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

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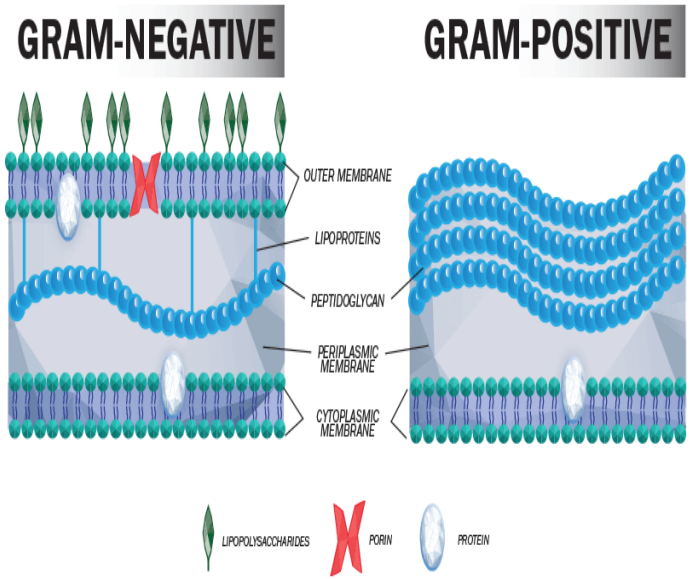
Abbreviations

- 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[1]



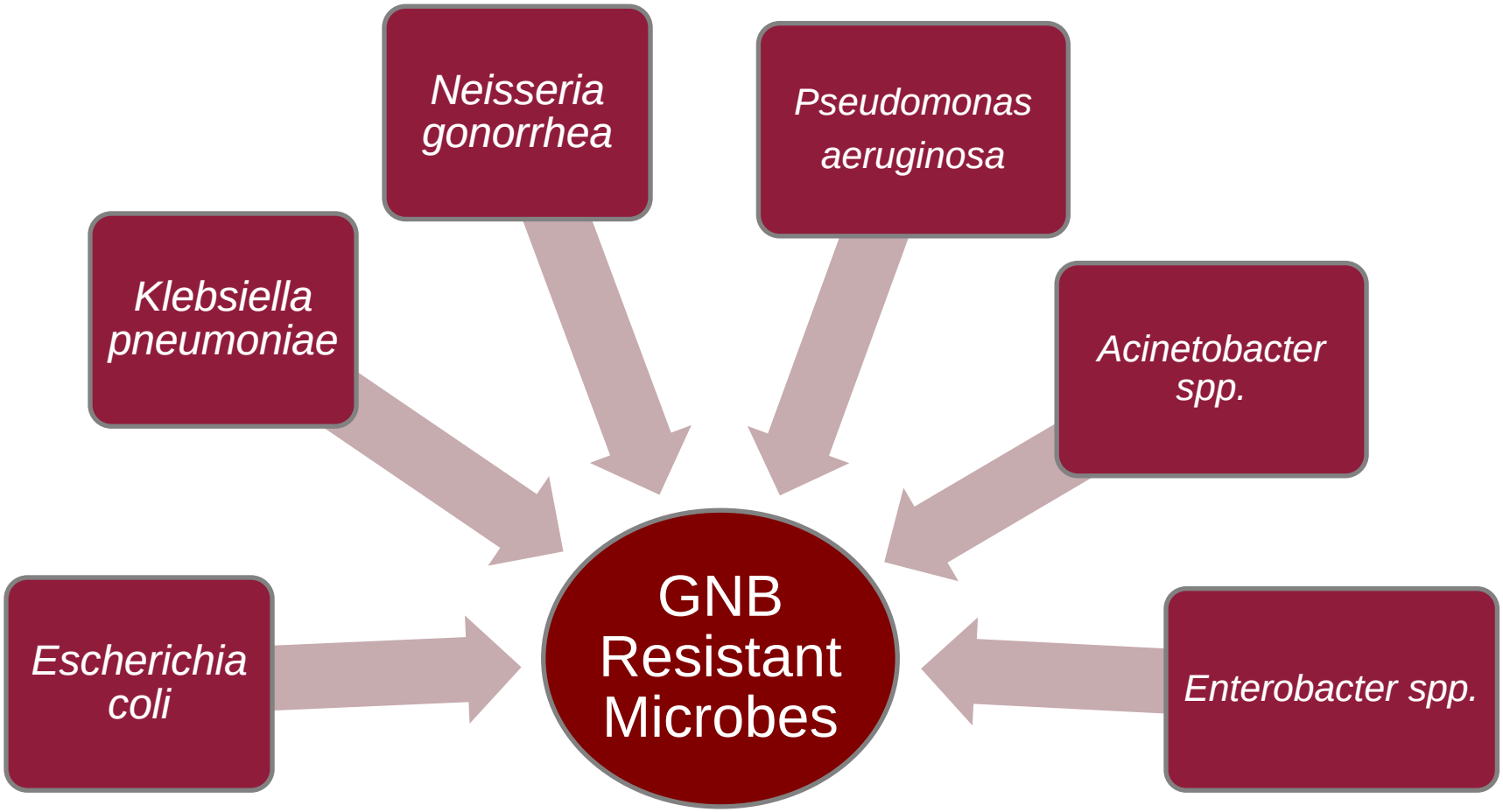
- The Gram-negative bacteria (GNB) envelope consists of the following three principal layers :
- The outer membrane (lipopolysaccharide/ endotoxin)
- The peptidoglycan cell wall with peptide chains
- The cytoplasmic inner membrane

GNB Multidrug Resistance[4-7]

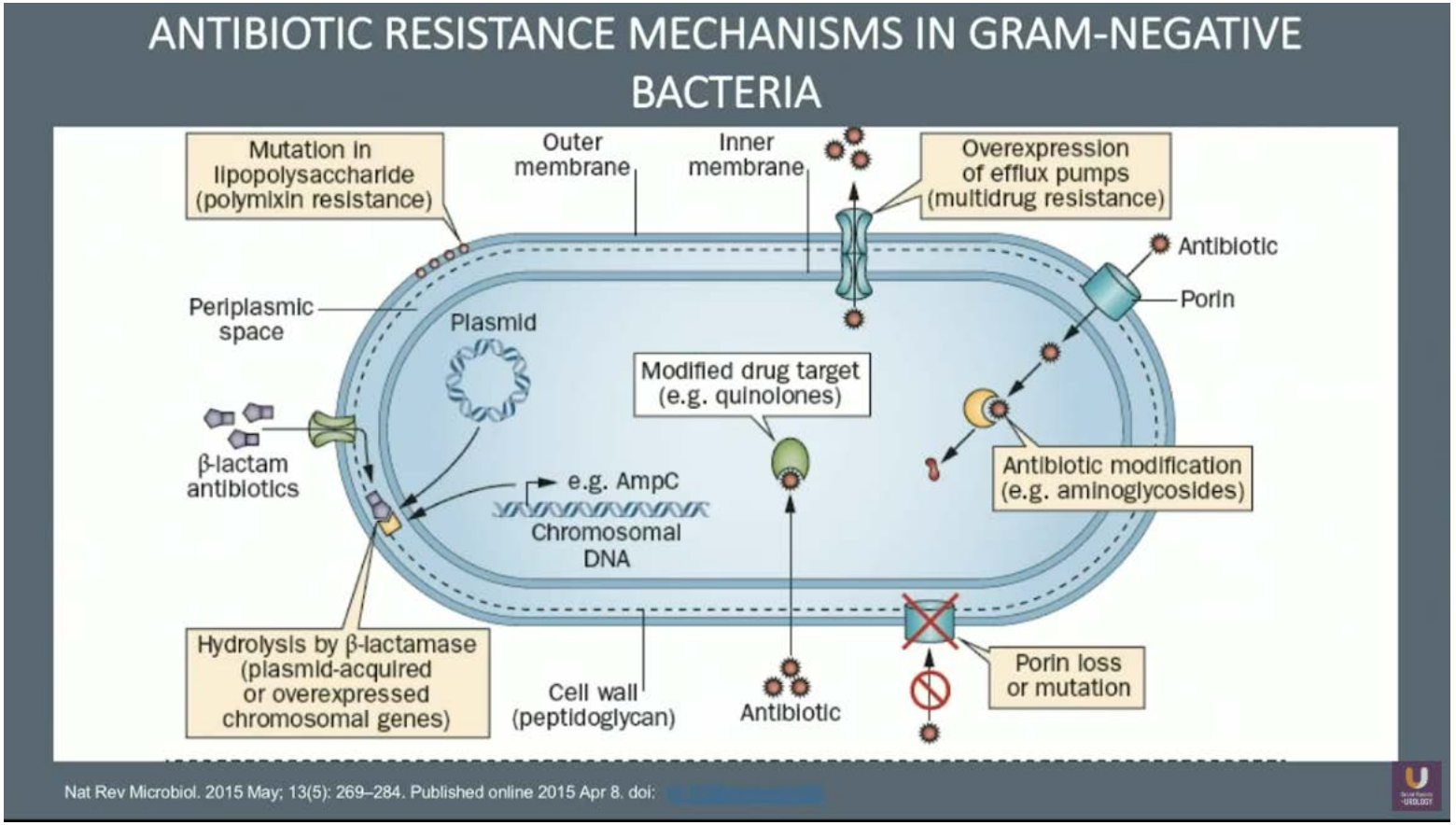
GNB Multidrug-Resistance[5-7]

- 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[3-7]



Mechanisms of Resistance[2]



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 carbapenamses” of particular relevance:
  1. *Klebsiella pneumonia* carbapenamases (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 carbapenamases (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 (cefiderocol)
- 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[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

Antimicrobial Combination Therapy[3-12]

- 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)*

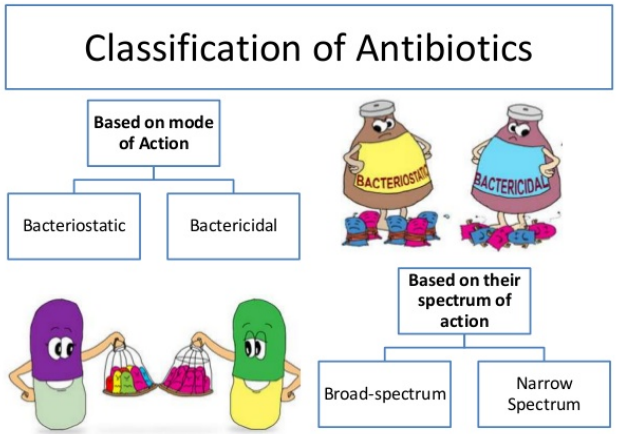
Antimicrobial Combination Therapy[9,13-16]

» 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

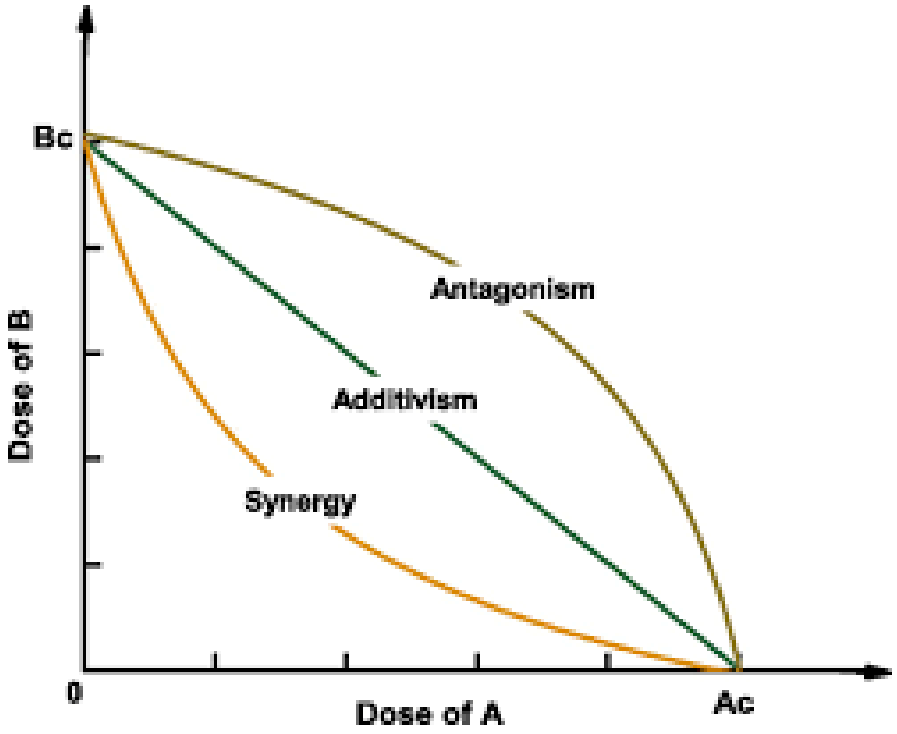
Broad Spectrum of Activity[11]

- 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



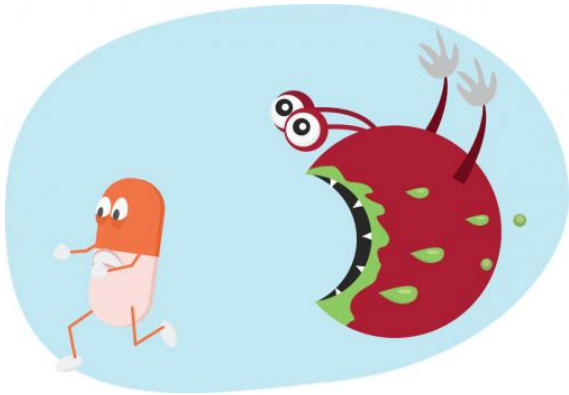
Synergy[9,13]

- Antimicrobial combination therapy can present with more rapid killing of an organism
- Synergy is defined as:
  - a greater that 2-log increase in bactericidal activity
- The rate of bactericidal activity can be shown in **MUTLIPLE** agents by:
  - time-kill assay (fixed concentration)
  - checkboard assay (various concentrations)
  - E-test (various concentrations)



Prevention of Resistance[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[15-17]

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

Disadvantages with Antimicrobial Combination Therapy [15-17]

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

- Nephrotoxicity
- Ototoxicity
- *Clostridium difficile* infection

Antimicrobial Combination Therapy Application

» 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

Targeted Therapy for Patients With Life-Threatening CRE Infections [15-18]

- 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

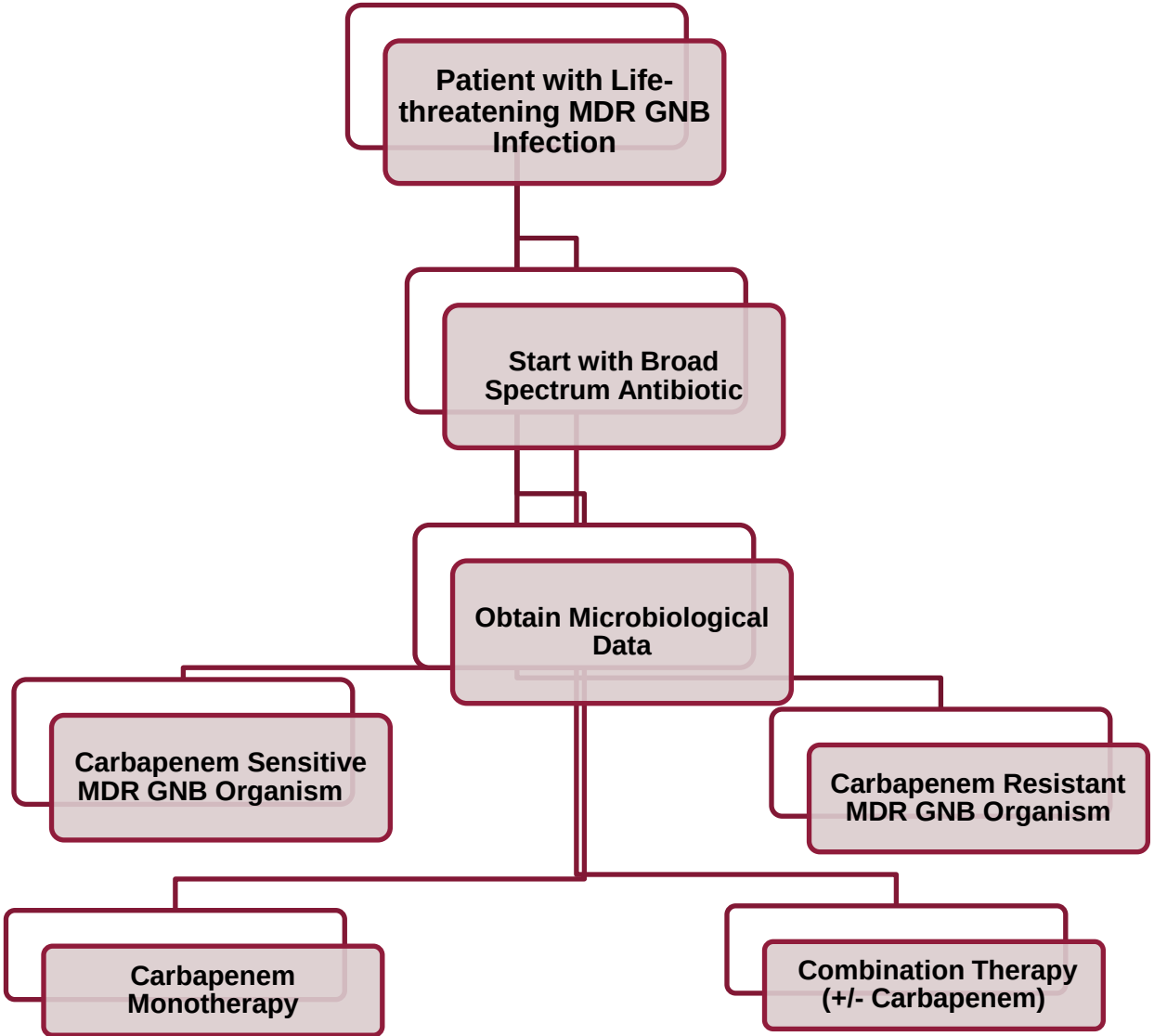
Therapy for Septic Patients With Multiorgan Failure[15-18]

- 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[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



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

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Thank you!
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