Multidrug-resistant Gram-negative Bacterial Infections in Critically Ill

Manohar Gandhi¹, Rakshay Shetty²

ABSTRACT

Antimicrobial resistance (AMR) in gram-negative bacteria (GNB) is persisting to be a significant cause of severe infections across the world, with increasing morbidity and mortality rates. Extended spectrum beta lactamase (ESBL) rates are alarmingly increasing in Escherichia coli and Klebsiella species, which is about 70% and there has been an increase in the resistance to carbapenems over the past few years in India. Current scenario of rapidly growing multidrug resistant (MDR) organisms in our Indian intensive care units is posing difficulties with regard to detecting these infections and starting appropriate empirical antibiotics. A clear understanding of the epidemiological, microbiological, and pharmacological aspects of these MDR gram-negative organisms is very important. This article tries to brief the risk factors for MDR GNB infections, spectrum of MDR GNB infections, mechanisms of resistance, and beta-lactamase enzyme classification and outlines the clinically important types and the treatment considerations for these MDR gram-negative organisms.

Keywords: Beta lactamases, Extended spectrum beta lactamase, Multidrug resistant gram-negative bacteria.

Pediatric Infectious Disease (2019): 10.5005/jp-journals-10081-1214

INTRODUCTION

Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter species, Pseudomonas aeruginosa, and Enterobacter species (ESKAPE) are the common multidrug resistant (MDR) organisms; of these organisms, the most important emerging threats are gram-negative bacilli. Antimicrobial resistance (AMR) in gram-negative bacteria (GNB) is persisting to be a significant cause of severe infections across the world, with increasing morbidity and mortality rates.

It is mainly due to the presence of beta lactamas, which accounts for the widespread infections. Beta lactamas are of diverse types, of which extended spectrum beta lactamases (ESBLs) and carbapenemases are most important. Carbapenem resistance is increasing in the last few years in India. Extended spectrum beta lactamase rates are alarmingly increasing in E. coli and Klebsiella spp., which accounts for about 70%. Three hundred and seventy percentage ICU patients surveyed in India showed resistance to multiple antibiotics, prevalence of metallobeta lactamase (MBL)-producing organisms ranges from 7% to 65% in India. Hospital-acquired Klebsiella infections which are resistant to carbapenem increased from 2% in 2001 to 10% in 2011. This article tries to brief the risk factors associated with MDR GNB, types of infections caused by MDR GNB, various mechanisms of resistance, and beta-lactamase classification and outlines the clinically important types and the treatment considerations for these MDR gram-negative organisms in critically ill.

EPIDEMIOLOGY

Study for monitoring antimicrobial resistance trends (SMART) which was done during 2004 shows that ESBL-producing bacteria were highest in Latin America, the Middle East, Africa, and Asia. The SMART has showed that prevalence of cephalosporin resistance mediated by ESBL production in Escherichia coli and Klebsiella pneumoniae is 40.8% and 21.5%, respectively, in the Asia-Pacific region. Community-acquired urinary tract infections (UTIs) caused by ESBL-producing E. coli which are resistant to cephalosporins and fluoroquinolones are increasing in the US, Europe, and Asia.

In 2007, the prevalence of community-acquired ESBL-producing E. coli infections is as common as hospital-acquired ones and 79% of the E. coli isolates tested were ESBL producers (Table 1). Why do we have so much of MDR organisms?

- Decades of overuse and misuse of antibiotics.
- Excess use of antibacterials by the public over the counter and animal industry.
- Inappropriate antibiotic therapy.
- Overzealous antibiotic prescription by clinicians.
- Colonization pressure by resistant pathogens.

Common MDR GNB are the following:

- ESBL-producing enterobacteriaceae—E. coli, Klebsiella spp.
- Carbapenem-resistant enterobacteriaceae (CRE)—Klebsiella, Enterobacter, etc.
- Non fermenting gram negatives—Pseudomonas, Acinetobacter, Stenotrophomonas.

Risk Factors for MDR GNB Infections

- Community-acquired infections: diabetes mellitus, previous hospitalization, urine catheterization, previous beta lactam antibiotic usage.

© The Author(s). 2019 Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by-nc/4.0/), which permits unrestricted use, distribution, and non-commercial reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.
Multidrug-resistant Gram-negative Bacterial Infections in Critically Ill

- Hospital-acquired infections: invasive procedures, prolonged hospitalization, and previous use of cephalosporins and fluoroquinolones.
- Risk factors for carbapenemase-producing *Klebsiella pneumoniae* infections are the following:
  - Severe underlying disease, diabetes mellitus, ICU admission, mechanical ventilation, and exposure to betalactams, and fluoroquinolones.

Definitions of MDR, Extensively Drug Resistance, and Pan Drug Resistance

- MDR: the isolates are not susceptible to at least one antibiotic in three or more antimicrobial categories.
- Extensively Drug Resistance (XDR): the isolates are not susceptible to at least one antibiotic in all but two or fewer antimicrobial categories (i.e., they are susceptible to only one or two categories).
- Pan Drug Resistance (PDR): the isolates are not susceptible to all antibiotics in all antimicrobial categories (i.e., no agents tested as susceptible for that organism).

Mechanisms for AMR in MDR GNB

GNB can adopt various mechanisms of resistance to a single class or to multiple classes of antibiotics, as depicted in Table 2.

Beta-lactamase production is the most important mechanism of resistance to betalactams adopted by GNB, and beta-lactamase enzymes break the amide bond of the betalactam ring and inactivates the betalactams.

Ambler Classification of ESBLs

Beta lactamases are classified based on their molecular structure and aminoacid pattern.

There are four classes:

- Classes A, C, and D have serine at their active site, and class B beta lactamases are also called MBLs such as they have zinc at their active site.

Table 1: Differences in resistance patterns in gram-negative organisms between Indian and western ICU

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Western world</th>
<th>India</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common isolates</td>
<td>Gram +ve</td>
<td>Gram –ve</td>
</tr>
<tr>
<td>Prevalence of ESBL GNB</td>
<td>Less</td>
<td>High</td>
</tr>
<tr>
<td>ICU type</td>
<td>Closed type</td>
<td>Open type</td>
</tr>
<tr>
<td>Generic medicines</td>
<td>Few</td>
<td>Many</td>
</tr>
<tr>
<td>Antibiotic policy</td>
<td>Strict</td>
<td>Not strict</td>
</tr>
</tbody>
</table>

Table 2: Mechanism of resistance by GNB and targets

<table>
<thead>
<tr>
<th>Mechanism of resistance</th>
<th>Antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of porins</td>
<td>Carbenems (imipenem)</td>
</tr>
<tr>
<td>Beta lactamases</td>
<td>Betalactams</td>
</tr>
<tr>
<td>Efflux pumps</td>
<td>B-lactams, quinolones,</td>
</tr>
<tr>
<td></td>
<td>aminoglycosides, tigecycline,</td>
</tr>
<tr>
<td></td>
<td>and chloramphenicol</td>
</tr>
<tr>
<td>Mutations in the targets</td>
<td>Quinolones (DNA gyrase and</td>
</tr>
<tr>
<td></td>
<td>topoisomerase)</td>
</tr>
<tr>
<td>Ribosomal mutations</td>
<td>Tetracyclines, aminoglycosides</td>
</tr>
<tr>
<td>Bypassing targets</td>
<td>Trimethoprim, sulfonamides</td>
</tr>
<tr>
<td>Antibiotic modifying enzymes</td>
<td>Aminoglycosides, ciprofloxacin</td>
</tr>
</tbody>
</table>
reported in the US and UK primarily associated with travel history to India or Pakistan.\textsuperscript{22,28} They inhibit all betalactams except aztreonam. They reside on mobile gene cassettes inserted into integrons which harbor additional antibiotic resistance genes leading to MDR. These genes are transferred to other species via transposons and plasmids.\textsuperscript{23,29}

In class D, clinically important enzymes are OXA family,\textsuperscript{30} and they are found primarily in \textit{P. aeruginosa} and \textit{Acinetobacter} species.\textsuperscript{26}  VIM (37%), NDM (17%) in \textit{Pseudomonas aeruginosa} and OXA-23 (98%), and NDM (22%) in \textit{Acinetobacter baumannii} are the most prevalent carbapenemases noted in India.\textsuperscript{31}

Other resistance mechanisms against carbapenemes are impermeability and efflux, and these are common in \textit{Pseudomonas} species.\textsuperscript{35}

\textbf{Fluoroquinolone Resistance}

They acquire fluoroquinolone resistance by altering the drug targets (DNA gyrase and/or topoisomerase IV) and also by efflux pumps especially in \textit{E. coli} and \textit{Pseudomonas aeruginosa}.\textsuperscript{32}

\textbf{Aminoglycoside Resistance}

They acquire aminoglycoside resistance by producing inactivating enzymes which can cause phosphorylation, adenyllylation, or acetylation.

Alternatively, methylation of the 16S rRNA drug target causes resistance to the entire aminoglycoside class, including novel aminoglycosides.\textsuperscript{33} These methylases are plasmid-mediated and are spread among GNB along with carbapenemases leading to MDR.\textsuperscript{34}

\textbf{Multidrug Resistance}

GBN can activate several mechanisms at a time, like ESBL production, loss of porin channels, efflux pumps when they are exposed to an antibiotic leading to MDR. Transfer of plasmids with ESBL genes and other inactivating enzyme genes leads to the development of MDR strains. \textit{Pseudomonas aeruginosa} and \textit{Acinetobacter baumannii} most likely to become MDR in this fashion.\textsuperscript{35}

\textbf{Common Infections caused by GNB}

Blood stream infections (BSIs), ventilator-associated pneumonias (VAP), intra-abdominal infections (IAIs), skin and soft tissue infections, and urinary tract infections (UTIs) are the most commonly encountered infections.\textsuperscript{2}

The epic 2 study showed that lungs are the most common site (64%), followed by abdominal infection (19%) and BSI (15%).\textsuperscript{36}

\begin{table}[h]
\centering
\caption{Classwise important beta lactamas and their spectrum\textsuperscript{25}}
\begin{tabular}{|l|p{8cm}|p{3cm}|p{8cm}|}
\hline
\textbf{Class} & \textbf{Enzymes} & \textbf{Spectrum} & \textbf{Epidemiology} \\
\hline
Class A & ESBLs (TEM, SHV, CTX-M) & Penicillins, cephalosporins except cefamycins, aztreonam, inhibited by beta-lactamase inhibitors & Worldwide, community acquired and nosocomial infections \\
Class B & Metallobeta lactamases (NDM, VIM, IMP) & Penicillins, cephalosporins, carbapenemases. But aztreonam is susceptible. & Worldwide spread. Nosocomial outbreaks and endemic situations \\
& Amp C (CMY, DHA, FOX) & Not inhibited by beta-lactamase inhibitor & \\
Class D & OXA (OXA-48, OXA-181) & Penicillins, carbapenemases, and aztreonam & Nosocomial outbreaks. \\
& & Not inhibited by beta-lactamase inhibitor & \\
\hline
\end{tabular}
\end{table}

\textbf{When should We suspect ESBL and Carbapenemase-producing GNB?}

Based on antibiogram, if the isolate is resistant to third and fourth generation cephalosporins but sensitive to beta-lactamase inhibitors (Tazobactam), ESBL production should be suspected. If the isolate is resistant to carbapenem also, carbapenem production has to be suspected.\textsuperscript{29}

Most \textit{Klebsiella} and \textit{E. coli} without carbapenemases have minimal inhibitory concentrations (MICs) to imipenem and meropenem that are <0.5 \mu g/mL. Overt resistance of \textit{Klebsiella} and \textit{E. coli} to any of the carbapenem should arise suspicion of carbapenemase producers.

\textbf{Treatment of MDR GNB}

Early suspicion of MDR GNB by risk factors and timely initiation of appropriate antibiotic is very important step in treating these infections, and it decreases the mortality and improves the survival rate.\textsuperscript{37,38} Starting with broad-spectrum antibiotics and once the susceptibility report is available the antibiotics has to be optimized to more appropriate and narrow spectrum.\textsuperscript{38}

\textbf{Empirical Therapy}

Local institutionwise antibiograms have to be prepared based on the local prevalence of MDR organisms,\textsuperscript{39} and based on susceptibility patterns, broad-spectrum antibiotics or combination of antibiotics has to be started empirically after obtaining appropriate cultures.\textsuperscript{26}  As susceptibility rates to cephalosporins are severely decreasing, cephalosporins should not be a preferable choice for empirical therapy.\textsuperscript{3}

Carbapenem are the treatment of choice for empirical therapy of severe infections caused by ESBL-producing organisms.\textsuperscript{40}

\textbf{Current Treatment Options for treating MDR GNB Infections}

- Carbapenems.
- Polymyxins.
- Fosfomycin.
- Plazomicin.
- Tigecycline.
- Eravacycline.
- Betalactam-beta lactamase inhibitors (BL-BLIs):
  - Ceftazidime/avibactam, meropenem/vaborbactam, and ceftolozane/tazobactam.
Carbapenems (Meropenem and Imipenem)

Carbapenems are the drug of choice for treating life-threatening infections caused by ESBL-producing GNB. Studies have shown that 2-week mortality in patients with *Klebsiella pneumoniae*. BSI treated with meropenem was very less compared to other betalactam antibiotics.\(^{3,4}\) Carbapenems have wide distribution in different sites of the body like lung, blood, urine, and cerebrospinal fluid.\(^{42}\) They act in time-dependent bacterial fashion; 40–50% of the time, the drug levels have to be above the MIC.\(^{43}\) As they are excreted unchanged through kidney, to maintain their concentration constantly above MIC, they can be administered as continuous infusion.\(^{43}\)

For treating susceptible KPC-producing *Klebsiella* infection, colistin and meropenem combination can be used when the MIC is 8 mg/L and prolonged meropenem infusion should be considered if the MIC is >8 but <32 mg/L.\(^{44}\)

**Polymyxins**

Polymyxins are bactericidal agents which act on outer membrane of GNB.

They bind with the anionic lipopolysaccharide molecules by displacing calcium and magnesium from the outer cell membrane, leading to permeability changes in the cell envelope, leading to leakage of cell contents and cell death.\(^{45}\) Colistin (polymyxin E) and polymyxin B are in wide usage, and colistin is parenterally available in the form of colistimethate sodium (CMS) which gets hydrolyzed to colistin and sulfomethylated derivatives once it enters the body. It acts in a concentration-dependent fashion and is excreted through kidney.\(^{46}\)

**Colistin-loading Dose**

As discussed earlier, the parenteral CMS has to get converted to active colistin which is slow process, and colistin kills the bacteria in a concentration-dependent fashion. In view of large volume of distribution in critically ill patients and as the half-life of colistin is 2–3 days, it is important to give colistin-loading dose to achieve higher concentrations rapidly.\(^{46,47}\) The loading doses do not affect kidney function, but the maintenance doses have to be adjusted depending on the kidney function.\(^{48}\)

Colistin nebulization should be used in addition to intravenous therapy in patients with VAP due to MDR GNB.\(^{49}\) Colistin combination therapy: colistin with meropenem combination had better outcome than any other combination with colistin. MIC for colistin and meropenem combination is 0.12 μg/mL, which is fivefold less when compared to meropenem 4 μg/mL and colistin 0.38 μg/mL when tested as single agents.\(^{50}\) Colistin can be combined with amikacin or tigecycline in treating carbapenem-resistant GNB infections if they are sensitive to these antibiotics.\(^{54}\)

**Fosfomycin**

Similar to colistin fosfomycin is also an old broad-spectrum bactericidal antibiotic, which acts on bacterial cell wall by interfering with formation of UDP N-acetylmuramic acid, a peptidoglycan precursor. It is used in treating MDR GNB infections often in combination with other agents when there are no alternatives.\(^{51}\)

**Tigecycline**

It is a newer agent in tetracycline class which has shown good activity against CRE. *Pseudomonas aeruginosa* is inherently resistant to tigecycline.\(^{52}\) Tigecycline rapidly redistributes into tissues and achieves low serum levels; hence, it is not useful in treating BSIs and VAP.\(^{53}\)

Food and Drug Administration (FDA) has approved tigecycline only in the treatment of soft tissue infection and IAIs caused by MDR GNB.\(^{44}\)

**Eravacycline**

It is newer drug structurally similar to tigecycline, and it has been approved by FDA and European Medicines Agency (EMA) approved for the treatment of complicated IAIs (cIAIs). It is not affected by efflux pumps and ribosomal alterations by the GNBs, which is unique when compared to other tetracyclines. It has in vitro activity against KPC-producing bacteria and also acenatobacter baumannii. It has 90% oral bioavailability and also available in intravenous preparation. It has broad-spectrum of action covering gram-positive, GNB, and anaerobic bacteria except *Pseudomonas* and billhioldaria.\(^{54}\)

**Plazomicin**

It is a newer aminoglycoside, and it stable against several aminoglycoside-modifying enzymes. It is active against CRE. It is currently approved by the FDA for the treatment of complicated UTI (cUTI).\(^{55}\)

**Ceftazidime/Avibactam**

This combination has been approved by FDA and EMA for cUTIs, cIAIs, hospital-acquired pneumonia (HAP), and VAP. Studies showed a lower 30-day mortality with this combination for treating bacteremia caused by KPC-producing *klebsiella* isolates.\(^{56}\)

Hence, ceftazidime/avibactam is an effective option for the treatment of CRE. This combination is available in India.

**Meropenem/Vaborbactam**

It is another new BL-BLI, and it has a potent activity against class A (e.g., KPC) carbapenemase-producing CRE. It is FDA and EMA approved for cUTI, cIAI, HAP, and VAP in adult patients with limited treatment options.\(^{37}\)

Ceftolozane/tazobactam: it is another newer BL-BLI, and it is effective against *Pseudomonas* infections, but it is not active against CRE. It is approved by FDA and EMA for the treatment of cIAI and cUTI.\(^{58,59}\)

**Proposed Treatment Options for MDR-GNB Infections in Critically Ill Patients\(^ {57}\)**

**Current Treatment Options for CRE**

- Ceftazidime/avabactam (as preferred empirical choice when both KPC and OXA carbapenemases are reported locally) or meropenem/vaborbactam.
- For empirical therapy—add aminoglycoside or polymyxin or fosfomycin.
- In case of resistance to newer BL-BLI: consider polymyxin or aminoglycoside based combinations with carbapenem and/or fosfomycin and/or rifampin.
- For empirical and targeted therapy: combination with old (colistin, polymyxin B, old aminoglycosides, and fosfomycin) or novel agents (plazomicin, eravacycline, and double BL-BLI) could be considered on case-to-case basis (although lack of high-level evidence).
- Concomitant use inhaled polymyxins/aminoglycosides when they are used intravenously for VAP.

**Current Treatment Options for Carbapenem Resistance Pseudomonas aeruginosa**

- Ceftolozane/tazobactam (as preferred empirical choice in absence of concomitant risk of CRE) or ceftazidime/avabactam.
• For empirical therapy, administer a second antipseudomonal agent (an aminoglycoside or polymyxin or fosfomycin).
• In case of resistance to newer BL-BLI: consider polymyxin or aminoglycoside-based combinations with carbapenems and/or fosfomycin and/or rifampin.
• For targeted therapy: combination with old (colistin, polymyxin B, old aminoglycosides, and fosfomycin) or novel agents (plazomicin and double BL-BLI) could be considered on case-to-case basis (although lack of high-level evidence).
• Concomitant use inhaled polymyxins/aminoglycosides when they are used intravenously for VAP.

**Current Treatment Options for Carbapenem Resistance Acinetobacter baumannii**

• Administer polymyxin as the backbone agent.
• Consider combination with old (carbapenems, aminoglycosides, tigecycline, fosfomycin, and rifampin) or novel agents (plazomicin and eravacycline).
• Concomitant use inhaled polymyxins/aminoglycosides when they are used intravenously for VAP.

**Key Points**

- Incidence of carbapenemase-producing GNB infections are rapidly growing in Indian ICUs, especially NDM-1-producing gram negatives.
- Assessment of risk factors, MIC testing, and proper interpretation of antibiogram are vital in identifying these ESBL carbapenemase-producing and MDR GNB.
- Carbapenems are the drug of choice in treating serious infections caused by ESBL producers and are advised at high doses for carbapenemase-producing organisms (Klebsiella spp.) in combination with colistin as empirical therapy.
- Colistin is the backbone agent in treating carbapenem-resistant Acinetobacter baumannii, and loading dose has to be given to reach adequate drug concentration in critically ill patients.
- Inhaled colistin is advised in treating VAP along with intravenous colistin.
- Newer agents like plazomicin, eravacycline, fosfomycin, and BL-BLI combinations can be combined with colistin and meropenem for treating carbapenemase producers.

**Conclusions**

- All hospitals should have their own institutional antimicrobial stewardship program, and it should be based on local antibiograms and international guidelines to prevent the emergence of MDR GNB and even a more complex situation.
- Infection control practices should be strictly implemented to prevent MDR GNB infections in ICUs.
- Differentiate true infection from colonization and avoid unnecessary antibiotic prescriptions.
- Suspect MDR GNB infections and start adequate empirical antibiotics as soon as possible as delay in starting appropriate antibiotic is associated with poor outcomes.
- Deescalate to appropriate antibiotic as soon as the sensitivity pattern is available.

**References**
