

National Resistance Alert 3 **ADDENDUM**

Carbapenemase-producing Enterobacteriaceae in the UK: NDM (New Delhi Metallo- β -lactamase: repeated importation from Indian subcontinent

- Numbers of carbapenemase-producing Enterobacteriaceae referred to ARMRL continue to increase sharply
- Many recently referred carbapenemase producers have NDM (New Delhi Metallo)- β -lactamase
- Many patients with NDM-1 positive isolates have recent medical contact in India or Pakistan, where the enzyme is accumulating swiftly, probably via efficient plasmid transfer
- Patterns of human travel and migration mean that repeated future challenge of the UK healthcare system by producers of NDM-1 enzyme is to be expected
- Most producers are resistant to ALL antibiotics except polymyxins and tigecycline and may pose a serious treatment challenge in severe infections
- Vigilance and good infection control are essential to minimise transmission and accumulation in the UK

Background

In January 2009 we issued a National Resistance Alert concerning carbapenemases in UK Enterobacteriaceae. This followed consultation with ARHAI and stressed: (i) the growing number of producer isolates referred to the HPA's Antibiotic Resistance Monitoring & Reference Laboratory (ARMRL) (8 in all years to 2007; ultimately 21 in 2008); (ii) the diversity of these, variously with metallo (VIM or IMP), KPC and OXA-48 enzymes and (iii) that many producer isolates were from patients previously hospitalised in Greece, Turkey and Israel.

This addendum is issued: (i) because the number of referred producers continues to increase sharply (>40 so far in 2009) and (ii) because a novel enzyme, NDM-1 (New Delhi Metallo β -Lactamase) is increasingly dominant. NDM-1 is strongly linked to India and Pakistan and many of the UK cases have recent medical exposure in the Indian-subcontinent. Recognition of risk patients and prevention of transmission in the UK is critical, since most producers are resistant to ALL reliable antibiotics.

Basis for alert

During 2008 ARMRL investigated 17 referred Enterobacteriaceae with known carbapenemases, as detailed in National Resistance Alert 3. We also received 4 isolates that had a metallo-carbapenemase phenotype (i.e. strong EDTA/imipenem synergy), but lacked known carbapenemase genes. We have since identified their enzyme as NDM-1, a type first described in 2008 in a patient transferred from India to Sweden: he had an infection with NDM-1⁺ *K. pneumoniae*, and gut carriage of *E. coli* with the enzyme. Up to 20/6/2009 we received 17 further producers. The total of 21 UK producers comprise *K. pneumoniae* (14), *E. coli* (4), *Enterobacter* spp., (1) and *C. freundii* (2), from 18 patients and 16 hospitals scattered across England, with one in Scotland. NDM-1 has become the most frequent carbapenemase in isolates referred to ARMRL, and the most widely scattered. Even when producers belong to the same species they are diverse in strain type with only one possible transmission, involving two patients.

Case follow-up is ongoing but, strikingly, 12/18 patients have names linked to the Indian subcontinent and at least 8 have had medical contact in India or Pakistan. They include one patient dividing treatment for haematological malignancy between India and the UK and another who developed a wound infection following cosmetic surgery in India. Denominators are weak, but surveys co-ordinated by Prof Walsh at the University of Cardiff, Wales suggest that NDM-1 is widely distributed in India and one of ARMRL's collaborators has found producer *E. coli* in Karachi, Pakistan. Work by Prof Walsh's group suggests promiscuous plasmid transfer as a mode of dissemination, and the diversity of producers referred to ARMRL supports this.

Allowing patterns of human travel and migration, and the many UK residents who receive medical treatment in India, we believe that UK healthcare will be repeatedly challenged by imported producers. These organisms mostly are resistant to ALL antibiotics except polymyxins and, less consistently, tigecycline. The activity of obscure agents (fosfomycin, arbekacin and isepamicin) and novel compounds is under investigation, but none is readily available for therapy. In these circumstances it is vital to detect producers and to prevent their onward transmission.

Actions advised

- Be alert to the increase in carbapenemase-producing Enterobacteriaceae, and the growing importance of NDM-1 enzyme
- Recognise exposure to healthcare systems in India and Pakistan as additional major risk factors for infection or colonization with multiresistant, carbapenemase-producing Enterobacteriaceae
- Refer ALL carbapenem-resistant Enterobacteriaceae to ARMRL, except (i) *Proteus* spp. and *Morganella* spp. with borderline resistance only to imipenem (common in these genera) and (ii) *E. cloacae* with intermediate resistance to ertapenem only, as these are generally just derepressed for AmpC. NDM production will be investigated promptly.
- Patients infected with producers should be isolated to prevent onward transmission in hospitals; carriage in the patient's faecal flora should be examined for producers of the same or different species; similar screening of close unit contacts should be strongly considered.

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