Carbapenemases in Enterobacteriaceae: 2012

Prof P. Nordmann
Bicêtre hospital, South-Paris Med School
Antibiotic resistance would make simple surgery too risky to attempt

WHO chief's stark warning about danger of resistance to antibiotics

Growing crisis' may 'turn common infections into untreatable disease

Calls for restrictions on use in animals to halt the spread of E.coli

WHO chief's stark warning about danger of resistance to antibiotics

Growing crisis' may 'turn common infections into untreatable disease

Calls for restrictions on use in animals to halt the spread of E.coli

continued from PAGE 1

Like hip replacements, organ transplants, cancer chemotherapy, and care of preterm infants, would become far more difficult or even too dangerous to undertake.'

Britain has seen a 20 per cent rise in cases of blood poisoning caused by E.coli bacteria between 2005 and 2009, from 18,000 to more than 25,000 cases. Those resistant to antibiotics have risen from 0.1 per cent at the beginning of the century to 19 per cent.

The most powerful antibiotics are carbapenems, which are used as a last line of defence for the treatment of resistant infections.

In 2009, carbapenem-resistant K. pneumoniae, a bugmenm in the gut, were first detected in Greece but by the following year had spread to Italy, Austria, Cyprus and Hungary.

The European Centre for Disease Control and Prevention reported that the percentage of carbapenem-resistant K. pneumoniae had doubled from 7 per cent to 13 per cent. An estimated 25,000 people die each year in the European Union from antibiotic-resistant bacterial infections.

In the UK, the Government pledged £500 million for research into the threat last month.

Dr Chan was speaking as the World Health Organisation launched The Evolving Threat of Antimicrobial Resistance: Options for Action, a book which warns that breakthrough treatments discovered in the last century for flu, tuberculosis, malaria and HIV may become ineffective in the coming years.

She called for measures to tackle the threat by doctors prescribing antibiotics appropriately, patients following their treatment and restrictions on the use of antibiotics in animals.

But she said attention was still sporadic' and actions 'inadequate'.

"At a time of multiple calamities in the world, we cannot allow the loss of essential medicinal, essential care for many millions of people, to become the next global crisis," she said.
Carbapenemase producing *Enterobacteriaceae*:
Here is the storm!
Defining a “Carbapenemase”

- Definition debated........
  - β-lactamases able to hydrolyse carbapenems; imipenem, meropenem, ertapenem....
  - Enzymes with imipenemase activity;
  - Most, but not all, hydrolyse many β-lactams - i.e. cephalosporins
  - Not all ‘carbapenemases’ confer clinically significant carbapenem resistance......
The carbapenemases in *Enterobacteriaceae*

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Penicillins</th>
<th>Cephalosporins 1st et 2\textsuperscript{nd} generation*</th>
<th>Cephalosporins 3\textsuperscript{rd}/4\textsuperscript{th} generation cefepime cefpirome</th>
<th>(\beta)-lactams/Inhibitors of (\beta)-lactamases</th>
<th>Carbapenems</th>
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<tbody>
<tr>
<td>Ambler class</td>
<td>Penicillinases: KPC, IMI, GES..</td>
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<td>A</td>
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<td>B</td>
<td>Metallo-enzymes: VIM, IMP, NDM-1</td>
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<tr>
<td>D</td>
<td>Oxacillinases = OXA-48, OXA-181</td>
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</tr>
</tbody>
</table>

* Cephamycins excluded for most class A

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* The carbapenemases in *Enterobacteriaceae* are enzymes that resist beta-lactam antibiotics. They are classified according to the Ambler class system, which includes Penicillinases, Metallo-enzymes, and Oxacillinases.

- **Penicillinases:** KPC, IMI, GES..
- **Metallo-enzymes:** VIM, IMP, NDM-1
- **Oxacillinases:** OXA-48, OXA-181

* Cephamycins are excluded for most class A enzymes.
Novel Carbapenem-Hydrolyzing β-Lactamase, KPC-1, from a Carbapenem-Resistant Strain of Klebsiella pneumoniae

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Received 19 September 2000; Returned for modification 21 November 2000; Accepted 23 January 2001
Rapid Spread of Carbapenem-Resistant Klebsiella pneumoniae in New York City

A New Threat to Our Antibiotic Armamentarium

Simona Bratu, MD; David Landman, MD; Robin Hsang, RN; Rene Recco, MD; Antonella Eramo, RN; Maqsood Alam, MD; John Quale, MD

Background: Carbapenem antibiotics are used to treat serious infections caused by extended-spectrum β-lactamase–carrying pathogens. Carbapenem resistance has been unusual in isolates of Klebsiella pneumoniae. In this study, the prevalence and molecular epidemiologic characteristics of carbapenem-resistant K pneumoniae are analyzed, and the experience involving 2 hospital outbreaks is described.

Methods: A citywide surveillance study was conducted in hospitals in Brooklyn. An observational study involving subsequent outbreaks at 2 hospitals was undertaken. Isolates were genetically fingerprinted by ribotyping and were examined for the presence of KPC-type carbapenem-hydrolyzing β-lactamases.

Results: Of 602 isolates of K pneumoniae collected during the citywide surveillance study, 43% had extended-spectrum β-lactamases. Of the extended-spectrum β-lactamase–producing isolates, 3.3% carried the carbapenem-hydrolyzing β-lactamase KPC-2. Several isolates were reported by the clinical microbiology laboratories as being susceptible to imipenem. Although all the isolates were resistant using agar diffusion methods, minimal inhibitory concentrations of imipenem were substantially lower for several isolates using standard broth microdilution tests and were highly dependent on the inoculum used. Two hospitals experienced the rapid spread of carbapenem-resistant isolates involving 31 14-day mortality for bacteremic patients isolates belonged to a single ribotype.

Conclusions: Carbapenem-resistant isolates are rapidly emerging in New York City strains that possess a carbapenemase has occurred in regional hospitals. Isolates are resistant to virtually all β-lactam antibiotics. Control of their spread is crucial. Broader systems used for susceptibility testing accurately identify all these isolates, thus enabling control efforts.

Arch Intern Med. 2005;165:1430-1435

Evolution of antimicrobial resistance among Pseudomonas aeruginosa, Acinetobacter baumannii and Klebsiella pneumoniae in Brooklyn, NY

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Received 16 February 2007; revised 22 March 2007; accepted 5 April 2007

Objectives: To document resistance patterns of three important nosocomial pathogens, Pseudomonas aeruginosa, Acinetobacter baumannii and Klebsiella pneumoniae, present in hospitals in Brooklyn, NY.

Methods: Susceptibility profiles of pathogens gathered during a surveillance study in 2006 were analyzed and compared with similar surveys performed in 1999 and 2001. MICs were determined according to CLSI standards, and selected isolates were screened by PCR for the presence of VIM, IMP and KPC β-lactamases.

Results: For P aeruginosa, susceptibility to most antimicrobials fell in 2001 and then reached a plateau. However, there was a progressive decrease in the number of patients with P aeruginosa during the three surveys. While the total number of isolates of A baumannii remained steady, there was a progressive decrease in susceptibility to most classes of antimicrobial agents, and approximately one-third had combined resistance to carbapenem, fluoroquinolones and aminoglycosides. There was a noticeable rise in the number of isolates of K pneumoniae over the surveillance periods, suggesting that this has become the predominant pathogen in many medical centers. Over one-third of K pneumoniae collected in 2006 carried the carbapenemase KPC, and 22% were resistant to all three classes of antimicrobial agents.

Conclusions: Hospitals in our region have been beset with antimicrobial-resistant Gram-negative bacteria. K pneumoniae has rapidly emerged as the most common multidrug-resistant pathogen. Improved therapeutic agents and methods of detection are needed to reduce transmission of these bacteria.
Rapid Spread of Carbapenem-Resistant Klebsiella pneumoniae in New York: A New Threat to Our Antibiotic Armamentarium

E. coli, et E. cloacae (Petrella, AAC, 2008)
### The carbapenemases in *Enterobacteriaceae*

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<tr>
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<tr>
<td></td>
<td>Metallo-enzymes: NDM-1, VIM, IMP</td>
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</tbody>
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* Cephamycins excluded for most class As
Combined Mechanisms of Resistance

ESBL (SHV-12) and metallo-ß-lactamase (IMP-4)  Poirel et al., Pathology, 2004, 36, 366-8
NDM-1
Characterization of a New Metallo-β-Lactamase Gene, bla\textsubscript{NDM-1}, and a Novel Erythromycin Esterase Gene Carried on a Unique Genetic Structure in \textit{Klebsiella pneumoniae} Sequence Type 14 from India

Dongeun Yong,\textsuperscript{1,2} Mark A. Toleman,\textsuperscript{2} Christian G. Giske,\textsuperscript{3} Hyun S. Cho,\textsuperscript{4} Kristina Sundman,\textsuperscript{5} Kyungwon Lee,\textsuperscript{1} and Timothy R. Walsh\textsuperscript{2*}

Yonsei University College of Medicine, Research Institute of Antimicrobial Resistance, Seoul, Republic of Korea\textsuperscript{1}; Department of Medical Microbiology, Cardiff University, Cardiff, United Kingdom\textsuperscript{2}; Clinical Microbiology, MTC—Karolinska Institute, Karolinska University Hospital, Stockholm, Sweden\textsuperscript{2}; Yonsei University College of Life Science and Biotechnology, Seoul, Republic of Korea\textsuperscript{4}; and Department of Clinical Microbiology, Örebro University Hospital, Örebro, Sweden\textsuperscript{5}
Spread of NDM-1 from India/Pakistan to the UK

MDR plasmids?

$bi_{NDM-1}$-positive bacterial clones?

Courtesy N. Woodford
# Multidrug resistance patterns of NDM-1 producers

<table>
<thead>
<tr>
<th></th>
<th>UK (n=37)</th>
<th></th>
<th>Chennai (n=44)</th>
<th></th>
<th>Haryana (n=26)</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>MIC&lt;sub&gt;50&lt;/sub&gt;: MIC&lt;sub&gt;90&lt;/sub&gt; (mg/L)</td>
<td>Proportion susceptible&lt;sup&gt;*&lt;/sup&gt;</td>
<td>MIC&lt;sub&gt;50&lt;/sub&gt;: MIC&lt;sub&gt;90&lt;/sub&gt; (mg/L)</td>
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<td>MIC&lt;sub&gt;50&lt;/sub&gt;: MIC&lt;sub&gt;90&lt;/sub&gt; (mg/L)</td>
<td>Proportion susceptible&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Imipenem</td>
<td>32: 128</td>
<td>0%</td>
<td>64: 128</td>
<td>0%</td>
<td>32: 128</td>
<td>0%</td>
</tr>
<tr>
<td>Meropenem</td>
<td>32: 32</td>
<td>3%</td>
<td>32: 32</td>
<td>3%</td>
<td>&gt;32: &gt;32</td>
<td>3%</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>&gt;64: &gt;64</td>
<td>0%</td>
<td>&gt;64: &gt;64</td>
<td>0%</td>
<td>&gt;64: &gt;64</td>
<td>0%</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>&gt;256: &gt;256</td>
<td>0%</td>
<td>&gt;256: &gt;256</td>
<td>0%</td>
<td>&gt;256: &gt;256</td>
<td>0%</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>&gt;256: &gt;256</td>
<td>0%</td>
<td>&gt;256: &gt;256</td>
<td>0%</td>
<td>&gt;256: &gt;256</td>
<td>0%</td>
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<tr>
<td>Ceftiraxone</td>
<td>&gt;64: &gt;64</td>
<td>0%</td>
<td>&gt;64: &gt;64</td>
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<td>&gt;64: &gt;64</td>
<td>0%</td>
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<tr>
<td>Aztreonam</td>
<td>&gt;64: &gt;64</td>
<td>11%</td>
<td>&gt;64: &gt;64</td>
<td>0%</td>
<td>&gt;64: &gt;64</td>
<td>8%</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>&gt;8: &gt;8</td>
<td>8%</td>
<td>&gt;8: &gt;8</td>
<td>8%</td>
<td>&gt;8: &gt;8</td>
<td>8%</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>&gt;32: &gt;32</td>
<td>3%</td>
<td>&gt;32: &gt;32</td>
<td>3%</td>
<td>&gt;32: &gt;32</td>
<td>3%</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>&gt;32: &gt;32</td>
<td>0%</td>
<td>&gt;32: &gt;32</td>
<td>0%</td>
<td>&gt;32: &gt;32</td>
<td>0%</td>
</tr>
<tr>
<td>Amikacin</td>
<td>&gt;64: &gt;64</td>
<td>0%</td>
<td>&gt;64: &gt;64</td>
<td>0%</td>
<td>&gt;64: &gt;64</td>
<td>0%</td>
</tr>
<tr>
<td>Minocycline</td>
<td>16: &gt;32</td>
<td>0%</td>
<td>32: &gt;32</td>
<td>0%</td>
<td>8: &gt;16</td>
<td>0%</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>1: 4</td>
<td>64%</td>
<td>4: 8</td>
<td>56%</td>
<td>1: 2</td>
<td>67%</td>
</tr>
<tr>
<td>Colistin</td>
<td>0.5: 8</td>
<td>89%†</td>
<td>1: 32</td>
<td>94%†</td>
<td>1: 2</td>
<td>100%†</td>
</tr>
</tbody>
</table>

**MIC** - minimum inhibitory concentration. <sup>*</sup>Susceptibility defined by British Society for Antimicrobial Chemotherapy and European Committee on Antimicrobial Susceptibility Testing breakpoints; doxycycline breakpoints were used for minocycline. <sup>†</sup>Colistin-resistant UK isolates were one isolate of *Morganella morganii* and one *Providencia* sp (both intrinsically-resistant species), also one *Klebsiella pneumoniae* and one *Enterobacter* sp.

**Table:** Antibiotic susceptibilities for NDM-1-positive Enterobacteriaceae isolated in the UK and north (Chennai) and south India (Haryana)
Resistance genes including:
- 9 β-lactamase genes including 3 carbapenemase gene and 1 ESBL gene
- 16S RNA methylase gene
- Rifampicin ribosylation gene
- Chloramphenicol acetylase
- Point mutation in gyrases

C. freundii NDM-1, France

Dissemination of NDM-1 positive bacteria in the New Delhi environment and its implications for human health: an environmental point prevalence study

Timothy R Walsh, Janis Weeks, David M Livermore, Mark A Tolser

Summary
Background Not all patients infected with NDM-1-positive bacteria have a history of hospital admission in India, and extended-spectrum β-lactamases are known to be circulating in the Indian community. We therefore measured the prevalence of the NDM-1 gene in drinking water and seepage samples in New Delhi.

Methods Swabs absorbing about 100 µL of seepage water (i.e., water pools in streets or rivulets) and 15 mL samples of public tap water were collected from sites within a 12 km radius of central New Delhi, with each site photographed and documented. Samples were transported to the UK and tested for the presence of the NDM-1 gene, blaNDM-1, by PCR and DNA probing. As a control group, 100 µL sewage effluent samples were taken from the Cardiff Wastewater Treatment Works, Tremorfa, Wales. Bacteria from all samples were recovered and examined for blaNDM-1 by PCR and sequencing. We identified NDM-1-positive isolates, undertook susceptibility testing, and, where appropriate, typed the isolates. We undertook Inc typing on blaNDM-1-positive plasmids. Transconjugants were created to assess plasmid transfer frequency and its relation to temperature.

Findings From Sept 26 to Oct 10, 2010, 171 seepage samples and 50 tap water samples from New Delhi and 70 sewage effluent samples from Cardiff Wastewater Treatment Works were collected. We detected blaNDM-1 in two of 50 drinking-water samples and 51 of 171 seepage samples from New Delhi; the gene was not found in any sample from Cardiff. Bacteria with blaNDM-1 were grown from 12 of 171 seepage samples and two of 50 water samples, and included 11 species in which NDM-1 has not previously been reported, including Shigella boydii and Vibrio cholerae. Carriage by enterobacteria, aeromonads, and V cholerae was stable, generally transmissible, and associated with resistance patterns typical for NDM-1; carriage by non-fermenters was unstable in many cases and not associated with typical resistance. 20 strains of bacteria were found in the samples, 12 of which carried blaNDM-1 on plasmids, which ranged in size from 140 to 400 kb. Isolates of Aeromonas caviae and V cholerae carried blaNDM-1 on chromosomes. Conjugative transfer was more common at 30°C than at 25°C or 37°C.

Interpretation The presence of NDM-1 β-lactamase-producing bacteria in environmental samples in New Delhi has important implications for people living in the city who are reliant on public water and sanitation facilities. International surveillance of resistance, incorporating environmental sampling as well as examination of clinical isolates, needs to be established as a priority.
Infections with NDM producers

E. coli, Klebsiella, Enterobacter, Serratia, Citrobacter, Pseudomonas, Acinetobacter

Asymptomatic colonisation
Wound infection / Diabetic foot
Lower urinary tract infection
Upper urinary tract infection
Nosocomial pneumonia / VAP
Intra-abdominal / pelvic infection
Bacteraemia / septicaemia
Neurosurgical meningitis
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- Bacteraemia / septicaemia
- Neurosurgical meningitis

- No difference between NDM and non-NDM producers
- No known virulence factors for NDM producers
- NDM producers will not respond to conventional antibiotics!!!
Escherichia coli

- 1st human bacterial pathogen
- 1st community-acquired pathogen
- 1st cause of urinary tract infections and diarrhea
A successful story

Hygiena

Diarrhea

Population: overcrowded

Antibiotics: misuse and overuse, over-the-counter sale

Spread of NDM-1 producers in *E. coli*, *K. pneumoniae*...

...and then higher mortality rate and length of hospitalization, overuse of broad-spectrum of antibiotics....
Retail sales of carbapenem antibiotics to treat Gram-negative bacteria are increasing rapidly in India and Pakistan.
World map according to land size
World map according to population size
World map according to diarrhea

Children deaths below 10 years old
Prevalence of faecal carriage of Enterobacteriaceae with NDM-1 carbapenemase at military hospitals in Pakistan, and evaluation of two chromogenic media


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Objective: To determine the prevalence and antimicrobial susceptibility of carbapenemase-producing Enterobacteriaceae among hospitalized patients and outpatients attending two military hospitals in Rawalpindi, Pakistan, and to compare the performance of two chromogenic culture media for the isolation of these organisms.

Methods: Stool samples from 200 distinct patients were cultured on MacConkey agar and subsequently on two chromogenic media—Colorex KPC and a prototype chromogenic medium, ID Carba—designed for the isolation of carbapenemase-producing Enterobacteriaceae. All Gram-negative isolates growing on either chromogenic medium were investigated for carbapenemases by phenotypic and molecular methods. Producers were subjected to susceptibility testing with 40 antimicrobials by VITEK 2 or agar dilution.

Results: In total, 64 NDM-1-positive isolates of Enterobacteriaceae, belonging to seven distinct species, were recovered from 37 (18.5%) of the stool samples. No other carbapenemase types were confirmed. Nineteen positive samples were identified among 120 from inpatients, giving a prevalence of 15.8%, and there were 45 positive samples among 130 from outpatients (prevalence 13.8%). Fifty-six isolates (87.5%) harbouring the NDM-1 enzyme were recovered on ID Carba compared with 41 isolates (64.1%) on Colorex KPC (P=0.012). Multidrug resistance was prevalent, but no pan-resistant isolates were found, with most isolates susceptible in vitro to colistin (97%), mecillinam (95%), fosfomycin (94%), tigecycline (89%) and nitrofurantoin (78%).

Conclusions: This study shows a high prevalence of multidrug-resistant Enterobacteriaceae with the NDM-1 enzyme in Rawalpindi. The new chromogenic medium, ID Carba, was more sensitive than Colorex KPC and has potential as a screening medium for isolation of Enterobacteriaceae harbouring the NDM-1 enzyme.

Keywords: β-lactamases, antimicrobial resistance mechanisms, Escherichia coli
J Antimicrob Chemother
doi:10.1093/jac/dkr580

No NDM-1 carriage in healthy persons from Mumbai: reassuring for now

Payal Deshpande, Viral Vadwai, Anjali Shetty, Reeta Dalal, Rajeev Soman and Camilla Rodrigues*

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Keywords: ESBLs, carbapenems, ertapenem
E. coli NDM-1: community-acquired!
in India

The plasmid-mediated bla<sub>NDM-1</sub> gene that encodes a powerful carbapenemase was first identified in Escherichia coli and in Klebsiella pneumoniae in Sweden from a patient who was transferred from India. It was then identified from many patients in the UK, India, and Pakistan in different enterobacterial species. Here we report a woman aged 60 years who was admitted to hospital in April 2009, for treatment of a breast cancer.

The patient came from Darjeeling, India, where she had lived for several years and had never been hospitalised. Upon her admission in France, bacterial cultures from the surface of her breast tumour were grown. The cultures were of the E coli isolate GUE that was resistant to most β-lactams (remaining susceptible to aztreonam) and that had reduced susceptibility to carbapenems (minimum inhibitory concentrations of imipenem 3 μg/mL, ertapenem 3 μg/mL, and meropenem 2 μg/mL). This isolate was also resistant to gentamicin, kanamycin, tobramycin, sulfonamides, tetracyclines, and fluoroquinolones, but remained susceptible to amikacin, chloramphenicol, rifampicin, and colistin. PCR and sequencing revealed that E coli GUE harboured the bla<sub>NDM-1</sub> gene. Mating-out assays allowed the bla<sub>NDM-1</sub> gene to be identified on a 110 kb plasmid, with markers for kanamycin, gentamicin, tobramycin, trimethoprim, and sulfonamide resistance. Multilocus sequence typing identified E coli GUE as an ST133-type strain, which corresponds to a genetic background that is also responsible for the worldwide diffusion of another common resistance determinant, CTX-M-15.

This case is the first identification of an NDM-1-producing E coli isolate in France, and corresponds again to an imported case from India. This example confirms the recent data suggesting that the Indian subcontinent might represent an important reservoir, and therefore a source, of NDM-producing isolates. The patient had not been hospitalised in India; therefore, the multiresistant resistant isolate had likely been community acquired. Worryingly, this resistance gene has been identified here in an E coli strain belonging to a genotype that has proved its ability to disseminate widely in the community.

We declare that we have no conflicts of interest. This study was mostly funded by the INSERM (U914), France, and by grants from the Ministère de l’Éducation Nationale et de la Recherche (UPRES EA 3539), Université ParisXI, France, and from the European Community (TSUPOtest-QC, HEALTH 2009-241742).

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www.the lancet.com/infection Vol 10 December 2010
Correspondence

Emergence of an Autochthonous and Community-Acquired NDM-1-Producing Klebsiella pneumoniae in Europe

To the Editor—The recently identified carbapenemase New Delhi metallo-beta-lactamase (NDM-1) inactivates all beta-lactams except aztreonam [1]. The corresponding gene that is usually plasmid-borne has spread mostly in Escherichia coli and Klebsiella pneumoniae [1, 2]. NDM-1 producers are multidrug resistant or even resistant to all antibiotics [1, 2]. Whereas contamination with NDM-1 producers is mostly hospital associated, rare cases of community acquisition are known and have been traced to the Indian subcontinent [2].

Here, we report a woman aged 83 years who had cystitis due to a multidrug-resistant K. pneumoniae in June 2011. She had a history of multiple and recurrent episodes of urinary tract infections caused by diverse Enterobacteriaceae that were always treated with narrow-spectrum antibiotics. Because the patient's symptoms tended to disappear spontaneously and rapidly, the latest cystitis episode had not been treated.

K. pneumoniae EDU was resistant to all beta-lactams, including carbapenems, as detected with the Vitek-2 automated suspen-

Polymerase chain reaction, sequencing, and plasmid analysis, performed as described elsewhere [5], revealed that K. pneumoniae EDU harbored the blaNDM-1 carbapenemase gene and the blaCTX-M-15 extended-spectrum beta-lactamase gene, which were located on two different plasmids (both being approximately 150 kb in size). The isolate coexpressed the CMY-2 cephalosporinase gene, which was located on the blaNDM-1 plasmid. In addition, it possessed the qnrB gene encoding resistance to quinolones and the blaOXA-1 gene encoding a restricted-spectrum oxacillinase, both genes being located on the blaNDM-1 plasmid. Both plasmids were self-transferable by conjugation, and the blaNDM-1 plasmid was found to be of the IncA/C broad-host range type [6]. Multilocus sequence typing [7] results showed that K. pneumoniae EDU belonged to the sequence type 1, whereas previously reported NDM-1-positive K. pneumoniae isolates were of other sequence types (eg, ST14 and ST147) [6].

Neither this patient nor her husband had traveled to any country in the previous 3 years, including countries with a high prevalence of NDM-1 producers (India, Pakistan, Bangladesh, United Kingdom, Balkan states, and Middle Eastern nations) of NDM-1 producers outside its main reservoir (Indian subcontinent). The source of contamination remains unknown but may be difficult to find, because persistence of NDM-1 producers in human flora has been evidenced to be >1 year [9].

This present report may indicate the ongoing spread of NDM producers in the community worldwide. A nightmare perspective could be its spread similar to that reported for extended-spectrum beta-lactamases of the CTX-M-type, which are now uncontrolled.

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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## The carbapenemases in *Enterobacteriaceae*

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Penicillins</th>
<th>Cephalosporins 1st et 2nd generation</th>
<th>Cephalosporins 3rd/4th generation</th>
<th>β-lactams/Inhibitors of β-lactamases</th>
<th>Carbapenems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambler class</td>
<td>Penicillinases: KPC, IMI, GES..</td>
<td>Metallo-enzymes: VIM, IMP, NDM-1</td>
<td>Cefepime</td>
<td></td>
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<tr>
<td>A</td>
<td></td>
<td></td>
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<td>Penicillins</td>
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<td>B</td>
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<td>Cephalosporins 3rd/4th generation</td>
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<td>Carbapenems</td>
</tr>
</tbody>
</table>

*Oxacillinases = OXA-48, OXA-181*  
*Cephemycins excluded for most class As*
Emergence of oxacillinase-mediated resistance to Imipenem in Klebsiella pneumoniae
Poirel L, Héririer, Nordmann P. Tolün, AAC 2004
OXA-48 + CTX-M-15
Single OXA-48-like-producing isolates

Outbreaks of OXA-48-like-producing isolates

Nationwide distribution of OXA-48-like-producing isolates
Single OXA-48-like-producing isolates
Outbreaks of OXA-48-like-producing isolates
Nationwide distribution of OXA-48-like-producing isolates

An unique ca. 62 kb OXA-48 plasmid
European dissemination of a single OXA-48-producing *Klebsiella pneumoniae* clone

A. Potron¹, J. Kalpoe², L. Poirel¹ and P. Nordmann¹

¹) Service de Bactériologie-Virologie, INSERM U914 «Emerging Resistance to Antibiotics», Hôpital de Bicêtre, Assistance Publique/Hôpitaux de Paris, Faculté de Médecine et Université Paris-Sud, K. Bicêtre, Department of Medical Microbiology and Infection Prevention, Hospital, Amsterdam, the Netherlands

Outbreak of OXA-48-Positive Carbapenem-Resistant *Klebsiella pneumoniae* Isolates in France

Gaelle Cuzon¹, Jocelyne Ouahchich², Henny Gondret², Thierry Naas³, and Patrice Nordmann¹

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Received 20 October 2010; revised for publication 2 January 2011; accepted 15 February 2011

Seventeen *Klebsiella pneumoniae* isolates producing the OXA-48 carbapenemase, obtained from 10 patients hospitalized from April to June 2010, mostly in the medical intensive care unit of the Villeneuve-Saint-Georges Hospital in a suburb of Paris, France, were analysed. Seven patients were infected, of whom five were treated at least with a carbapenem, and the patients died. Molecular analysis showed that the isolates belonged to a single clone that harbored a 764-bp plasmid carrying the *blaOXA-48* gene and coproduced CTX-M-15 and TEM-1 β-lactamases. This is the first reported outbreak of OXA-48-producing *K. pneumoniae* isolates in France.
Letter to the Editor

Occurrence of the Carbapenem-Hydrolyzing β-Lactamase Gene bla\textsubscript{OXA-48} in the Environment in Morocco

Anais Potron
Laurent Poirot
Florence Bussy
Patrice Nordmann*

Service de Bactériologie-Virologie
INSERM U914, Emerging Resistance to Antibiotics
Hôpital de Bicêtre
Carbapenemases - Enterobactericeae reservoirs
Spread of carbapenemase producers in *Enterobacteriaceae* in Europe

- **Endemic**
- **Interregional spread**
- **Regional spread**
- **Independent hospital outbreaks**
- **Single hospital outbreaks**
- **Sporadic occurrence**
- **Not reported / no data**

*Canton R et al. CMI in press*
Non-susceptibility rates of *Klebsiella pneumoniae* in Europe - 2010

Canton R et al. CMI in press
Case number (single case + outbreaks) of carbapenemases reported in France since 2004

Source: InVS, Raisin

152 épisodes au total
Carbapenemase producers according to carbapenemase type and origin - France

<table>
<thead>
<tr>
<th>Pays</th>
<th>OXA-48</th>
<th>KPC</th>
<th>NDM</th>
<th>VIM</th>
<th>OXA-181</th>
<th>Total</th>
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<tr>
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<td>1 (2011)</td>
<td>9 (2010)</td>
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<td>10a</td>
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<td>Lybie</td>
<td>5 (2011)</td>
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<td>Tunisie</td>
<td>5 (2011)</td>
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<tr>
<td>Turquie</td>
<td>4 (2010)</td>
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<td>Sénégal</td>
<td>3 (2011)</td>
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<td>Koweit</td>
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<td>Israël</td>
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<td>Serbie</td>
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<td>États-Unis</td>
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<td>Espagne</td>
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<td>Afrique du Nord</td>
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<td>Ile Maurice</td>
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<td>Cameroun</td>
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</tbody>
</table>
Transfer of OXA-48-like producers to France
A nightmare?
However...

- Carbapenem non-susceptible isolates do not necessarily produce carbapenemases.

  ⇒ ESBL production + permeability defects may lead to resistance, in particular to ertapenem.

  ⇒ AmpC production + permeability defects may lead to resistance, including to imipenem.
ESBL + decreased outer membrane permeability

Ertapenem Resistance of *Escherichia coli*

Marie-Frédérique Lartigue,* Laurent Poirel,* Claire Poyart,† Hélène Réglier-Poupet,† and Patrice Nordmann*

Emerging Infectious Diseases • www.cdc.gov/ eid • Vol. 13, No. 2, February 2007

An ertapenem-resistant *Escherichia coli* isolate was recovered from peritoneal fluid in a patient who had been treated with imipenem/cilastatin for 10 days. Ertapenem resistance may be explained by a defect in the outer membrane protein and production of extended-spectrum β-lactamase CTX-M-2.
Conclusion

- Increase prevalence of carbapenemase producers worldwide

- Carbapenemase producers; multiplicity of clones and of genetic vectors

- Spread of carbapenemase producers (NDM, OXA-48) in the community (++) E. coli) is an important source of concern

- Difficult detection; a need for rapid identification techniques

- Multidrug resistance and pandrug resistance: reversion of multidrug resistance in Gram negatives is rare
Antibiotics in the pipeline

Number of compounds

Focus of activity

Gram-pos. old
Gram-pos. novel
Staph. only
Gram-neg. old
Gram-neg. novel
Pseud. only

Our medical duty in 2012; preventing the SPREAD of carbapenemase producers in *Enterobacteriaceae*
Carriage detection

Hospitalized patients abroad

[Diagrams of hospitals, airplanes, and world map]
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Direction générale de l'offre de soins
Sous-direction de la qualité et du fonctionnement des établissements de santé

Le directeur général de la santé

La directrice générale de l'offre de soins

à

Mesdames et Messieurs les directeurs généraux des agences régionales de santé
(pour attribution)

Mesdames et Messieurs les directeurs des établissements de santé
(pour attribution)

Mesdames et Messieurs les directeurs des laboratoires de microbiologie
(pour attribution)

CIRCULAIRE N° DGS/RI/DGOS/PF/2010/413 du 6 décembre 2010 relative à la mise en œuvre de mesure de contrôles des cas importés d’entéro-bactéries productrices de carbapénémases (EPC)

Date d’application : immédiate
NOR : ETSP1031198C
Grille de classement :
Validée par le CNF le 3 décembre 2010 - Visa CNP 2010-284

Résumé : Contrôle des cas importés d’EPC.

Mots-clés : prévention, bactéries multi résistantes


Textes abrogés : Aucun
Detection of carbapenemase producers as colonizers of the intestinal flora

1. CHROMagar KPC (carbapenemase producers) contains a carbapenem

2. ESBL ID bioMérieux (Carbapenemase and ESBL producers) contains a cephalosporin

3. Oxoid Brillance CRE agar (Thermo Fisher) contains a carbapenem
A novel screening medium
(SUPER CARBA medium)

Combines many advantages

• Excellent sensitivity
  • for OXA-48 producers thanks to a low concentration of the carbapenem
  • for MBL producers (especially NDM) thanks to the addition of zinc ions

• Excellent specificity
  • supplemented with a carbapenem, not a cephalosporin (no growth of an ESBL+ and carbapenem susceptible strain)
  • supplemented with cloxacillin (no growth of an AmpC-mediated carbapenem non-susceptible strain)

Carbapenem-resistance; *K. pneumoniae*: Europe, 2009
Le destin exemplaire de FLEMING (1881-1955)

Fils de modestes fermiers écossais, Victor FLEMING doit quitter sa famille pour gagner sa vie. Mais il se sent attiré vers la science et veut s'y consacrer.

En 1928, il remarque qu'autour de moisissures sur une de ses cultures, les microbes se décomposent et meurent.

Sir FLEMING est reçu à l'Académie de Médecine. Il fait entendre la parole de PASTEUR. "La chance favorise les intelligences qui sont prêtes."

L'étude de ce phénomène conduit FLEMING à la découverte de la Pénicilline qui sauvera d'innumérables malades et blessés.

La fabrication de la Pénicilline se développe alors dans tous les pays. La plupart des maladies infectieuses sont vaincues.

Ce grand savant était sobre. C'est pourquoi il a pu mettre au service de la science la grande clarté de son esprit.

TOI AUSSI, TU SERAS SOBRE!