

## EDITORIAL

# Carbapenem-resistant Hypermucoviscous *Klebsiella pneumoniae* – Emerging Superbug

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Healthcare-associated Infections (HAIs) are infections patients can get while receiving medical treatment in a healthcare facility. These are a major, yet often preventable, threat to patient safety.<sup>1</sup> Hospital acquired infection (HAI) as per the World Health Organization (WHO) is defined as “an Infection occurring in a patient in a hospital or other healthcare facility in whom the infection was not present or incubating at the time of admission”.<sup>2</sup> It also includes an infection acquired during hospital stay and manifesting after discharge. The South East Asian region has HAI prevalence of 10%. Surveillance of HAIs helps to track infection trends, antibiotic susceptibility and resistance patterns.

In 2011, Indian ministry of health released National Antibiotic policy to rationalise antibiotic usage. National treatment guidelines for antimicrobial use in infectious diseases (version 1, 2016) have been released by the National Centre for Disease Control and Directorate of health services, Government of India in an attempt to reduce the rising threat of antimicrobial resistance.<sup>3</sup>

Infection with carbapenem-resistant *Enterobacteriaceae* (CRE) or carbapenemase-producing *Enterobacteriaceae* is emerging as an important challenge in health-care settings.<sup>4,5</sup>

WHO priority pathogen list for research and development of new antibiotics lists enterobacteriaceae (Carbapenem resistant and extended spectrum beta lactamase producing) of critical first priority.<sup>6</sup> These multidrug resistant (MDR) bacteria pose a threat in hospitals and nursing homes and among patients who require invasive ventilation and have indwelling catheters and devices. They can cause severe and often deadly infections like pneumonia and blood stream infections and remain resistant to a large number

of antibiotics.

*Klebsiella pneumoniae* belongs to the family enterobacteriaceae and is the most common species of *klebsiella* genus implicated in healthcare associated infections. *Klebsiella pneumoniae* isolates resistant to most of the commonly used antibiotics have been recognized as emerging infectious organisms of clinical significance. The mechanism for its resistance is possibly due to the extended spectrum beta-lactamases and carbapenemases produced by these bacteriae. *Klebsiella* is one of the commonly isolated gram negative bacteria (GNB) amongst blood stream infections caused by MDR GNB.

Hypermucoviscous/hypervirulent *Klebsiella pneumoniae* (hvKP) was reported initially in Taiwan and Southeast Asia in the mid-1980s<sup>7</sup>. It is now increasingly recognized globally.<sup>8,9</sup>

This phenotype was implicated in community acquired life threatening infections like liver abscess and has a tendency to cause metastatic infections like pneumonia, meningitis, endophthalmitis in immunocompetent young healthy hosts. Among hvKP, eight capsular serotypes occur; of them K1 and K2 are the most virulent that have been described to date. The capsules of K1 and K2 serotype essentially protect the bacteria from phagocytosis.<sup>8</sup> Appearance of colonies grown on an agar plate is hypermucoviscous. This phenotype has been semi-quantitatively defined by a positive “string test.” The string test is positive when a bacteriology inoculation loop or needle is able to generate a viscous string > 5 mm in length by stretching bacterial colonies on an agar plate. Genotype markers for the same are *rmpA*, *rmpA2* and *magA* genes.

Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) is resistant to almost all available antimicrobial agents, and infections with CRKP have been associated with high rates of morbidity and mortality, particularly among persons with prolonged hospitalization and those who are critically ill and exposed to invasive devices (e.g., ventilators or central venous catheters).<sup>10,11</sup> *K. pneumoniae* isolates need to be identified by antimicrobial susceptibility testing, string test, extended-spectrum  $\beta$ -lactamase (ESBL) gene detection, capsular serotypes, virulence gene profiles, and multilocus sequence typing. For CRKP, the most important mechanism of resistance as per western studies is the production of a carbapenemase enzyme, *bla<sub>kpc</sub>*. The gene that encodes the *bla<sub>kpc</sub>* enzyme is carried on a mobile piece of genetic material (transposon), which increases the risk for dissemination. Analysis of 2007 data regarding healthcare associated infections reported to CDC indicated that 8% of all *Klebsiella* isolates were CRKP, compared with less than 1% in 2000. In India, carbapenemase resistance is due to NDM and OXA enzymes.

Antibiotic-resistant hvKP isolates are increasingly being reported.<sup>12-15</sup> Because carbapenem-resistant hvKP strains may cause severe, untreatable infections in healthy individuals, the emergence of these strains poses a great threat to public health. The threat of hvKP acquiring carbapenem resistance is becoming a reality in certain countries, such as China, where both carbapenem-resistant cKP and carbapenem-susceptible hvKP strains are prevalent.<sup>13</sup> The prevalence of hvKP among carbapenem-resistant *K. pneumoniae* isolates in China is high, ranging from 7.4% to 15%.<sup>7,8</sup>

Recent outbreaks of duodenoscope associated CRE/CRKP infections have been described. The global spread of this organism is proving to be quite a challenge for physicians who are left with limited therapeutic options when dealing with such cases.

Recommended measures to control spread of MDR GNB are improved laboratory detection and reporting, enhanced infection surveillance and control measures in ICUs, prevention of spread by barrier precautions like gowns and gloves, hand washing and restricted use of 3rd generation cephalosporins.

Some of the new antibiotics for treatment of CRKP are ceftazidime-avibactam, plazomicin, meropenem-varobactam, imipenem-relabactam, aztreonam-avibactam and cefiderocol.<sup>16</sup> These are not yet available in India and many other countries.

In this issue of the journal, Chaitra Shankar et al. in the article titled "Extremely high mortality rates in patients with carbapenem resistant hypermucoviscous *Klebsiella pneumoniae* blood stream infections" have attempted to find out the incidence of hypermucoviscous strains among hospitalized patients with carbapenem resistant *klebsiella* in blood. They report 31% hypermucoviscous strains (by string test) among 86 isolates of carbapenem resistant *Klebsiella pneumoniae* from blood culture of hospitalized patients. 92% of CRkp

infections were hospital acquired and had a higher mortality. High meropenem MIC was a significant risk factor for mortality. Isolates with both string test positivity and meropenem MIC of  $\geq 16\mu\text{g/ml}$  had a very high mortality rate of 84.2%.

Understanding the mechanisms of resistance by genetic tests and Polymerase chain reaction has significant implications for antimicrobial stewardship and treatment strategy. Phenotypic tests can help predict the molecular mechanisms to guide empiric antibiotic therapy. Therapy should be based on in vitro testing and not by random antibiotics selection.

Strengthening the microbiological service, surveillance and reporting of new cases of resistant bacteria in healthcare facilities and countries is necessary to monitor the epidemiology and for periodic review and modification of preventive strategies to control these superbugs.

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