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PATHCHAT

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Update on the management of carbapenemase-producing *Enterobacteriaceae* (CPE)

Dr Tom Frieden, Director of the US Centres for Disease Control and Prevention, has called carbapenem-resistant *Enterobacteriaceae* (CRE) "nightmare bacteria". CRE emerged in South Africa in 2011 when the first cases of *Klebsiella pneumoniae* carbapenemase (KPC) and New Delhi metallo-β-lactamase (NDM) were described. In the five years since then, numerous outbreaks of CRE have occurred across the country. Carbapenemase-producing *Enterobacteriaceae* (CPE) pose a major threat to the healthcare system both in South Africa and the rest of the world.

What is CRE?

CRE refers to *Enterobacteriaceae* (e.g. *Klebsiella pneumoniae*) that are resistant to one or more of the carbapenems. This resistance is caused by two main mechanisms:

- The overproduction of extended spectrum β-lactamase (ESBL) or inducible AmpC β-lactamase, combined with porin loss
- Carbapenemase production

Carbapenemases are enzymes that can hydrolyse the β-lactam ring of carbapenem antibiotics, rendering them ineffective. Different carbapenemases can be distinguished on a molecular basis, including NDM, Verona Integron mediated metallo-β-lactamase (VIM) OXA-48 and OXA-48-like enzymes (see Figure 1).

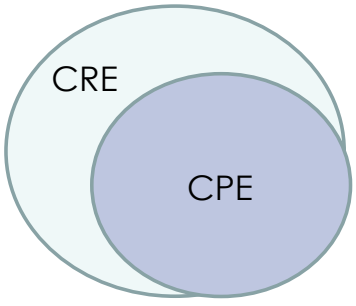

Figure 1: CRE versus CPE

Laboratory detection of CRE and CPE

All *Enterobacteriaceae* that have reduced sensitivity to carbapenems must be tested for carbapenemase production. The classes of carbapenemases differ in their ability to hydrolyse β-lactam antibiotics. In some cases, the carbapenems might test within the susceptible range, even when carbapenemase enzymes are present. This is often seen in cases of OXA-48 and OXA-48-like isolates. Upon exposure to antibiotics though, the levels of resistance in these isolates increase.

Ampath uses PCR testing to screen *Enterobacteriaceae* with reduced susceptibility to carbapenems for the most commonly occurring carbapenemases, including NDM, VIM, KPC, GES and OXA-48.

Rectal swabs or stool samples can also be screened directly by means of a PCR for the presence of these carbapenemases.

Carbapenemases in South Africa

The number of patients with clinical isolates of CPE in South Africa has increased dramatically since it first emerged five years ago (see Figure 2 overleaf). The predominant carbapenemases vary according to region and/or hospital. Although all the commonly found carbapenemases are found countrywide, OXA-48 and OXA-48-like enzymes have become the dominant enzyme in large parts of the country.

Why is it a problem?

The carbapenemases are encoded by genes, e.g. OXA-48, which are carried on plasmids. Plasmids are extra-chromosomal circular DNA that are transmitted between bacteria. The bacteria that carry these plasmids are then transmitted between patients through the hands of healthcare workers and by contaminating the healthcare environment.

Unfortunately, the bacteria that carry these plasmids are usually not only resistant to all the β-lactam antibiotics, but also to other classes of antibiotics, e.g. fluoroquinolones and aminoglycosides.

Identification of high-risk patients

CPE is usually hospital-acquired. Risk factors for acquisition include the following:

- Prolonged hospitalidation and ICU stay
- Invasive devices, including central venous and urinary catheters

- Immunosuppression (e.g. oncology patients)
- Exposure to multiple antibiotic agents, especially antibiotics with anaerobic activity.

As the incidence of CPE in South Africa increases, more cases of community-associated infections can be expected. Patients who are colonised or infected with CPE are discharged into stepdown, rehabilitation or frail care units, where they are a potential source of infection to other patients outside the hospital environment.

Clinical spectrum of CPE

The clinical spectrum of CPE infections ranges from exposure, colonisation, non-invasive infection (e.g. urinary tract infection) and invasive infection (bloodstream). Colonisation usually precedes infection, and the gastro-intestinal tract (especially in stool) is the most common site of colonisation. Patients may, however, be colonised on skin or other sites, such as endotracheal tubes without rectal carriage being present.

Clinical management of CPE infections

The first and most important principle is to distinguish between colonisation and infection. Patients who are colonised with CPE do not need any antibiotic treatment, and unnecessary antibiotics must be avoided.

The optimal treatment of CPE infections is not well established, and the outcome data that is available is mostly based on observational studies. Evidence would suggest that combination therapy with at least two active agents is associated with an improved outcome. The minimum inhibitory concentrations (MICs) of carbapenems should always be determined for clinical CPE isolates. A Class 2 carbapenem (imipenem, meropenem or doripenem) should always be included in the combination, provided the MIC is ≤ 8 µg/mL.

Carbapenem monotherapy has much lower associated success rates and should be avoided, even if the isolate tests phenotypically susceptible.

The antibiotic management of patients with established CPE infections should occur in consultation with a clinical microbiologist and/or infectious diseases physician.

Infection control measures

The timely identification of patients colonised or infected with CPE and the rapid institution of appropriate infection control measures are essential components in preventing the spread of these organisms. Each institution should develop its own policy based on the characteristics and risk factors of its patient population.

Ideally, you want to identify patients who have been colonised or infected with CPE before it spreads into the environment and to other patients. An active screening policy should therefore be implemented. Surveillance of either stool or rectal swabs is acceptable.

Once a patient who has been colonised or infected with CPE is identified, the following actions need to be taken:

- Strict isolation of the index case, with contact precautions.
- Handwashing before and after patient contact should be emphasised.
- Cohorting of all colonised or infected patients.
- Dedicated nursing of all colonised or infected patients
- Extensive screening of all potential contacts of the index case.
- Once all colonised patients have been identified and cohorted, regular surveillance can be carried out (e.g. weekly) until no new cases are detected.
- Special emphasis should also be put on terminal disinfection and the environmental cleaning of potentially contaminated patient contact areas

The continued spread of CPE in hospitals in South Africa is placing a huge burden on our healthcare system. The cost associated with laboratory detection, infection, prevention and control (IPC) strategies, and salvage therapy for infections due to these organisms has escalated over the past five years. It should be realised, however, that these organisms pose a significant threat to the efficacy of the antibiotics currently at our disposal, and every effort should be made to control the further spread of CPE.

Suggested reading:

1. Lowman W, et al. 2014. The SASCM CRE-WG: consensus statement and working group guidelines for the screening and laboratory detection of carbapenemase-producing *Enterobacteriaceae*. *South African Journal of Infectious Diseases* 29(1):5–11
2. Wilson APR, et al. 2015. Prevention and control of multi-drug-resistant Gram negative bacteria: recommendations from a Joint Working Party. *Journal of Hospital Infection*. Available online: http://dx.doi.org/10.1016/j.jhin.2015.08.007.

Number of patients with CPE from clinical cultures

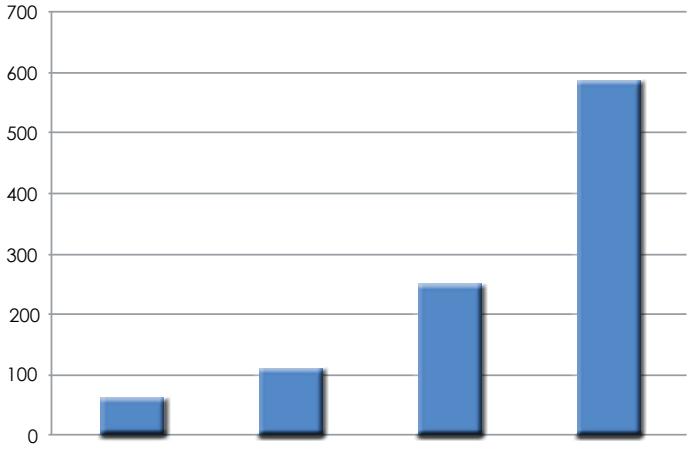

Figure 2: Patients with clinical cultures of CPE in South Africa (Ampath NRL data, 2012–2015)

Number of patients colonised with CPE

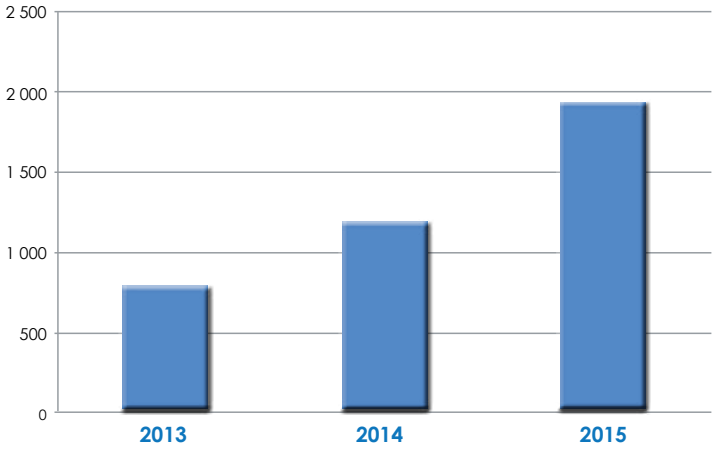

Figure 3: Patients colonised with CPE in South Africa (Ampath NRL Data, 2013–2015)