Case Report

Detection of an Ambler class D OXA-48-type β -lactamase in a *Klebsiella pneumoniae* strain in The Netherlands

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Traditionally, bacteria in The Netherlands have low levels of resistance to antibiotics. This report describes what is believed to be the first carbapenem-resistant *Klebsiella pneumoniae* producing an OXA-48 type β -lactamase in The Netherlands. The isolate co-produced a CTX-M-15 type β -lactamase and was recovered from a patient who was transferred from a hospital in India to an intensive care unit in The Netherlands. His recovery in The Netherlands was complicated by pneumonia due to the carbapenem-resistant *K. pneumoniae* to which he eventually succumbed. Pre-emptive screening for carbapenem-resistant *Enterobacteriaceae* in selected patients could be imperative to maintain the low prevalence of these highly resistant bacteria in Dutch hospitals.

Introduction

Carbapenems are the drugs of last resort, especially for infection with extended-spectrum β -lactamase-producing *Enterobacteriaceae*, which are often resistant to fluoroquinolones, aminoglycosides, trimethoprim–sulfamethoxazole (co-trimoxazole) and other antibiotics. The emergence and ongoing global dissemination of carbapenem-resistant *Enterobacteriaceae* impose a significant threat to health-care facilities. Carbapenem resistance in *Enterobacteriaceae* may be caused by the combined mechanisms of an outer-membrane permeability defect and extended-spectrum β -lactamases or hyperproduction of AmpC and upregulation of efflux systems (Bradford *et al.*, 1997), but is mostly due to the production of carbapenem-hydrolysing β -lactamases (carbapenemases) (Poirel *et al.*, 2007). Carbapenemases can be metallo- β -lactamases (Ambler class B), *Klebsiella pneumoniae* carbapenemases or KPC (Ambler class A), or more rarely carbapenem-hydrolysing oxacillinases of the OXA-48-type (Ambler class D) (Poirel *et al.*, 2007). The carbapenem-hydrolysing class D β -lactamase OXA-48 was first identified in a *K. pneumoniae* isolate from Turkey (Poirel *et al.*, 2004). Since then, several other OXA-48-producing isolates of various enterobacterial species (*Citrobacter freundii* and *Escherichia coli*) have been reported, mainly from Turkey but also from other countries, including

Belgium (Cuzon *et al.*, 2008a), the UK (Livermore, 2009) and India (Bell *et al.*, 2009). Here we describe a case of what is believed to be the first carbapenem resistant OXA-48-type producing *K. pneumoniae* isolate from The Netherlands.

Case report

In March 2010, a 63-year-old Dutch man was transferred from a hospital in New Delhi, India, to an intensive care unit (ICU) in Amsterdam, The Netherlands. During his vacation in New Delhi, he was admitted to a local ICU after surgical intervention to resolve a tension pneumothorax. Upon arrival in Amsterdam, surveillance cultures were performed to screen for multi-resistant bacteria and contact precautions were installed. The first surveillance culture of sputum showed a *K. pneumoniae* isolate resistant to broad-spectrum cephalosporins, meropenem, ertapenem and imipenem as determined by the Vitek-2 system (bioMérieux), the Phoenix microbiology system (Becton Dickinson) and Etest (AB Biodisk) according to European Committee on Antimicrobial Susceptibility Testing criteria. In addition the isolate was also resistant to fluoroquinolones, co-trimoxazole, tobramycin and gentamicin, and remained susceptible only to tigecycline and colistin (Table 1). Since the patient showed no signs of infection, antibiotic treatment was not initiated at this time. Surveillance cultures were continued biweekly and the multi-resistant *K. pneumoniae* was repeatedly recovered from respiratory surveillance cultures.

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Abbreviation: ICU, intensive care unit.

Table 1. MICs of antibiotics for *K. pneumoniae* (AMS-1)

Antibiotic	Susceptibility	MIC ($\mu\text{g ml}^{-1}$)
Amoxicillin	R	>32
Amoxicillin + clavulanic acid	R	>32
Cefuroxime	R	>64
Ceftriaxone	R	>64
Ceftazidime	R	>64
Gentamicin	R	>16
Tobramycin	R	>16
Meropenem	R	>16
Imipenem	R	8
Ertapenem	R	>16
Ciprofloxacin	R	>4
Co-trimoxazole	R	>320
Colistin	S	1
Tigecycline	S	1

R, Resistant; S, susceptible.

PCR and sequence analysis with primers for detection of Ambler class D and class B, and class A β -lactamase-encoding genes (Cuzon *et al.*, 2008b), identified an OXA-48-type β -lactamase together with the *bla*_{CTX-M-15} genes. Sequencing identified a variant of the class D carbapenemase OXA-48 (differing by 4 amino acid substitutions) that corresponds to the carbapenemase OXA-181. The latter enzyme was recently identified from Indian isolates (Castanheira *et al.*, 2011; Poirel *et al.*, 2011). Four weeks after his transfer from New Delhi, the patient developed pneumonia, with surveillance cultures as well as diagnostic sputum cultures positive for the OXA-48-producing *Klebsiella*, upon which simultaneous treatment with intravenous tigecycline (starting dose 100 mg, followed by 50 mg twice daily) and intravenous colistin (160 mg three times daily) was started. The infection was soon resolved and the patient was moved to the pulmonary ward where he repeatedly developed pulmonary distress, presumably sustained by the multi-resistant *Klebsiella* to which he eventually succumbed, 40 days after his admission to the ICU. No other patients with carbapenem-resistant *Enterobacteriaceae* were identified in the hospital at the time of his admittance and during the case. Carbapenemases of the OXA-48 type have been described in patients in India (Bell *et al.*, 2009). This is believed to be the first evidence of an OXA-48-type β -lactamase-producing *Enterobacteriaceae* in The Netherlands, in a patient transferred from an Indian ICU to Amsterdam.

Conclusion

Traditionally, The Netherlands has low levels of bacterial resistance to antibiotics and no major outbreaks with carbapenemase-producing *Enterobacteriaceae* have been reported yet. Therefore, it is of great relevance to maximize efforts to prevent or slow down the dissemination of carbapenemase-producing bacteria in Dutch hospitals, when the presumed prevalence of such bacteria is still among the lowest in Europe. Pre-emptive screening for carbapenem-resistant *Enterobacteriaceae* in patients transferred from high incidence areas or from any foreign hospital could be imperative to maintain this low prevalence.

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