Gram-negative organisms: double coverage or no double coverage?

Gram-negative bacilli are the cause of significant morbidity and mortality in the hospital setting. Covering these organisms, specifically *P. aeruginosa*, with two antimicrobial agents has become the standard of care due to results of a study conducted in 1989 indicating improved mortality in patients receiving combination therapy compared to monotherapy. However the evidence supporting double coverage has been questioned. This issue of CLIPs briefly summarizes an article that explores the advantages and disadvantages of using two antimicrobial agents to treat gram-negative organisms and discusses the necessity of combination therapy. If you need further information, please contact the Samford University Drug Information Service at (205) 726-2659.


Current Guidelines

- No true guideline exits regarding double coverage of extended spectrum β-lactamases.
- The Infectious Disease Society of America (IDSA) does not recommend first-line combination therapy for treatment of febrile neutropenic patients.
- The IDSA-American Thoracic Society recommends combination therapy for late-onset pneumonia or patients who have risk factors for multidrug-resistance.

Empirical antimicrobial therapy

- Risk factors for infections with gram-negative organisms should be considered when evaluating empirical therapy.
- Risk factors for gram negative infections include: increase length of hospital stay, admission to an intensive care unit, comorbid conditions, use of a catheter, mechanical ventilation, and hemodialysis.
- Patients with risk factors should receive an antimicrobial regimen that includes at least one antipseudomonal agent with a broad spectrum of coverage.
- Empiric therapy should be modified when hospital-specific susceptibility data is identified. Monotherapy, if applicable, should be initiated when culture and sensitivity data is available.

Advantages and disadvantages of combination antimicrobial therapy

- Several advantages and disadvantages of combination therapy have been identified. The table below describes these advantages and disadvantages.

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>Potential for synergistic activity</td>
<td>Increased potential for resistance.</td>
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<td>Expanded spectrum of coverage</td>
<td>Increased cost potential.</td>
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<td>Additional antimicrobial coverage of resistant organisms that may be</td>
<td>Lack of guidelines for double coverage of extended-spectrum β-lactamase</td>
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<td>resistant to monotherapy.</td>
<td>producing gram-negative organisms.</td>
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<td>Prevention of antimicrobial resistance during course of treatment.</td>
<td>Increased risk for adverse reactions.</td>
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<td>Increased risk of developing superinfections such as candidemia or pseudomembranous colitis.</td>
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Agents used for double coverage

- Combination regimens should be chosen based on individual hospital susceptibility.
- Initial regimes used to include mainly a β-lactam plus an aminoglycoside that are active against *P. aeruginosa* used for synergistic activity.
- Use of combination therapy with aminoglycosides and β-lactams have fallen out of favor due to adverse reactions (e.g., nephrotoxicity, ototoxicity), and additional monitoring.
- One meta-analysis indicated that combination therapy showed similar or better outcomes as β-lactam monotherapy in immunocompetent patients treated for sepsis; however, another meta-analysis of combination therapy found no differences in mortality rates between combination therapy and monotherapy.
- Additional benefit may be conferred with combination therapy in patients with shock or neutropenia.
- Combination therapy with a fluoroquinolone and β-lactam antibiotic was assessed in a retrospective study in patients with febrile neutropenia. No differences in outcomes were observed.
- Current evidence indicates that combination therapy with a fluoroquinolone and a β-lactam antibiotic may result in a survival benefit for patients who had bacteremia from a urinary source (p<0.01) compared to critically ill patients.
- Combination therapy with two β-lactam antibiotics may be considered. However, data supporting this combination does not include combinations that are in use today.

Conclusions

- There is not enough clinical evidence to support the regular use of multiple antimicrobial agents for the treatment of gram-negative organisms.
- Conflicting evidence exists regarding the use of monotherapy versus combination therapy.
- However there is evidence to support use of combination therapy in patients with shock or neutropenia.
- Individual hospital susceptibility patterns should drive which agents are used empirically for the treatment of infectious diseases.