Clinical microbiology considerations related to the emergence of New Delhi metallo-beta-lactamases (NDM-1) and Klebsiella pneumoniae carbapenemases (KPC) amongst hospitalized patients in South Africa

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Introduction

Both New Delhi Metallo-beta-lactamase-1 (NDM-1) and Klebsiella pneumonia carbapenemase (KPC)-producing Gram negative bacteria (GNB) have rapidly emerged as important causes of extreme-drug resistance worldwide and as such have become an international health issue, posing a major threat to the viability of currently available antibiotics.

Numerous epidemics have been reported, with strains becoming endemic in several institutions resulting in increased mortality.

South Africa recently became the 3rd African country to document the emergence of the carbapenemases NDM-1 (K.pneumoniae), as well as the 1st on the continent to report KPC (Enterobacter cloacae and K.pneumoniae).

This report briefly highlights the important clinical microbiological considerations related to these carbapenemases with the main focus on early detection and laboratory confirmation, as well as the antibiotic management and prevention of transmission.

Identification of high-risk patients

Patient risk factors typically associated with the hospital acquisition of KPC-and Metallo-β-lactamase (MBL)-producing bacteria include:

- Prolonged hospitalization and ICU stay
- Invasive devices
- Immunosuppression
- Therapy with multiple antibiotic agents before initial culture.
- The risk increases with increasing duration of prior antibiotic treatment

In the case of NDM-1, travel to and from India is not a pre-requisite for acquisition, neither is prior carbapenem therapy. The genes conferring such resistance usually reside on large plasmids, with additional resistance determinants such as fluoroquinolones. As a consequence, prior use of most of the antibiotic classes may select for carbapenemase-producing GNB.

**Laboratory confirmation**

- The rapid recognition of carbapenemase expression is the key to:
  - Appropriate treatment of carbapenem-resistant *Enterobacteriaceae*
  - Prevention of transmission and cross infection of such genotypes
- However, due to heterogeneous expression of resistance, clinical laboratories may encounter difficulties when trying to detect carbapenemase production during routine diagnostic procedures (including utilization of the Hodge test as screening method).
- This is particularly the case when using automated susceptibility testing, where the sensitivity and specificity for the identification of a carbapenemase with Vitek 2, is only 74% and 38% respectively.
- KPC-producers phenotypically may have carbapenem MICs below the CLSI breakpoints.
- Unusual multi-resistant antibiograms (such as those often seen for *Pseudomonas aeruginosa* or *Acinetobacter baumannii*) and elevated MICs (such as ertapenem and imipenem but not meropenem or doripenem) amongst clinical strains of *Escherichia coli, K.pneumoniae, E.cloaceae* etc. arouse suspicion but do not prove resistance.
➢ To complicate matters other mechanisms of carbapenem resistance may be involved.

➢ In South Africa, *K. pneumoniae* with reduced susceptibility to carbapenems due to CTX-M extended-spectrum beta-lactamases (ESBLs) in conjunction with porin loss had previously been described.

➢ Therefore, in order to optimize antibiotic therapy and prevent transmission of NDM-1 or KPC-producing bacteria, only rapid molecular confirmation can reliably detect the presence of *bla*<sub>KPC</sub> and *bla*<sub>NDM-1</sub> in clinical isolates.

➢ Inter-species transfer may occur *in vivo*, and routine testing for KPCs should be promptly extended to all *Enterobacteriaceae* reported from any infected/colonized patient, and those hospitalized in the same unit.

**Clinical management**<sup>10-12</sup>

The optimal treatment of such infections is not well established, and clinical outcome data remain sparse.

➢ Emerging evidence based on relatively small patient numbers, suggests that combination therapy is associated with improved outcome.

➢ For KPC infections the success rate with colistin monotherapy is low but much higher when used in combination with either tigecycline or an aminoglycoside.

➢ In contrast, carbapenem monotherapy has much lower associated success rates and therefore, even if phenotypically susceptible, should be avoided.

➢ However, double carbapenem therapy that includes ertapenem has been suggested for KPC-producing *K. pneumoniae* infections. The rationale for double-carbapenem therapy
relates to the preferential affinity of ertapenem for and hydrolysis by KPC, such that it acts as a “suicide substrate”.

➢ Other options are the combination of rifampicin with doripenem and colistin or combination therapy with intravenous fosfomycin (which is not available in South Africa).

**Infection control measures**\(^{13-16}\)

Lack of adequate and timely interventions appears to be common with the carbapenemase-producing pathogens.

To avoid this, a comprehensive, multi-disciplinary “action plan” is necessitated that should be developed prior to, and rapidly implemented after, a 1\(^{st}\) case has been detected and microbiologically confirmed.

Control measures for sporadic cases of NDM- or KPC-producing pathogens in our hospitals may warrant a “search and destroy strategy” that include:

➢ **Isolation precautions** that are strictly applied.

➢ Unfortunately patient isolation on its own has failed to control the spread of such bacteria.

➢ In contrast **cohorting** of such patients with dedicated nursing in a separate ward/ICU have been shown to be a crucial component of successful institutional control measures. This might be problematic for some of our institutions

➢ **Active screening policies** (such as all patients in contact with the index case).
Screening needs to be adopted depending on the circumstances and the institution at stake.

The primary screening site is stool or rectal swabs using either PCR or chromogenic agar but could be extended to clinical specimens in patients with indwelling devices (e.g. aspirated sputum in ventilated patients).

Mandatory involvement of clinicians from an antibiotic selective pressure (stewardship) point of view.

Rapid routine molecular detection is essential to optimize therapy, improve outcomes, and limit the spread of KPC and NDM in our institutions through aggressive infection control measures, including the screening of potentially colonized high-risk patients.

In addition, antibiotic selective pressure in our hospitals warrants urgent attention. It is envisaged for the next decade that the emergence of both NDM and KPC in our health care facilities will significantly escalate health-care costs associated with laboratory detection, IPC strategies and salvage combination therapy for infections due to these pathogens.

References


12. Endimiani et al. *In vitro* activity of fosfomycin against $bla_{KPC}$-containing *Klebsiella pneumoniae* isolates, including those nonsusceptible to tigecycline and/or colistin. *Antimicrob Chemother Agents* 2010;54:526-529.


