Exploring the Use Of Antimicrobial Combination Therapy Against Multidrug-Resistant Gram-Negative Infections

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Abbreviations

» Gram-negative bacteria: GNB
» Combination: Combo
» Multidrug-resistant: MDR
» Extremely Drug Resistant: XDR
» Carbapenem resistant Enterobacteriaceae: CRE
» Carbapenem resistant Acinetobacter baumannii: CRAB
» Carbapenem resistant Pseudomonas aeruginosa: CRPA
» Constipation, urea, respiratory rate, blood pressure, age 65+= CURB-65
Objectives

» Discuss mechanisms of Gram-negative pathogen drug resistance

» Identify typical Multidrug-resistant Gram-negative pathogens

» Describe previously investigated antimicrobial combination therapy treatment regimens

» Explain the disease states in which the use of antimicrobial combination therapy would be advantageous
Gram-negative Bacteria

- The Gram-negative bacteria (GNB) envelope consists of the following three principal layers:
  - The outer membrane (lipopolysaccharide/ endotoxin)
  - The peptidoglycan cell wall with peptide chains
  - The cytoplasmic inner membrane
GNB Multidrug Resistance\textsuperscript{4-7}

Multidrug-resistant (MDR) GNB
Extremely drug-resistant GNB
Pan drug-resistant GNB
GNB Multidrug-Resistance\textsuperscript{5-7}

- MDR GNB is a major threat to hospitalized patients
  - Mortality rated range from 30-70%

- The inappropriate use of broad spectrum agents contribute to MDR GNB

- There are limited agents to treat MDR GNB infections

- It is important to balance the need for broad empiric coverage with the need to preserve antibiotics
GNB Resistance

- Neisseria gonorrhea
- Pseudomonas aeruginosa
- Klebsiella pneumoniae
- Acinetobacter spp.
- Escherichia coli
- Enterobacter spp.
Mechanisms of Resistance

ANTIBIOTIC RESISTANCE MECHANISMS IN GRAM-NEGATIVE BACTERIA

- Mutation in lipopolysaccharide (polymixin resistance)
- Overexpression of efflux pumps (multidrug resistance)
- Periplasmic space
- Plasmid
- Cell wall (peptidoglycan)
- Hydrolysis by β-lactamase (plasmid-acquired or overexpressed chromosomal genes)
- Modified drug target (e.g. quinolones)
- Antibiotic modification (e.g. aminoglycosides)
- Porin loss or mutation

Nat Rev Microbiol. 2015 May; 13(5): 269–284. Published online 2015 Apr 8. doi: 10.1038/nrmicro1433
Carbapenem- resistance in GNB$^{7-8}$

» Carbapenems have been readily used against MDR GNB

» Acquired resistance, or degrading enzymes (carbapenemases), has limited their efficacy

» The following "five carbapenemases" of particular relevance:
  1. *Klebsiella pneumonia* carbapenemases (KPC; Ambler Class A)
  2. New Delhi metallo beta-lactamase (NDM; Ambler Class B)
  3. *Imipenemase* metallo-beta-lactamase (IMP; Ambler Class B)
  4. Verona integron-encoded metallo-beta-lactamase (VIM; Ambler Class B)
  5. Oxacillin carbapenemases (OXA; Ambler Class D)
Alternative Antimicrobial Agents

In the presence of MDR GNB, including carbapenem resistance, the following agents have been utilized:

- Polymyxins (Polymyxin B and colistin)
- Glycylcycline (tigecycline)
- Aminoglycosides (amikacin, plazomicin)
- Novel siderophore cephalosporin (ceferoocol)
- Monobactam (aztreonam; stability against Ambler Class B beta-lactamases)

Beta-lactam/beta-lactam inhibitor combinations:
- Ceftolozane/ tazobactam
- Ceftazidime/avibactam
- Meropenem/ vaborbactam
- Imipenem/relebactam
Antimicrobial Combination Therapy\textsuperscript{9-12}

» The spread of MDR GNB, including those with carbapenamases, has minimized single agent efficacy

» Current literature reports that there may be utility in using multiple agents with different mechanisms of activity

» Observational studies show that between 25 and 50\% of patients with the following infections are administered combination therapy:
  • Bacteremia, surgical site infections, or pneumonia
Whether antimicrobial combination therapy is more efficacious than monotherapy remains controversial.

MDR GNB antimicrobial combination therapy is usually utilized against the following organisms:
- *Klebsiella pneumoniae* (CRE)
- *Escherichia coli* (CRE)
- *Enterobacter* spp. (CRE)
- *Serratia marcescens* (CRE)
- *Acinetobacter baumannii* (CRAB)
- *Pseudomonas aeruginosa* (CRPA)
The initial use of antimicrobial combination therapy for infections with MDR GNB is often justified by one of the following reasons:

- Broadening the empiric coverage with two agents with differing spectra of activity
- Synergy observed in vitro between two agents
- Preventing or delaying the emergence of resistance
Broad Spectrum of Activity

- Increased MDR GNB empiric coverage reduces mortality
- When combination therapy is used:
  - Use local antibiogram to inform empiric decisions
  - Individualize empiric therapy based on patient characteristics
  - De-escalation of antimicrobial therapy when susceptibility results are known
» Antimicrobial combination therapy can present with more rapid killing of an organism

» Synergy is defined as:
  • a greater than 2-log increase in bactericidal activity

» The rate of bactericidal activity can be shown in multiple agents by:
  • time-kill assay (fixed concentration)
  • checkboard assay (various concentrations)
  • E-test (various concentrations)
Prevention of Resistance\textsuperscript{12}

» The use of multiple agents has been shown to slow the rate of resistance

» This can be shown through an increase to susceptibility to an individual antibiotic

» Typically requires that the antibiotics be of different drug class (i.e. levofloxacin and imipenem)
Clinical Studies Assessing the Benefit of Antimicrobial Combination Therapy

<table>
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<tr>
<th>Infection (Organism evaluated)</th>
<th>Drug Combinations evaluated</th>
<th>Outcome(s) assessed</th>
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<td>MDR GNB (fermenters and non-fermenters)</td>
<td>Colistin vs. colistin plus meropenem, ampicillin/sulbactam, or piperacillin/tazobactam</td>
<td>Clinical response; nephrotoxicity; mortality</td>
<td>No difference in response; favorable outcomes with either mono or combo therapy</td>
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<td>MDR <em>P. aeruginosa</em> (multiple sites)</td>
<td>Colistin vs. colistin plus aztreonam, anti-pseudomonal beta-lactam, rifampin, or fluroquinolone</td>
<td>Clinical response; nephrotoxicity</td>
<td>No difference in response nor nephrotoxicity</td>
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<td>Carbapenem-resistant <em>K. pneumoniae</em></td>
<td>Colistin vs. Carbapenem plus colistin or aminoglycoside, polymyxin B plus tigecycline</td>
<td>Mortality; increase in polymyxin (MIC)</td>
<td>Patients treated with carbapenem had higher survival, polymyxin plus tigecycline may prevent resistance</td>
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<td>Carbapenem-resistant <em>A. baumannii</em></td>
<td>Tigecycline vs. tigecycline plus aminoglycoside</td>
<td>Clinical failure</td>
<td>Improved outcomes with the use of combo therapy</td>
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Disadvantages with Antimicrobial Combination Therapy 15-17

» The following disadvantages/ adverse effects with antimicrobial combination therapy have been reported:

• Nephrotoxicity
• Ototoxicity
• Clostridium difficile infection
Combination therapy can be helpful in the following conditions:

- Targeted therapy for patients with life threatening CRE infections
- Therapy for sepsis patients with multiorgan failure
- Therapy for severe community acquired pneumonia with bacteremia
CRE infections can include a single or multiple carbapenamases

Many of these infections are also resistant to other antimicrobials

Studies have revealed that there are more treatment failures associated with antimicrobial monotherapy vs. combination therapy

Combination therapy in these infections most often include colistin or a polymyxin B base

Despite their resistance and decreased susceptibility carbapenems are often used in combination with the polymyxin base
Therapy for Septic Patients With Multiorgan Failure15-18

» The sepsis guidelines suggest the use of combination therapy in the empirical regimens of septic patients

» Severely ill patients (increased APACHE score, etc.) have a high microbiological burden

» Kumar et al showed that combination therapy had the largest impact in those with a high risk of death

» The benefit of the combination therapy was lost in those patients with a decreased risk of death
Therapy for Severe Community Acquired Pneumonia (CAP) with Bacteremia\textsuperscript{15-18}

» Patients with an elevated CURB-65 score (3 or more) require ICU care

» About 10\% of patients with CAP develop bacteremia

» Patients with bacteremia secondary to CAP have been shown to respond well to combination therapy

» Combination therapy with a beta-lactam and a macrolide has been shown to be superior to monotherapy

» Macrolides inhibit neurolysin production and immunomodulatory action on neutrophils
Combination Therapy Algorithm

Patient with Life-threatening MDR GNB Infection

Start with Broad Spectrum Antibiotic

Obtain Microbiological Data

Carbapenem Sensitive MDR GNB Organism
  - Carbapenem Monotherapy

Carbapenem Resistant MDR GNB Organism
  - Combination Therapy (+/- Carbapenem)
Summary

» The rapid dissemination of MDR GNB organisms is a global health concern

» MDR GNB carbapenem resistant infections continue to increase

» There are limited monotherapy options available to treat carbapenem resistant infections

» Limited evidence shows favorable results in certain subgroups of patients treated with antibiotic combinations

» Further research is needed to guide rational use of antimicrobial combination regimens
References

Thank you!
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