Outbreak of NDM-1-producing *Acinetobacter baumannii* in France, January to May 2013

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We report the first outbreak of carbapenem-resistant NDM-1-producing *Acinetobacter baumannii* in Europe, in a French intensive-care unit in January to May 2013. The index patient was transferred from Algeria and led to the infection/colonisation of five additional patients. Concurrently, another imported case from Algeria was identified. The seven isolates were genetically indistinguishable, belonging to ST85. The bla_{NDM-1} carbapenemase gene was part of the chromosomally located composite transposon Tn*125*. This report underscores the growing concern about the spread of NDM-1-producing *A. baumannii* in Europe.

Background

The emergence and spread of New-Delhi metallo-beta-lactamase (NDM)-producing Gram negative isolates constitutes a new wave of multidrug-resistant (MDR) bacteria [1]. First identified from *Enterobacteriaceae*, the bla_{NDM} gene has since been identified in non-fermenting bacterial species such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii* [2,3]. Considering its ability to be the source of nosocomial outbreaks, carbapenem-resistant *A. baumannii* (AB) represents a threat for critically ill hospitalised patients [4]. We report here the first outbreak of NDM-1-producing AB in Europe, which occurred in a French surgical intensive-care unit in January to May 2013.

Outbreak description

The index case (Patient 1) was a female patient in her early 80s suffering from end-stage cirrhosis. She originated from Algeria but lived mostly in France. During a stay in Algeria in December 2012, she was admitted into a private hospital in the city of Tizi Ouzou following renal failure, which required dialysis. After one month in hospital, she was repatriated to France due to liver decompensation. On 18 January 2013, she was admitted to a 15-bed surgical intensive-care unit of a tertiary care university hospital in a Paris suburb. In accordance with local and national policy, she was screened on admission for carriage of MDR bacteria. Rectal screening revealed MDR-*A. baumannii* (MDR-AB) (Isolate 1) that was susceptible only to amikacin, netilmicin and colistin (Table). The same day, she was intubated for respiratory failure. Protected distal bronchial brushing yielded a culture of MDR-AB with the same antibiotic resistance profile. A combination of intravenous tigecycline and amikacin was given. On 24 January, she developed multivisceral failure and died four days later. During the following days, three additional patients with MDR-AB infection and/or colonisation were identified in the same unit. A cirrhotic male patient in his mid-60s (Patient 2) – who had been hospitalised since 3 January 2013 and confirmed free of MDR bacteria on admission – developed a ventilator-associated pneumonia on 26 January. Culture of a distal protected specimen yielded MDR-AB (Isolate 2). This patient was successfully treated by a combination of tigecycline and amikacin and was extubated two days later. Patient 3 was a male liver-transplant patient in his mid-60s who was not colonised on admission but developed a dialysis catheter-related bloodstream infection due to a MDR-AB on 28 January (Isolate 3). Imipenem and amikacin combination was prescribed but the patient died of haemorrhagic shock before antibacterial susceptibility results could be obtained. Patient 4 was a dual renal- and liver-transplant female patient in her late 40s from whom an abdominal drain yielded an MDR-AB culture on 2 February (Isolate 4). This patient recovered without receiving any antibiotic therapy and was discharged from the hospital on 11 February.

Two weeks after the admission of the index case, a woman in her early 80s (Patient 5) suffered from a cerebrovascular accident and was repatriated from the

Table

Antimicrobial susceptibility of carbapenem-resistant NDM-1-producing *Acinetobacter baumannii* isolates, France, January–May 2013 (n=7)

Antibiotic	Isolates MIC [µg/mL] (S/I/R[a])[b]						
	1	2	3	4	5	6	7
Ampicillin-sulbactam	16	24	16	24	24	32	192
Ticarcillin-clavulanic acid	›256	›256	›256	›256	›256	›256	›256
Piperacillin	›256	›256	›256	›256	›256	›256	›256
Piperacillin-tazobactam	›256	›256	›256	›256	›256	›256	›256
Aztreonam	›256	›256	›256	›256	›256	›256	192
Ceftazidime	›256	›256	›256	›256	›256	›256	›256
Cefepime	›256	›256	›256	›256	›256	›256	›256
Meropenem	›32 (R)	›32 (R)	›32 (R)	›32 (R)	›32 (R)	›32 (R)	›32 (R)
Imipenem	›32 (R)	›32 (R)	›32 (R)	›32 (R)	›32 (R)	›32 (R)	›32 (R)
Imipenem/ imipenem + EDTA ratio[b]	96	96	64	128	96	64	128
Doripenem	›32 (R)	›32 (R)	›32 (R	›32 (R)	›32 (R)	›32 (R)	›32 (R)
Ciprofloxacin	›32 (R)	›32 (R)	›32 (R)	›32 (R)	›32 (R)	›32 (R)	›32 (R)
Gentamicin	32 (R)	24 (R)	24 (R)	32 (R)	24 (R)	32 (R)	64 (R)
Amikacin	8 (S)	12 (I)	8 (S)	8 (S)	8 (S)	8 (S)	64 (R)
Tobramycin	24 (R)	32 (R)	24 (R)	24 (R)	24 (R)	32 (R)	64 (R)
Netilmicin	0.75 (S)	1.5 (S)	0.5 (S)	0.75 (S)	0.75 (S)	0.75 (S)	1 (S)
Tetracycline	4	2	2	2	2	2	2
Tigecycline	0.75	1	1	1	1	0.25	0.38
Colistin	0.125 (S)	0.19 (S)	0.38 (S)	0.25 (S)	0.38 (S)	0.25 (S)	0.38 (S)
Trimethoprim-sulfamethoxazole	›32 (R)	›32 (R)	›32 (R)	›32 (R)	›32 (R)	›32 (R)	›32 (R)
Fosfomycin	256	384	384	192	256	256	192
Rifampicin	6	6	6	6	6	32	8

MIC: mimimum inhibitory concentration; NDM: New-Delhi metallo-beta-lactamase.

[a] Susceptible/Intermediary Resistant/Resistant categories from the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines [5], if determined.

[b] Except for the imipenem/imipenem + EDTA ratio. The ratio was considered significant if ›4.

same Algerian county that Patient 1 was repatriated from (but from a different healthcare facility) to the emergency unit of our hospital. A screening test performed on admission identified MDR-AB (Isolate 5).

Two months after this first cluster of five patients with MDR-AB, two additional patients free of MDR bacteria on admission to the surgical intensive-care unit described acquired a MDR-AB during their stay in this unit. A woman in her late 50s (Patient 6) was admitted to the surgical intensive-care unit on 6 April and placed in the room where the index case had stayed. This patient was found positive for MDR-AB on 15 April in specimens from a catheter and the respiratory tract (Isolate 6). She was treated with intravenous tigecycline and aerosolised colistin. She underwent successful liver transplantation on 22 April and recovered well. The last patient (Patient 7) was a man in his late 50s admitted to the surgical intensive-care unit on 3 April for a liver transplant and from whom a rectal swab yielded MDR-AB a month later (Isolate 7). The patients' duration of hospital stay, time of infection and/or colonisation and location in the hospital are reported in Figure 1.

Laboratory analysis

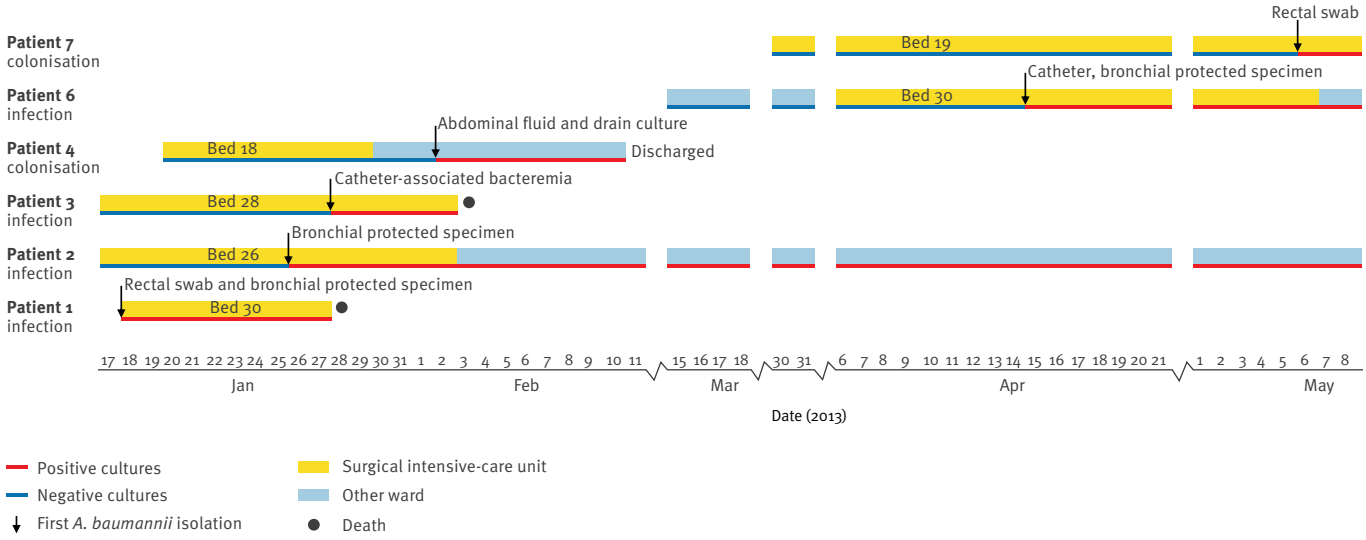
Identification of the seven MDR-AB strains at the species level was confirmed by 16S RNA sequencing (data not shown). Their antimicrobial susceptibilities were tested by minimum inhibitory concentration (MIC) determination (Etest, bioMérieux, France) (Table) and interpreted according to EUCAST guidelines [5]. All isolates exhibited a high level of resistance to penicillins, broad-spectrum cephalosporins, carbapenems, fluoroquinolones and trimethoprim-sulfamethoxazole. Those isolates remained susceptible only to netilmicin, colistin and amikacin. The production of a class B carbapenemase was suspected by the positive results of the imipenem/imipenem plus EDTA test using MIC double strips (Etest, bioMérieux, France) (Table 1) and confirmed by UV spectrophotometry [6]. Carbapenemase genes were screened by PCR as described and the bla_{NDM-1} gene was amplified in the seven isolates [7]. Genotypic comparison by pulsed-field gel electrophoresis using restriction enzyme *Sma*I revealed an indistinguishable profile (data not shown). Diversilab (bioMérieux, France) analysis and multilocus sequence typing (MLST) typing confirmed that these isolates were clonally related and belonged to the same sequence type, ST85 (Figure 2) [8]. The genetic environment of bla_{NDM-1} was investigated as previously described [8] and showed that it was located in the composite transposon Tn*125* made of two copies of insertion sequence (IS) ISAba*125*.

Discussion

Carbapenem-resistant *A. baumannii* are a source of deep concern due to their multidrug resistance pattern and the ability of this bacterial species to persist in the environment [4,9,10]. Intensive-care units are particularly susceptible to outbreaks associated with

Figure 1

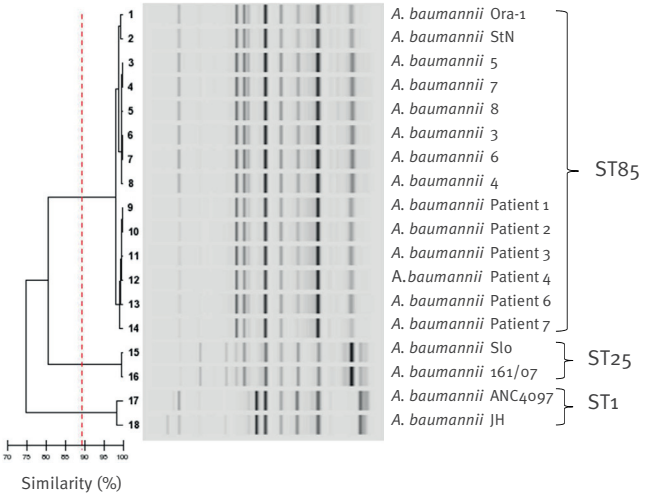
Timeline of patients infected/colonised with carbapenem-resistant NDM-1-producing *Acinetobacter baumannii* hospitalised in a surgical intensive-care unit, Créteil, France, January–May 2013 (n=6)



NDM: New-Delhi metallo-beta-lactamase.

Figure 2

Results of Diversilab and multilocus sequence typing analysis of isolates from patients infected/colonised with carbapenem-resistant NDM-1-producing *Acinetobacter baumannii* hospitalised in a surgical intensive-care unit, Créteil, France, January–May 2013 (n=6)



NDM: New-Delhi metallo-beta-lactamase.

The isolates from the hospitalised patients were compared with a collection of characterised strains [8,17]. A similarity line (89.4%) shows the cut-off to separate different clones.

MDR-AB: it is sometimes difficult for them to adhere strictly to infection control measures when patients require a high and persistent care-load. Four years ago, the same hospital faced a hospital-wide outbreak of MDR-AB colonisations and infections due to the importation of an index case from Tahiti [11]. Despite this experience and the implementation in 2010 at the national and local level of strict measures on hospital admission to detect, screen and place under contact-isolation precautions repatriated patients, another outbreak linked to the admission of a patient previously hospitalised abroad again occurred [12].

Since 2010, NDM-producing MDR-AB has been identified in various parts of the world, in particular in North Africa and the Middle East [8,13-17]. A series of imported cases have been identified recently in Europe, such as in the Czech Republic, Germany, Slovenia, Switzerland and Belgium [8,13,14,17]. In France, the emergence of an NDM-1-producing MDR-AB strain originating from North Africa was recently highlighted [15,17]. We describe here the first outbreak associated with the importation of this NDM-1-producing *A. baumannii* clone ST85 in Europe. This report underlines the need for dedicated measures for patients previously treated in a hospital located in a 'high risk' geographical area. Such measures (e.g. screening for colonisation/infection with MDR organisms and isolation nursing) should be maintained until the screening for colonisation/infection (e.g. using rectal, throat and wound swabs) has shown that these patients are free of MDR organisms. Because of intermittent carriage or lack of sensitivity of the current culture-based screening methods, repeated specimen collection and

molecular-based methods of detection may help to control such outbreaks.

Taking in account the relationship between North African countries and many European countries, it is possible that the spread of NDM-1 carbapenemase may occur rapidly, mostly through *A. baumannii* rather than Enterobacteriacae, since *A. baumannii* may become much more difficult to eradicate.

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Conflict of interest

None declared.

Authors' contributions

Jean-Winoc Decousser: laboratory work, manuscript preparation. Chloé Jansen: infection control, manuscript preparation. Aurélie Emirian: laboratory and clinical work. Rémy Bonnin: laboratory work. Leslie Anais: laboratory work. Jean-Claude Merle: clinical work. Patrice Nordmann: manuscript preparation, analysis of data. Laurent Poirel: manuscript preparation, analysis of data.

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