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Editorial

# Rapid Diagnostics Against Carbapenem-resistant Enterobacterales - From Bench to Bedside

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## INTRODUCTION

Carbapenem-resistant Enterobacterales (CRE) pose a significant global threat to hospitals worldwide. They are categorized as priority pathogen 1 in the World Health Organization's list of global priority pathogens. The prevalence of CRE varies across different regions in India. According to the Antimicrobial Resistance Surveillance Network of the Indian Council of Medical Research (ICMR), Klebsiella pneumoniae shows approximately 56% carbapenem resistance, while Escherichia coli shows about 30% resistance. CRE infections pose significant economic challenges for both patients and healthcare institutions, and may also result in fatal outcomes.[1] The bench to bedside approach of identifying infectious diseases using rapid diagnostic methods enable faster diagnosis and targeted antimicrobial therapy.

## BENCH TO BEDSIDE APPROACH

The bench to bedside approach refers to the use innovations in the clinical laboratory that can be used for diagnosis of infectious diseases at bedside. The minimum turnaround time for conventional culture based diagnostic methods is around 72 hours. This causes a delay in the initiation of targeted antimicrobial therapy by 2-5 days which in turn causes adverse prognosis in the patients. Rapid diagnostic techniques, such as nucleic acid amplification tests, offer a swift turnaround time and significantly reduce the period needed to initiate appropriate antimicrobial therapy for patients. These methods also facilitate prompt implementation of infection control measures, thereby aiding in the prevention of outbreaks and the containment of infectious diseases.[2]

## TECHNOLOGIES IN CRE RAPID DIAGNOSTICS (TABLE 1)

The following tests can be used for rapid diagnosis of CRE infections,

1. **Carba NP Test:** This is a phenotypic test which uses the principle of colorimetry for the identification of carbapenemase enzyme. The in vitro hydrolysis of imipenem by the carbapenemase enzyme results in a color change in the test[3].
2. **Matrix-Assisted Laser Desorption Ionization–Time of Flight (MALDI-TOF):** MALDI-TOF can be used to identify the hydrolyzed products of meropenem based on the mass-to-charge ratio (m/z). The absence of m/z 383 and/or 405 peaks indicates meropenem hydrolysis, while the presence of m/z 401, 423, 445, and 467 indicates hydrolyzed products[4].
3. **Nucleic Acid Amplification Tests (NAATs):** NAATs, including DNA microarrays, have several advantages over conventional antimicrobial resistance detection systems. The GeneXpert Carba-R assay is an example of a NAAT available for CRE detection.[5]
4. **Next-Generation Sequencing (NGS):** NGS can be used for the rapid identification of resistance genes

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and other determinants responsible for carbapenem resistance in Enterobacterales. It includes targeted sequencing, whole-genome sequencing, and metagenomics[7]

5. **Immunodiagnostic Tests:** These tests utilise the monoclonal antibodies for the detection of carbapenemase proteins.[6].
6. **Microfluidics:** It is an emerging diagnostic technique for rapid CRE detection. Loop-Mediated Isothermal Amplification (LAMP) of carbapenemase genes can be performed using microfluidic platforms[8]. Similarly, CRE can also be identified using magnetic digital microfluidics based on a colorimetric methodology.[9]

**Table 1: Rapid diagnostic tests for the detection of Carbapenem resistant Enterobacterales(CRE)**

| Type of Rapid Diagnostic Test | Accuracy | Sensitivity(Sn) | Specificity (Sf) | Turnaround time (TAT) | Methodology | Limitation |
|---|---|---|---|---|---|---|
| Carba NP Test | >90% | ~100% | ~100% | ~2 hours | Ability to detect carbapenemase activity | Limited sensitivity for detection of OXA 48 and mucoid bacterial isolates |
| MALDI-TOF | >90% | ~96.7% | ~97.9% | ~3-4 hours | Ability to detect carbapenemase activity | High cost; Expertise required for interpretation of results |
| NAAT | >90% | >85% | >95% | Same day (hours) | Ability to detect only the specific carbapenemase gene | Inability to detect novel carbapenemase genes |
| NGS | >90% | >90% | >90% | 24-48 hours | Ability to detect specific and novel carbapenem resistance mechanisms | High cost; Expertise required for interpretation of results |
| Immunodiagnostic tests | ~96.8% | >95% | >95% | ~1 hour | Detection of specific carbapenemase enzyme | Inability to detect other resistance mechanisms |
| Microfluidics | >90% | >90% | >90% | ~1 hour | Detection of specific carbapenemase enzyme | In Research ; not used in diagnostic platforms |

## STRENGTHS OF RAPID CRE DIAGNOSTICS

1. Rapid turnaround time: Identification of CRE is reduced from days to hours, enabling timely initiation of targeted antimicrobial therapy, quicker clinical decisions in intensive care units, and effective implementation of infection control measures.[10]
2. Accuracy: Most rapid diagnostic tests for CRE have been shown to precisely identify the genes responsible for carbapenem resistance.[11]
3. Bedside diagnostic potential: Some tests can be deployed as decentralized, bedside devices, which are particularly useful for outbreak prevention in resource-limited settings.
4. Support for antimicrobial stewardship: Rapid identification of CRE enables clinicians to choose the right drug for the right patient at the right time, helping to prevent inappropriate antibiotic use.[12]
5. Reduced healthcare expenditure: Rapid and targeted therapy decreases hospital length of stay and overall healthcare costs.[13]

## LIMITATIONS AND AREAS OF CAUTION:

1. Identification of genes: Rapid tests for CRE focus on detecting genes responsible for carbapenemase production and may fail to identify other mechanisms of carbapenem resistance.[14]
2. Sample limitations: Some rapid tests require cultured isolates for performance, which can delay clinical decision making.[10]
3. Complexity of interpretation: Discrepancies may occur between phenotypic and genotypic test results and in differentiating pathogens from commensals, making it difficult for clinicians to interpret and act on the findings. Clinical correlation of the results and expert input from a microbiologist is often required.[15]
4. Cost of the tests: The equipment needed for tests such as the GeneXpert Carba R assay and MALDI TOF are expensive, require trained personnel to operate them and cannot be utilised in low income countries.[16]

## CONCLUSIONS

Rapid diagnostic tests for CRE offer a bench to bedside approach by enabling swift diagnosis of infectious diseases using innovations made in the laboratory. This enables timely initiation of targeted antimicrobial therapy, outbreak prevention measures and antimicrobial stewardship practices to control and curb the spread of the infection in hospitals. Clinical correlation of results with expert microbiologist opinion is of paramount importance in the

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interpretation of the test results. Cost per test, infrastructure and complexity of interpretation of test results are some of the challenges of using rapid diagnostic tests for the detection of CRE.

### Practice Changing Points:

1. Rapid diagnostic tests for CRE decrease the 2-5 day delay caused by conventional diagnostic methods for the initiation of antimicrobial therapy
2. Carba-NP, MALDI_TOF, NAAT, NGS, Immunodiagnostic test and Microfluidics are some of the rapid diagnostic tests for CRE
3. Accuracy, bedside potential, rapid turnaround time are some of the advantages of utilising these tests.
4. Complexity of interpretation of test results, cost per test and infrastructure are some of the challenges in utilising these tests

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**KR:** Writing – review & editing

**LKV:** Writing – review & editing

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