) and organised by the local infection control team to ensure that barrier precautions were respected. If patients carrying IR-Kp were readmitted after discharge, they were directly hospitalised in the 'IR-Kp patients section'. If they presented as outpatients for consultation, the local infection control team was informed, control measures were taken and the patients were screened again for IR-Kp. Daily meetings between the medical and nursing staff at the abdominal surgery care centre and the local infection control team helped to strengthen compliance with the control measures. The local infection control team inspected the implementation of the measures at the bedside every day.

Thirdly, it was recommended that clinicians should optimise and restrict the use of antibiotics, in particular of imipenem/cilastatin. An information letter explaining the measures was posted at the information desk of each floor of the abdominal surgery care centre, given to all patients hospitalised in the centre and to their families and also distributed to the other units of the hospital. IR-Kp patients were informed of their status and received instructions when discharged: they were invited to come back preferentially to our hospital in case of medical problem and, if hospitalised in another hospital, to inform the medical staff there about their IR-Kp status.

Finally, the French health authorities organised a screening campaign targeting the contact patients discharged from the abdominal surgery care centre during Period 1 who had not been screened. They were invited to call a free helpline where two senior physicians and a resident physician were available from 26 July to 6 August 2004 and explained how to be screened either in our hospital or, alternatively, in any laboratory of the patients' choice. In the latter case, the procedure to detect IR-Kp was mailed to the chosen laboratory and the result was sent to our hospital.

In June 2004, an alert describing the antibiotic resistance pattern of the IR-Kp was posted on the website of the French institute of public health surveillance (Institut de Veille Sanitaire), and sent to the Early Warning Response System of the European health authorities.

The extended measures were maintained until the end of October 2004 when the last IR-Kp patient was discharged from the abdominal surgery care centre. This patient was transferred to the infectious disease unit located in a separated building of the hospital, where the same control measures were taken (i.e. establishing a special unit with dedicated nursing staff) until the patient died on 15 December. Screening of contact patients for IR-Kp was maintained at each re-admission of in- or outpatients to our hospital until the end of 2005. This measure was stopped because the number of contact patients coming back to the abdominal surgery care centre had decreased and all had had at least three (on average 10) successive negative screenings.

Microbiological diagnostic

Rectal swabs were plated on Drigalski agar containing 0.5 mg/L of cefotaxime, MacConkey agar containing 2 mg/L of ceftazidime. In Period 2 we added Drigalski agar plates containing 4 mg/L of imipenem until the end of 2005. Antibiotic susceptibility testing, including for imipenem, was performed by agar disk diffusion test according to the recommendations from the French Society for Microbiology [19]. A disk synergy test between imipenem and EDTA was used to detect MBL production. The presence of the ESBL in MBL-producing strains was detected by a synergy test between ceftazidime or cefepime and clavulanic acid by adding 4 µl of 0.5 M EDTA pH 8 on the disk of clavulanic acid [17]. Polymerase chain reaction (PCR) and pulsed-field gel electrophoresis (PFGE) were used to type IR-Kp strains [17].

All IR-Kp strains shared closely related resistance patterns: a high level of resistance to beta-lactams including imipenem (minimum inhibitory concentration (MIC) ≥ 32 mg/L), aminoglycosides (except gentamicin), fluoroquinolones and co-trimoxazole; a low level of resistance to gentamicin (MIC=8 mg/L) and susceptibility to colistin [17]. All strains carried the *bla_{VIM}* and *bla_{SHV-5}* genes. The isolates from our eight patients had the same restriction pattern, identical to the strain K5 reported in teaching hospitals in Greece [8,17]. The outbreak was consequently ascribed to the spread of a single strain. This strain has not been isolated in our hospital again since the last case of this outbreak was discharged.

Epidemiological analysis

Rates of IR-Kp infection or colonisation were calculated for all patients admitted between December 2003 (month of the first case) and June 2004 (month of the last case). Rates were calculated separately for those cases who had a liver transplantation and those who

stayed in the intensive care unit. Fischer's exact test was used to compare categorical variables and $p < 0.05$ was considered significant.

Period 1

During Period 1, 325 patients stayed in the intensive care unit (237 of them stayed also in the acute care facility) and 375 further patients were admitted only to the acute care facility (total=700 patients). Five secondary IR-Kp cases (Cases 2 to 6) were detected: all had IR-Kp infections (two bacteraemias, one bronchopulmonary infection, two urinary tract infections) (Table 1). Analysis of the synoptic curve of the patients' charts suggested that three of them (Cases 4, 5 and 6) acquired the infection in the intensive care unit, and the two others (Cases 2 and 3) in the acute care facility on the fourth floor before surgery (Figure 1).

Based on the analysis of the stays of the index case and the above secondary cases, 324 of the 700 patients admitted during this period were retrospectively defined as contact patients and had been exposed to IR-Kp. Of those, 171 were screened during their stay in abdominal surgery care centre. The remaining 153 contact patients, discharged during Period 1, were not screened in the abdominal surgery care centre, predominantly due to the short duration of their stay, and were the target of the screening campaign organised in Period 2 (see below).

Period 2

During the screening campaign (26 July to 6 August 2004) 75 of the 153 contact patients who had not been screened in Period 1 called the helpline for information and 67 subsequently accepted to be screened (54 in our hospital and 13 in another facility). A further 37 patients did not call the helpline during this campaign but were screened after the helpline had been closed when visiting our hospital as outpatients. Overall, 104 of the 153 patients who were not screened during Period 1 were screened in Period 2. None of them were found to carry IR-Kp.

In addition, two secondary IR-Kp cases (Cases 7 and 8) were identified in June and August 2004 after the extended infection control measures. Case 7 was a contact patient who had stayed in the intensive care unit from 8 March to 3 June, at the same time as Cases 2, 3 and 4. After discharge, this patient visited the abdominal surgery care centre as an outpatient on 17 June. According to the measures in force at this time, this patient was screened and identified as a IR-Kp carrier. Case 8, who had stayed in the acute care facility for four days in January 2004, at the same time as the index case, was re-admitted on 28 July on the fourth floor in the 'contact acute care patients section' where all patients were IR-Kp-negative (Figure 1). This patient was screened and transferred to the 'IR-Kp patients section' after IR-Kp was detected in the rectal swab. Based on the synoptic curve (Figure 1), Cases 7 and 8

are most likely to have acquired IR-Kp during Period 1. They did not develop IR-Kp infection.

Attack rate

A total of 277 of the 324 contact patients (85%) were screened (Figure 2). The global attack rate of secondary IR-Kp cases ($n=7$) among the screened contact patients ($n=277$) was 2.5%.

The attack rate of secondary cases was significantly higher among patients with liver transplant (six of 45 patients; 13%) as compared to screened patients without liver transplant (one of 230 patients; 0.4%) ($p=0.0001$). Although all secondary cases stayed at least some days in the intensive care unit, the likely place of IR-Kp acquisition for three of them was the acute care facility. Which hospital unit the patient stayed in was not a risk factor for acquisition of IR-Kp, as the attack rate was 1.2% in patients staying in the intensive care unit (four of 325 patients) and 0.6% in other patients (three of 375 patients) ($p=0.4$).

Cost of the screening campaign

The estimated cost of the screening campaign organised in period two (personnel costs for two seniors physicians and one resident physician maintained on duty, telephone bills, mailing costs, sampling and cultures) was EUR 18,830, i.e. a mean of EUR 190 per screened patient. The annual cost of the routine weekly screening for ESBL- or carbapenemase-producing *Enterobacteriaceae* that has been maintained up to now for the entire abdominal surgery care centre (81 beds) is approximately EUR 60,000.

Discussion

The emergence and spread of carbapenem-resistant *Enterobacteriaceae* due to MBL is an increasing international health problem. In Europe, the proportion of *K. pneumoniae* strains resistant to imipenem (IR-Kp) that are isolated from blood cultures is far below 5% in most countries but had in the year 2007 already reached a rate of 22% in Israel and 42% in Greece. In France, the incidence is still very low (<0.1%) and the very few identified cases are in relation with patients transferred from foreign countries [20].

We describe here the epidemiological characteristics and control of the first outbreak of MBL-producing *K. pneumoniae* that occurred in France, after the admission of a patient transferred from a hospital in Greece, where these bacteria are common [8]. To our knowledge, it is the first report on the control of an IR-Kp outbreak in a country with a low rate of these bacteria.

The national measures for controlling cross-transmission of multidrug-resistant bacteria in hospital [18], designed mainly for methicillin-resistant *Staphylococcus aureus*, were implemented during the first six months of the outbreak (Period 1) but were insufficient to achieve control, as five secondary cases occurred during that period. After implementation of the extended infection control measures (Period 2), the only two secondary cases identified were in fact, the consequence

of acquisition during Period 1. The extended measures were mainly based on (i) separating IR-Kp patients, contact patients and new patients in distinct sections of the hospital, each with dedicated staff, in order to minimise cross-transmission, (ii) stopping transfer of IR-Kp patients to other units or hospitals to block the extension of the outbreak and (iii) careful identification, screening and follow up of the contact patients. The outbreak was most likely due to cross-transmission by the staff since all the patients in abdominal surgery care centre facility are placed in single bedrooms, particularly in intensive care unit. Successive attempts failed to detect the epidemic strain in environmental samples (data not shown).

The present study was not a randomised controlled trial assessing causality between intervention and outcome. Indeed, the rapid spread of IR-Kp in our hospital triggered rapid and strong action to control the outbreak, making a randomised intervention impossible. However, the fact that the strength and nature of the implemented measures differed markedly during Periods 1 and 2 as well as the length of the follow-up (six years) suggest a causal association between reinforced measures and the control of the outbreak. Causes other than the intervention (e.g. regression to the mean or maturation effect) could have been involved in the decrease in IR-Kp cases [21]. However, spontaneous cessation of IR-Kp outbreaks was not observed in Greece, Israel or the New York City area, where IR-Kp are endemic [8,22-24]. In one setting the incidence of endemic IR-Kp was partially reduced by implementing strict infection control measures comparable to our control programme, whereas contact isolation alone was unsuccessful [25]. Similar measures have also been implemented successfully to control the emergence of vancomycin-resistant enterococci (VRE) [26-28] and are now recommended for VRE outbreaks in France [29] and in the Netherlands [25]. These measures, proposed by the central infection control team of AP-HP, are more stringent than those proposed by the US Centers for Disease Control and Prevention [30].

We faced some difficulties in the implementation of reinforced infection control measures. Defining distinct sections in the hospital to separate IR-Kp carriers, contact patients and IR-Kp-free patients required a strong involvement of hospital managers and the support of the central infection control team of the AP-HP institution. Dedicating teams of nurses to each of these sections was a difficult challenge. Assigning the re-admitted contact patients to the adequate sections required careful examination of medical records. Reinforcing screening procedures increased the workload markedly and required a reorganisation of the laboratory. Maintaining the activity of liver transplantation was made possible by referring part of the patients who did not require transplantation to other care centres. Careful and clear information of patients and staff while avoiding stress and panic required psychological tact.

Although extended measures such as those applied in our setting are difficult to implement and maintain for a long period of time, we believe that they are adequate to control outbreaks of emerging multiresistant organisms, particularly in countries where the incidence is very low [25,31,32]. Recent recommendations advocate implementing similar measures for the sporadic occurrence of IR-Kp [29]. The speed and strength of the intervention is likely to be crucial in limiting the size and duration of IR-Kp outbreaks.

The present study also suggests that pre-emptive isolation of patients at risk of carrying multidrug-resistant strains (i.e. resistant to VIM, KPC, NDM-1), particularly patients transferred from countries where these organisms are endemic, could help to prevent outbreaks. This measure should be combined with a preparedness plan to facilitate urgent and rapid action whenever a first case is detected [31].

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