

Multiple Antibiotic Resistant Gram-negative Bacteria

Increasing antibiotic resistance in Gram-negative bacteria is making initial antibiotic choice more difficult and therefore mortality is rising. Currently there are no new anti-Gram-negative antibiotics being developed by the pharmaceutical industry.

There are 3 main groups of multiple resistant Gram-negative bacteria:

- Enterobacteriaceae with ESBL or AmpC enzymes – *Escherichia coli*, *Klebsiella* spp., *Enterobacter cloacae*, *Citrobacter freundii*, *Morganella morganii*, *Serratia marcescens*
- *Acinetobacter* spp. – resistant to aminoglycoside antibiotics as well as occasionally carbapenems and Colistin
- *Pseudomonas* spp. – resistant to combinations of Ceftazidime, Piptazobactam, carbapenems, aminoglycosides and quinolones

Mode of Transmission

Transmission can occur via hands or via faecal-oral colonisation.

Incubation Period

Many Gram-negative bacteria are able to colonise people. Once the microorganism is part of the patient's normal flora it can potentially cause infection and be spread to others at any time. The majority of infections with Gram-negative bacteria follow previous colonisation.

Period of Communicability

Potential cross-infection can occur at any time whilst the patient remains colonised with the resistant bacteria. However, risk is highest with environmental contamination e.g. during outbreaks of diarrhoea.

Best Practice Control Measures

Careful antibiotic prescribing	Certain antibiotics have been implicated in the selection of antibiotic resistant Gram-negative bacteria e.g. Ciprofloxacin and the Beta-lactam-Beta-lactamase inhibitor combination antibiotics such as Co-amoxiclav and Piptazobactam
Hand Hygiene	With soap and water or alcohol hand gel
PPE	See section – Infection Control, Personal Protective Equipment Remove ALL PPE before leaving room
Isolation	Side room preferably with own toilet facility
Environmental decontamination	Deep cleaning of the clinical area daily and after patient is discharged

Next Generation Resistance – Carbapenemases

Recently, strains of ESBL-positive *Klebsiella* spp. and *Escherichia coli* have been isolated which are also resistant to the carbapenem antibiotics. A carbapenemase is any Beta-lactamase enzyme that:

- Can breakdown carbapenem antibiotics
- Gives resistance to **ALL** of the Beta-lactam antibiotics such as the penicillins and cephalosporins
- Is often associated with other genes giving resistance to other antibiotics such as the quinolones and aminoglycosides

Carbapenemases are important because the carbapenems (Ertapenem, Meropenem, Imipenem and Doripenem) are often seen as the last line of antibiotics in the fight against infections with Gram-negative bacteria. Carbapenem resistance is not associated with a specific infection but rather with a diverse clinical spectrum of diseases. Infections due to bacteria with these enzymes have a very high mortality in excess of 50%.

The genes which encode these enzymes are usually located on a mobile genetic element such as a plasmid and therefore have the potential to spread between bacterial species. The most important currently are known as the "Big Five":

- *Klebsiella pneumoniae* carbapenemase (KPC)
- New Delhi metallo-beta-lactamase (NDM)
- Verona integron-encoded metallo-beta-lactamase (VIM)
- Imipenemase metallo-beta-lactamase (IMP)
- Oxacillin carbapenemases (OXA)

Treatment of Patients with Infections

Most carbapenemase-producing bacteria remain susceptible to: Polymyxins e.g. Colistin, Tigecycline, Nitrofurantoin and Fosfomycin. The current recommendations for the treatment of patients with severe infections caused by carbapenemase producing bacteria are combinations of antibiotics: Colistin **PLUS** carbapenem, Colistin **PLUS** Tigecycline or Colistin **PLUS** aminoglycoside.

Patient Screening

On admission to hospital, patients will be classified as either:

- 1) **NOT** infected or colonised (no further action required)
- 2) **CONFIRMED** (infection or colonisation)
- 3) **SUSPECTED** (infection or colonisation)

How to Screen for Carbapenemase-Producing Bacteria

- Rectal charcoal swab with visible faecal material **OR** stool sample
- **PLUS** charcoal swab from any wound and device-related site if hospitalised within the previous 12 months in a country with a high prevalence of carbapenemase producing bacteria

CONFIRMED

- Patients who have a positive microbiological culture for a carbapenemase producing bacteria from a clinical specimen or screening test at any stage during their admission to any hospital

SUSPECTED

- Patients who have been an inpatient in a hospital abroad
- **OR** been an inpatient in a UK hospital known to have had problems with spread of carbapenemase-producing Enterobacteriaceae
- **OR** previously been colonised or had an infection with a carbapenemase producing Enterobacteriaceae
- **OR** had close contact with a person who has been colonised or had an infection with a carbapenemase producing Enterobacteriaceae

Best Practice Control Measures for CONFIRMED or SUSPECTED

Screening	Send weekly screening samples
Careful antibiotic prescribing	If patient has an infection seek specialist advice from a Microbiologist or Infectious Diseases Physician
Hand Hygiene	With soap and water or alcohol hand gel
Personal Protective Equipment	See section – Infection Control, Personal Protective Equipment Remove ALL PPE before leaving room
Isolation	Side room preferably with own toilet facility for duration of hospital stay
Environmental decontamination	Deep cleaning of the clinical area daily and after patient discharge

Patients with **CONFIRMED** infections or colonisation who have 3 negative screening samples should **ONLY** be moved out of isolation if there is a serious risk to their health from remaining in isolation. This is because the screening tests are not perfect and even if negative now, previously positive patients can become positive again, especially if given antibiotics. If in doubt discuss with the Infection Control Team.

Contact Screening and Management

If a patient has not been isolated in a side room and is found to have a carbapenemase-producing bacterium then all contacts within the bays or wards in which they have been should also be screened. This **DOES NOT** include household contacts or members of hospital staff.

All contacts should be isolated or cohorted together whilst awaiting results of screening samples if possible. If initial screening tests are negative they should have repeat screens samples sent on day 2 and day 4 and if they remain negative in all three samples they can then be managed as normal and the isolation or cohorting relaxed.

If a contact tests positive then they should be managed as a **CONFIRMED** infection or colonisation **AND** all of their contacts should be screened.

No further management is recommended after the patient is discharged from hospital although nursing care facilities would be recommended to consider the risk of transmission within their environments.

The patient and their General Practitioner should be made aware of the patient's status so that if they are re-admitted to hospital the hospital is made aware of their status.