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Concise Communication

Management of carbapenemase-producing *Enterobacteriaceae* in a low incidence area: A six-year experience in a university hospital

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Abstract

We conducted a 6-year retrospective analysis of monitoring of carbapenemase-producing *Enterobacteriaceae* (CPE) in a large hospital in a low CPE incidence area, and we evaluated the "search and isolate" strategy implemented. In total, 40 CPE isolates were collected from 32 patients, and only 1.4% of contact patients screened were CPE carriers.

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Carbapenemase-producing *Enterobacteriaceae* (CPE) are an emerging cause of healthcare-associated infections that pose a significant global threat to public health. The possibility that carbapenemases spread worldwide, as extended-spectrum β-lactamases (ESBL) did, is a matter of major concern.[1] Regular reports of local epidemiology of CPE will contribute to the global understanding of their dissemination, necessary to control their spread. We report here an active surveillance study of CPE between 2012 and 2017 in a university hospital located in a low incidence area, We evaluated the efficiency of the implementation of strict 'search and isolate' measures.

Material and Methods

Infection control measures

We implemented active surveillance of CPE at the beginning of 2010 s in the 1,200 acute-care beds of University Hospital of Besançon (UHB). All the CPE isolated between January 2012 and December 2017 were considered. They came from either from clinical samples collected from inpatients with unknown CPE carriage on admission or from systematic screening of 'at risk' patients. 'At risk' patients were patients that had been (1) repatriated from a foreign hospital to UHB, (2) admitted within the year in a healthcare facility in areas with high incidence of CPE, (3) previously known as CPE carriers, or (4) cared for with CPE carrier (ie, contact patients).[2] Screening of the 2 first categories relied on data regarding medical prescription upon admission. The 2 last categories were automatically identified through the alert system within our admission database.

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'At risk' patients were systematically placed under strict contact precautions and were screened for CPE with rectal swab. In the medical records, positive patients were flagged as CPE carriers. When CPE carriage was detected during hospital stay, all patients cared for in close proximity to the CPE carrier were considered contact patients.[2] Contact patients discharged at the time of CPE-carrier identification remained registered, and an alert was generated in the case of rehospitalization. Hospitalized contact patients were systematically screened for CPE carriage and were placed under contact precautions. After the identification of a CPE carrier, the unit neither transferred patients to other wards or healthcare facilities nor admitted new patients until 3 negative screening tests of contact patients at days 0, 3, and 7. Only the intensive care and nephrology transplant units could admit and transfer patients after 1 negative CPE screening at day 0. Contact patients were screened weekly for CPE during the entire hospitalization of the CPE carrier. Finally, an additional screening was performed after the discharge of the CPE carrier and contact patients with negative screening tests were no longer considered 'at risk' patients. In any case, whenever possible, contact patients were discharged home. During the outbreak period (ie, 1 index case and at least 1 secondary case among the contact patients), we upgraded infection control measures, and the CPE patients were cared for by a dedicated staff.

Microbiology

Intrarectal swab sampling was performed by nurses. Swab samples with no feces were discarded and reiterated. Swabs were tested for CPE on ChromID CARBA SMART (Biomérieux, Marcy-l'Etoile, France) and bacterial cultures were identified using matrix-assisted laser desorption/ionization time-of-flight mass spectroscopy (MALDI-TOF MS, Microflex LT; Bruker Daltonik GmbH, Bremen, Germany). For clinical routine isolates, CPE was suspected when the antibiogram showed an inhibition zone around the ertapenem disk (10 µg) < 25 mm.[3] Carbapenemase production

Table 1. Characteristics of Carbapenemase-Producing *Enterobacteriaceae* Identified in the University Hospital of Besançon (France) Between 2012 and 2017

Patient No.	Mode of Acquisition	Species	Pulso-type	Carbapenemase	Day of First Detection	Specimen	Hospital Department
1	ND	*Cf*	CF-1	VIM-1	28/04/2012	Urine	Nephrology
2	ND	*Sm*	SM-1	OXA-48	25/10/2012	Deep hematomas	Surgery
3	HAFA	*Ecl*	ECL-1	VIM-2	06/12/2012	Respiratory tract	Pneumology
4	ND	*Ko*	KO-1	OXA-48	23/01/2013	Respiratory tract	ENT
5	CT	*Cf*	CF-2	OXA-48	29/01/2013	Rectal screening	ENT
5	...	*Ko*	KO-1	OXA-48	29/01/2013	Rectal screening	ENT
5	...	*Kp*	KP-1	OXA-48	29/01/2013	Rectal screening	ENT
6	CT	*Cf*	CF-3	OXA-48	12/02/2013	Rectal screening	ENT
4	...	*Cf*	CF-4	OXA-48	18/02/2013	Rectal screening	ENT
7	CT	*Cf*	CF-2	OXA-48	04/04/2013	Rectal screening	ENT
7	...	*Ec*	ECO-1	OXA-48	04/04/2013	Rectal screening	ENT
8	CT	*Cf*	CF-2	OXA-48	13/05/2013	Rectal screening	ENT
9	AFA	(*Kp*)	...	OXA-48	25/05/2013	Urine	Pediatrics
10	CT	*Cf*	CF-5	OXA-48	13/06/2013	Rectal screening	ENT
11	AFA	*Ec*	ECO-2	OXA-48	04/11/2013	Urine	Geriatric
12	ND	*Kp*	KP-2	OXA-48	04/11/2013	Respiratory	MICU
13	AFA	*Kp*	KP-3	OXA-48	20/11/2013	Urine	Nephrology
14	HAFA	*Kp*	KP-4	OXA-48	13/01/2014	Rectal screening	Pneumology
15	HAFA	*Kp*	KP-5	OXA-48	14/05/2014	Rectal screening	MICU
15	...	(*Ec*)	...	OXA-48	14/05/2014	Rectal screening	MICU
16	CT	*Cf*	CF-6	OXA-48	05/06/2014	Rectal screening	ENT
16	...	*Kp*	KP-6	OXA-48	05/06/2014	Rectal screening	ENT
17	HAFA	*Kp*	KP-7	OXA-48	22/09/2014	Rectal screening	Nephrology
18	CT	*Kp*	KP-1	OXA-48	20/01/2015	Rectal screening	ENT
2	...	*Ko*	KO-2	OXA-48	18/02/2016	Rectal screening	Emergencies
19	HAFA	*Kp*	KP-8	OXA-48	26/02/2016	Bone	Surgery
20	CT	*Kp*	KP-8	OXA-48	11/04/2016	Urine	Geriatric
21	AFA	*Ec*	ECO-3	OXA-48	06/05/2016	Urine	Nephrology
22	CT	*Cf*	CF-7	OXA-48	18/07/2016	Urine	Nephrology
22	...	*Ec*	ECO-4	OXA-48	22/07/2016	Rectal screening	Nephrology
23	AFA	*Ec*	ECO-5	OXA-48	08/12/2016	Placenta	Obstetric
24	CT	*Ec*	ECO-5	OXA-48	08/12/2016	Respiratory tract	Obstetric
25	ND	*Kp*	KP-9	OXA-48	07/01/2017	Peritoneal fluid	Visceral surgery
26	CT	*Kp*	KP-9	OXA-48	11/01/2017	Rectal screening	Visceral surgery
27	AFA	*Kp*	KP-10	OXA-48	22/02/2017	Respiratory tract	SICU
28	CT	*Kp*	KP-10	OXA-48	27/02/2017	Rectal screening	SICU
29	CT	*Kp*	KP-10	OXA-48	27/02/2017	Rectal screening	SICU
30	ND	*Cf*	CF-8	OXA-48	13/07/2017	Urine	Nephrology
31	CT	*Cf*	CF-8	OXA-48	25/07/2017	Rectal screening	Nephrology
32	ND	*Ecl*	ECL-2	OXA-48	13/12/2017	Blood	Internal medicine

Note. ND, not determined; CT, cross-transmission among contact patients; AFA, acquisition from travel abroad or close households contact with returning travelers from abroad; HAFA, hospital acquisition from abroad; *Cf*, *Citrobacter freundii*; *Sm*, *Serratia marcescens*; *Ecl*, *Enterobacter cloacae*; *Ko*, *Klebsiella oxytoca*; *Ec*, *Escherichia coli*; *Kp*, *Klebsiella pneumoniae*; ENT, ear, nose, and throat unit; MICU, medical intensive care unit; SICU, surgical intensive care unit. Isolates mentioned in parenthesis were not conserved, and some analyses could not be performed.

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was confirmed with immunochromatography tests RESIST-3 O.K.N. K-SeT (Coris BioConcept, Belgium) or with carbapenemase gene screening by PCR.[4] Pulsed-field gel electrophoresis (PFGE) was used to investigate isolate clonality.[5]

Results

Over the 6-year surveillance period, 32 CPE carriers were detected in the UHB (Table 1). The median age of CPE carriers was 68 years with a sex ratio of 1.13 (male to female). In total, 13 patients were treated for CPE infection, whereas 19 were colonized. The origin of the CPE acquisition was inferred for 25 of the 32 patients (Table 1). Among CPE carriers, a total of 154 rectal swabs have been performed (min, 1; max, 16 per patient).

During the study period, we performed 2,287 screening tests and identified 1,789 contact patients among whom 985 had been screened at least once and 533 had been screened negative 3 times. CPE carriers had an average of 66 contact patients (min, 21; max, 152), and 38 contact patients (min, 7; max, 73) were screened. Finally, we detected only 14 carriers among the 985 contact patients screened (1.4%).

We collected 40 nonduplicate CPE isolates. Most patients ($n = 25$) had only 1 CPE isolate, but 6 patients carried 2 CPE species and 1 patient carried 3 CPE species (Table 1). The most frequently recovered CPE species were *Klebsiella pneumoniae* (40%), *Citrobacter freundii* (27.5%), and *Escherichia coli* (17.5%). The vast majority of isolates (95%) harbored $bla_{\text{OXA-48}}$ (Table 1).

Among the 40 CPE isolates, 38 isolates were available for PFGE analysis (Table 1). Molecular typing identified 4 cases of cross transmission involving *K. pneumoniae* (KP-1, KP-8, KP-9, and KP-10). Two cases involved *C. freundii* (CF-2, CF-8), and 1 involved *K. oxytoca* (KO-1). Except for a case of mother-to-child transmission (ECO-5), there was no microbiological evidence of in-hospital CPE cross transmission due to *E. coli*.

Finally, 5 clusters with in-hospital cross transmission were inferred from epidemiological and PFGE data analysis: (1) 1 cluster involved 8 patients in the ear, nose, and throat (ENT) unit, (2) 1 cluster involved 3 patients in the surgical intensive care unit (SICU), and (3) 3 other clusters implicated 2 patients each. The CPE cluster in ENT lasted discontinuously for 2 years and mostly implicated unrelated clones of OXA-48–producing species. *Citrobacter freundii* was the most common species isolated from patients during the ENT outbreak; it was also isolated in U-bends of 2 rooms during the environmental investigations conducted in April and June 2013 (CF-2).

Discussion

We conducted active CPE surveillance in a low CPE incidence area. The 'search and isolate' strategy efficiently controlled the CPE dissemination within our hospital. Indeed, the high clonal diversity in all the CPE species suggests a limited number of cross transmissions. Despite numerous transfers and readmissions of CPE cases and contact patients, we identified only 1 CPE strain ($bla_{\text{OXA-48}}$ *K. pneumoniae* with pulsotype KP-8) present in 2 different wards (Table 1).

However, such a policy requires additional human and material resources.[6] CPE screening of all 'at risk' patients, notably contact patients, is expensive, and poorly efficient with lots of screening for little detection of CPE carriers (1.4% of all contact patients). This questions the strategy of systematic screening. An approach targeting patients who had a longer and/or a closer proximity with index case could be more cost-effective.

Unsurprisingly (ie, this carbapenemase is widely disseminated throughout Europe), OXA-48 is the most common carbapenemase in the UHB.[1,7] The cluster of cases in the ENT unit implicated different strains of 4 species producing OXA-48. It probably relied (1) on the high transmissibility of the plasmid carrying the gene bla_{OXA48}[8] but also (2) on the contamination of water point of use. Similar outbreaks involving contaminated U-bends have been reported elsewhere.[9]

In conclusion, the 'search and isolate' French policy regarding CPE in hospital has demonstrated its efficacy since most of the reported CPE episodes are sporadic. However, such infection control measures will be difficult to maintain if the proportion of CPE isolates continues to increase.

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