ARHAI
Department of Health
Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection

Health Protection Agency

Advice on Carbapenemase Producers: Recognition, infection control and treatment

Carbapenems (imipenem, meropenem, ertapenem and doripenem) are invaluable for the treatment of infections due to multi-resistant gram-negative bacteria, including those with extended-spectrum β-lactamases. Carbapenem-resistant Enterobacteriaceae remain rare but are emerging. Their transmission characteristics and pathogenesis resemble those of more sensitive Enterobacteriaceae, but the infections are much more difficult to treat. For this reason, it is vital that NHS Trusts prevent their spread. Carbapenem resistance in Enterobacteriaceae can involve:

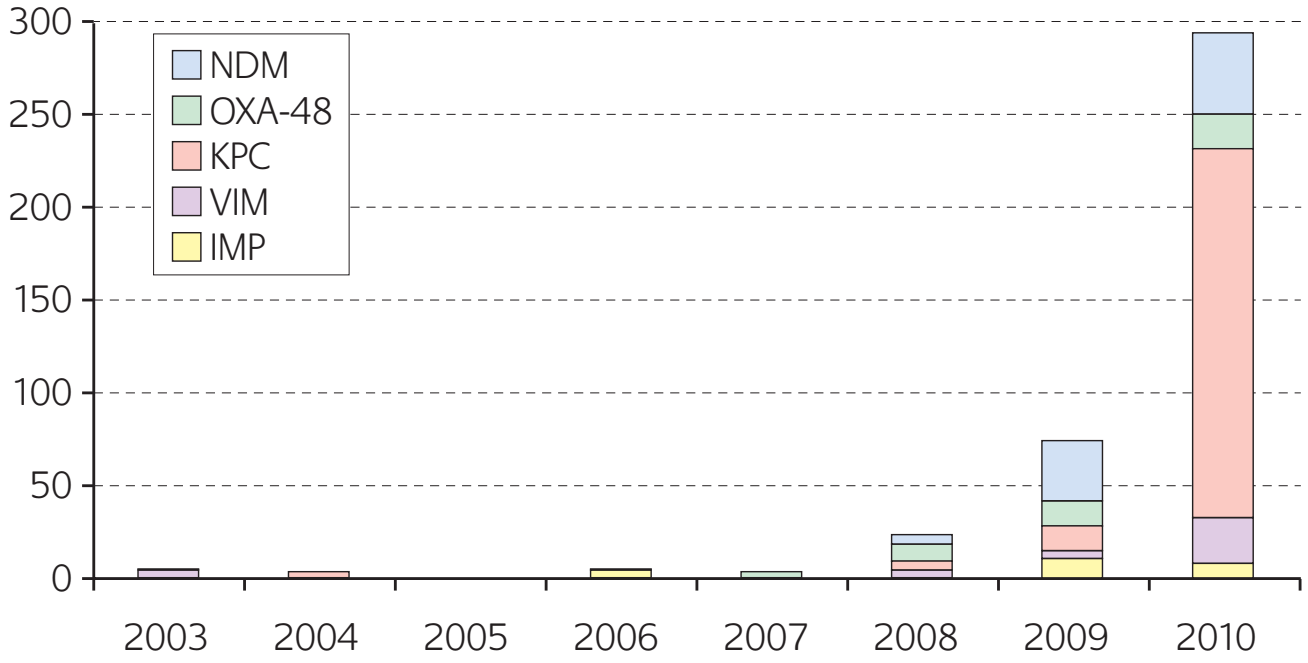
Combinations of ESBL or AmpC and porin loss: Porin loss is often unstable and may impose a fitness cost, meaning that these strains rarely spread. Ertapenem is particularly affected.

Acquired carbapenemases: These are the more serious risk and are beginning to spread in Enterobacteriaceae already resistant to multiple antibiotics. Several types occur, some with close geographic associations. They belong to three molecular classes: IMP, VIM and NDM types are metallo enzymes, with zinc at the active site; whereas KPC and OXA-48 belong to separate non-metallo families. Other carbapenemases (SME, IMI, SPM) occur, but are very rare.

Main Carbapenemases: distribution and molecular epidemiology

	Geographic distribution	Molecular epidemiology
NDM	Widespread in Enterobacteriaceae (esp. *K. pneumoniae* and *E. coli* in India and Pakistan. Imported to UK via patients with travel / hospitalisation / dialysis in India / Pakistan.	Diverse strain types in UK. Plasmid spread among strains and species is more important than clonal spread among patients. Nevertheless there have been a few cases of cross-infection in the UK.
VIM	Scattered globally, endemic in Greece; mostly *K. pneumoniae*. Sometimes imported to UK via patients previously hospitalised in Greece.	Plasmid spread among strains is more important than clonal spread of producer strains.
IMP	Scattered worldwide; no clear associations.	Mostly plasmid spread.
KPC	USA since 1999. Prevalent also Israel, and Greece; outbreaks elsewhere in Europe. Some UK cases imported via patient transfers, but local spread in NW England.	Some plasmid spread: mostly among *K. pneumoniae*, occasionally to other Entero-bacteriaceae. Also clonal spread, including global *K. pneumoniae* ST258 lineage.
OXA-48	Widespread *K. pneumoniae* in Turkey, Mid-East and N. Africa. Some import to UK and an outbreak in one London renal unit 2008-9.	Mixture of plasmid and clone spread.

Carbapenemase-producing Enterobacteriaceae referred to ARMRL



Detection of carbapenemase producers

Enterobacteriaceae with carbapenemases may only have small reductions in carbapenem susceptibility, meaning that laboratories should have a high index of suspicion about isolates with borderline sensitivity. Most producers are broadly resistant to β-lactams, but those with OXA-48 may remain susceptible to cephalosporins, and this can create problems for automated systems. Laboratories should participate in NEQAS, which will distribute carbapenemase producers in quality assurance exercises during 2011.

Suspect isolates should be sent for confirmation to:

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HPA Microbiology Services Colindale
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ARMRL and Laboratory of Healthcare Associated Infection will (i) confirm the antibiogram, (ii) seek to identify any carbapenemase, (iii) undertake typing to identify outbreaks and (iv) track disseminated clones where relevant.

Exceptions, NOT requiring referral for carbapenemase investigation are:

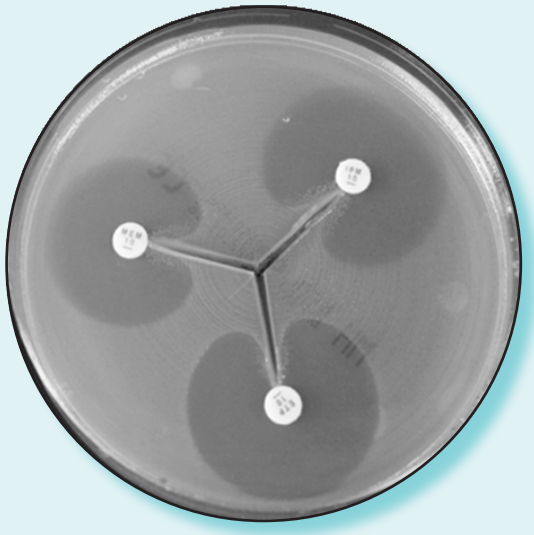
- Proteeae resistant to imipenem only; these species have inherently low susceptibility.
- *Enterobacter* spp. with cephalosporin and low-level ertapenem resistance but susceptibility to imipenem and meropenem – these generally have combinations of AmpC and impermeability.
- Carbapenem-resistant Acinetobacter or *P. aeruginosa*, unless these have exceptional levels of resistance (grow up to carbapenem discs) or give a positive EDTA-imipenem synergy test implying metallo-enzyme. Carbapenemases have **NOT** been found in UK cystic fibrosis isolates.

Laboratories wishing to undertake carbapenemase detection may find the following tests useful but none has clear interpretive standards so suspect Enterobacteriaceae should be referred:

Cloverleaf ('Hodge') test

- Agar is spread with *E. coli* NCTC10418 (or ATCC25922), as for a disc test.
- The test strain is then inoculated, as 3 arms, 120° apart, cut into or streaked heavily on the agar from the plate centre.
- Imipenem, meropenem and ertapenem 10 μg discs are put at the end of these arms.
- Indentation of the inhibition zone(s) indicates that the test strain attacks carbapenems.

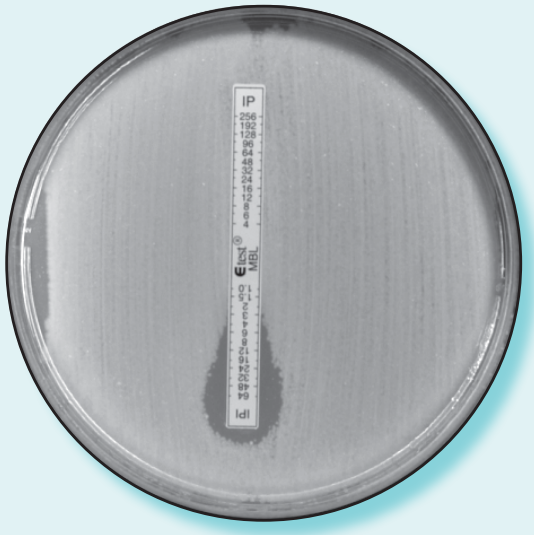
Caveats are that reading is subjective and that AmpC enzymes can give weak false positive results.



Synergy tests

- Metallo carbapenemases (IMP, NDM, VIM) are inhibited by EDTA or dipicolinic acid.
- Synergy between carbapenems and EDTA, indicating MBL production, can be detected with Etests (see below) or using double disc tests (with EDTA discs from e.g., Rosco).
- Caveats are that false-positive results are common with *P. aeruginosa* and *A. baumannii*, though rare with Enterobacteriaceae.

KPC carbapenemases are inhibited by boronic acids, and synergy between boronic acid discs (Rosco) and imipenem indicates their presence.



Actions to minimise risk of carbapenemase spread

Good practice actions	Number of cases		
Trust engagement	**0**	**1**	**>1**
Ensure the Board and Executive make it a high priority to mimimise carbapenemase spread, and are supportive of all prevention and eradication measures.	✓	✓	✓
Prepare a containment action plan (all trusts need to be prepared).	✓		
Laboratory			
Optimise and review laboratory methods to detect producers.	✓	✓	✓
Screen by plating faeces, rectal swabs and manipulated site swabs e.g. from skin breaks / catheter sites onto MacConkey or CLED agar with meropenem or ertapenem discs. Examine for colonies within the zone. Prior broth enrichment may be useful: use a rectal swab to inoculate 5-10 ml broth containing a 10 μg imipenem disc, then subculture as above.		✓	✓
Infection Prevention & Control			
Identify places for effective isolation, e.g. en-suite side rooms / cohort areas and prepare criteria for ward closure to new admissions / re-opening.	✓		
Develop an effective decontamination strategy for equipment. Employ dedicated or single use equipment where decontamination is impracticable.	✓		
Implement the containment action plan immediately, with meticulous adherence to standard and infection control precautions with patients isolated in a single room with en suite bathroom or dedicated commode.		✓	✓
Optimise care bundles and clinical practice for indwelling devices.	✓	✓	✓
Reinforce and optimise hand hygiene with soap and water.		✓	✓
Screen ALL index and secondary case contacts: case-find and isolate immediately, determining the extent of spread, flagging patient record.		✓	✓
Instigate weekly and discharge screening of all patients in affected units / wards until organism eliminated. Do not screen staff for carriage unless there is strong evidence to do so. Prolonged urine carriage has been noticed in some patients without faecal carriage. Screening of household contacts of patients is controversial, but could be considered.		✓	✓
Minimise spread by effective enhanced and terminal cleaning including of high contact and sanitary areas (consider increased frequency and use of a disinfectant).		✓	✓
Employ cohort staffing depending on risk assessment.		✓	✓
Review effective decontamination of equipment.		✓	✓
Ensure incident tracking, with epidemiological graphs and tables if transmission detected.		✓	✓
Prepare a readmission and transfer strategy for affected patients.		✓	✓
Ensure adequate communication to other healthcare providers.		✓	✓
Hospital-wide			
Run awareness and training campaign for medical and nursing staff.	✓	✓	✓
Screen high-risk patients on admission, e.g. known positives, those with previous hospitalisation /dialysis in countries where producers are prevalent.	✓	✓	✓
Hold regular incident management team meetings to review infection prevention and control strategies, including root cause analyses where applicable (if transmission detected).		✓	✓
Implement isolation strategy at triage / admission for high-risk patients.	✓		
Implement communication strategy. Report as SUI to SHA and HPU (DH letter PL/CMO/2003/4).			✓
Ensure that any transmission becomes a top Trust priority, with leadership from Board to Ward.			✓

Endoscopy and related procedures

- Several endoscope-related transmissions of carbapenem-resistant organisms have been reported in the UK and France. Similar risks are likely e.g. with colonoscopy.
- Trusts should ensure that relevant staff understand the risks and take adequate precautions – see www.mhra.gov.uk/Publications/Postersandleaflets/CON2022584 and www.mhra.gov.uk/Publications/Safetywarnings/MedicalDeviceAlerts/CON087958
- Special care should be taken to disinfect or protect equipment used with endoscopes, e.g. cameras that do not undergo the same routine sterilization.

Antimicrobial stewardship

A local multi-disciplinary group should ensure stewardship measures are in place to promote optimal and safe usage of antimicrobials in order to minimise the acquisition and spread of resistance. There should also be awareness that changes in antimicrobial policy may adversely patient outcome. Where practicable, lengths of stay and mortality should be monitored.

Treating infections due to carbapenemase producers

Most carbapenemase producers are extremely drug resistant.

β-Lactams: resistance to the whole class is common, but:

- Aztreonam is stable to metallo-carbapenemases, including IMP, VIM and NDM, but most producers are resistant owing to co-production of AmpC or ESBL enzymes; it is NOT stable to non-metallo-carbapenemases including OXA-48 and KPC types.
- Ceftazidime, cefotaxime and aztreonam remain active against Enterobacteriaceae with OXA-48 unless these also have AmpC or an ESBL, as many do.
- Temocillin is relatively stable to KPC enzymes (not others), but MICs mostly are narrowly out of range at licensed dosage (2g q12h).
- No available β-lactamase inhibitor inactivates carbapenemases.
- Carbapenems may still be active vs. some producers with low-level resistance.

Aminoglycosides: resistance to the whole class is common:

- Strains with NDM-1 almost always have a 16S rRNA methylase, conferring resistance to all aminoglycosides suitable for human use.
- ST258 *K. pneumoniae* with KPC are mostly susceptible to gentamicin (not other analogues).
- Other strains with KPC, VIM, IMP and OXA-48 enzyme are variably resistant to aminoglycosides, reflecting multiple modifying enzymes. Isepamicin is active against some isolates resistant to other analogues, but is not available in the UK.

Polymyxins, tigecycline & fosfomycin are the agents with most frequent *in vitro* activity, but all have limitations. Dosage will vary with the patient and infection site, but should be on the principle of 'highest safe' rather than 'minimum potentially effective'; durations should be as standard for the infection type.

Drug	Potential	Limitations
Polymyxin B and E (colistin) (i.v.)	Active vs. >90% of producers. Case reports of successful use in a range of infections due to carbapenemase producers.	Significant nephro- and neuro-toxicity and poor lung penetration. Use high dose, with possible addition of nebulised colistin in pneumonia.
Tigecycline (i.v.)	Active in vitro vs. most carbapenem-resistant *E. coli*. Licensed for skin and soft tissue and complicated intra-abdominal infections. Case reports of success in various infections with carbapenemase producers.	Low blood concentrations; off-label use should be cautious; unsuitable in urinary infections as only 22% excreted in urine. Excess deaths in some trials, esp. ventilator pneumonia (not a licensed indication). Many *Klebsiella* only intermediately susceptible (MIC, 2 mg/L); some resistant.
Fosfomycin (oral and i.v.)	Active against most *E. coli* with carbapenemases, including NDM-1. Effective in urinary infections.	Borderline susceptibility common in *Klebsiella* spp. Risk of mutational resistance. Not marketed in the UK, but pharmacists can import.

Others: a few isolates are susceptible to other antibiotics including e.g. chloramphenicol, ciprofloxacin and cotrimoxazole. Most producers, however, are resistant to these drugs.

Comments to:

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Further reading

Carbapenemase types and epidemiology

Nordmann P, Cuzon G, Naas T. The real threat of *Klebsiella pneumoniae* carbapenemase-producing bacteria. *Lancet Infect Dis* 2009; **9:**228-36.

Kumarasamy KK, Toleman MA, Walsh TR *et al.* Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. *Lancet Infect Dis.* 2010; **10:**597-602.

Vatopoulos A. High rates of metallo-β-lactamase-producing *Klebsiella pneumoniae* in Greece--a review of the current evidence. *Euro Surveill* 2008; **13**, i8203

Carrer A, Poirel L, Yilmaz M *et al.* Spread of OXA-48-encoding plasmid in Turkey and beyond. *Antimicrob Agents Chemother* 2010; **54:** 1369-73.

Laboratory detection

Cohen Stuart J, Leverstein-Van Hall MA; Dutch Working Party on the Detection of Highly Resistant Microorganisms. Guideline for phenotypic screening and confirmation of carbapenemases in Enterobacteriaceae. *Int J Antimicrob Agents*. 2010; **36:**205-10.

Pournaras S, Poulou A, Tsakris A. Inhibitor-based methods for the detection of KPC carbapenemase-producing Enterobacteriaceae in clinical practice by using boronic acid compounds. *J Antimicrob Chemother*. 2010; **65:**1319-21

Miriagou V, Cornaglia G, Edelstein M *et al.* Acquired carbapenemases in Gram-negative bacterial pathogens: detection and surveillance issues. *Clin Microbiol Infect* 2010; **16:**112-22.

Infection control and endoscopes

Guidance for Control of Infections with carbapenem-resistant or carbapenemase-produing Enterobacteriaceae in Acute Care Facilities *MMWR* 20 2009; **58:** 256-260

Carmeli Y, Akova M, Cornaglia G, et al. Controlling the spread of carbapenemase-producing Gram negatives: therapeutic approach and infection control. *Clin Microbiol Infect* 2010; **16:** 102-111

Naas T, Cuzon G, Babics A *et al.* Endoscopy-associated transmission of carbapenem-resistant *Klebsiella pneumoniae* producing KPC-2 β-lactamase. *J Antimicrob Chemother* 2010; **65:**1305-6.

Treatment of infections

Hirsch EB, Tam VH. Detection and treatment options for *Klebsiella pneumoniae* carbapenemases (KPCs): an emerging cause of multidrug-resistant infection. *J Antimicrob Chemother* 2010; **65:** 1119-25.

Li J, Nation RL, Turnidge JD *et al.* Colistin: the re-emerging antibiotic for multidrug-resistant Gram-negative bacterial infections. *Lancet Infect Dis* 2006; **6:** 589-601.

Daikos GL, Petrikkos P, Psichogiou M *et al.* G. Prospective observational study of the impact of VIM-1 metallo-β-lactamase on the outcome of patients with *Klebsiella pneumoniae* bloodstream infections. *Antimicrob Agents Chemother* 2009; **53:**1868-73

Patel G, Huprikar S, Factor SH, *et al*. Outcomes of carbapenem-resistant *Klebsiella pneumoniae* infection and the impact of antimicrobial and adjunctive therapies. *Infect Control Hosp Epidemiol*. 2008; **29:**1099-106.

Borer A, Saidel-Odes L, Riesenberg K *et al*. Attributable mortality rate for carbapenem-resistant *Klebsiella pneumoniae* bacteremia. *Infect Control Hosp Epidemiol.* 2009; **30**:972-6.

Reporting of serious untoward incidents associated with infection

www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4013410.pdf