Case SIGNOUT:

83yo F w/ HTN, hypothyroidism, hyponatremia 2/2 poor PO intake vs. SIADH (recent AICU admission for Na 123 and SBP in 50s), dementia w/ rapid functional decline, now bedbound with contractures, presenting w/ fever, worsened PO intake, and altered mental status of 3 days. In ED, was febrile to 39.6 and hypotensive w/ SBP in 70s that responded to 4L NS. With labs showing hyponatremia, leukocytosis, venous lactate 3.5 and pyuria, she was admitted for severe sepsis 2/2 pyelonephritis. Her prelim urine cultures were + for gram neg rods, and she initially improved on Zosyn but then became febrile, hemodynamically unstable (initially fluid responsive) with cultures speciating MDR pseudomonas sensitive to levofloxacin. She was switched to IV levofloxacin with transient improved of mental status and resolution of fever. Family meeting was held for discussion of goals of care, and patient was made DNR with pending decision regarding ICU transfer, DNI, and artificial nutrition. On day 4 of admission, the patient became again delirious and hypotensive w/ SBP 70-80s unresponsive to IVFs. Antibiotics were broadened w/ tobramycin and family notified of plan for ICU transfer; however patient became unresponsive and pulseless prior to transfer. Death was presumed to be due to septic shock 2/2 MDR pseudomonas pyelonephritis.

Clinical Question: Would the patient have benefited from early combination antimicrobial therapy?

Search Strategy:
Database: PubMed  Query: “severe sepsis” “antimicrobial therapy”  Filter: Clinical Trial → 23 results

Selected Article:

Background
• **Severe sepsis**, as defined by international consensus panel in 1992, is sepsis + organ dysfunction, hypoperfusion, or hypotension (e.g. lactic acidosis, oliguria, change in mental status). **Septic shock** is sepsis complicated by hypotension refractory to fluid resuscitation with signs of hypoperfusion.
• The Surviving Sepsis Campaign has promoted an 2 bundles of guidelines for treating sepsis within the first 6 hrs of presentation and later within the ICU.
• Our patient’s admission was complicated by the ambiguity of her family in regards to intensity of care given her rapid functional decline with multiple hospitalizations within the last year, including an ICU admission within the last month. In the setting of the patient’s initial responsiveness to treatment, the decision was made to defer ICU transfer and manage her on the medicine floor.
• A number of clinical trials have investigated the efficacy of different forms of volume resuscitation (colloid vs. crystalloid), use of vasopressors, steroids, and other elements of management in severe sepsis and septic shock, including the multi-center randomized controlled ProCESS study led by UPMC. However, the most important step is in the correct initial selection of antimicrobial therapy.
Senior Medicine Rotation: Based Medicine Project (Cont)

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<thead>
<tr>
<th>Group</th>
<th>Criteria or definition</th>
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<tbody>
<tr>
<td>Population screened</td>
<td>Patients at 44 intensive care units in Germany from October 16, 2007, to March 23, 2010</td>
<td>5607</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>1. fulfilled criteria for severe sepsis or septic shock</td>
<td>1088</td>
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<td></td>
<td>2. onset of symptoms &lt;=24hrs prior to study inclusion</td>
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<tr>
<td>Exclusion criteria</td>
<td>1. treated with more than 1 daily dose of a carbapenem or a quinolone within the 4 weeks prior to randomization</td>
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<td>2. received an antipseudomonal β-lactam antibiotic within 48 hours prior to randomization</td>
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<td></td>
<td>3. previously infected or colonized with MRSA or VRE</td>
<td></td>
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<tr>
<td>Treatment group</td>
<td>Moxifloxacin and meropenem combination therapy</td>
<td>298</td>
</tr>
<tr>
<td>Control group</td>
<td>meropenem monotherapy</td>
<td>302</td>
</tr>
</tbody>
</table>

Primary endpoints: degree of sepsis-related organ failure (mean of daily total Sequential Organ Failure Assessment [SOFA] scores over 14 days; score range: 0-24 points with higher scores indicating worse organ failure) or discharge from the ICU or death, whichever occurred first

Secondary endpoints: 28-day and 90-day all-cause mortality (also mean SOFA subscores; duration of ICU and hospital stay; clinical and microbiological treatment response; intervention-free days with a ventilator, vasopressor, dialysis, or antibiotic; secondary infections; emergence of antibiotic-resistant bacteria; and adverse events)

Are the Results of the Trial Valid?
- **Randomized?** Yes, patients were randomly allocated to receive 1 g meropenem q8h and 400mg moxifloxacin q24h or 1 g meropenem q8h alone. Balanced randomization via stratification by participating centers (modified Pocock minimization algorithm).
- **All patients accounted for at end?** Yes, 25 in monotherapy and 24 in combination were excluded due to delayed informed consent not obtained. Number of evaluable patients was 273 in monotherapy group and 278 in combination therapy group (intention to treat). Remainder of patients lost to follow-up/discontinued intervention/withdrew consent/ inadequate therapy/stopped due to toxicity or adverse event
- **Intention to treat?** Yes, 4 crossovers (1 from monotherapy, 3 from combination therapy)
- **Blinding?** No, the infusion requirements were different for meropenem (over 15-30min) and moxifloxacin (over 60min)
- **Groups similar at start of trial?** Yes, demographic and baseline characteristics, site and source of infection, pathogens present at the time of enrollment, indicators of severity of disease, and antibiotics used 1 week prior to randomization were well balanced. Median time from enrollment to initiation of study antibiotics was 0.7hrs (interquartile range [IQR], 0.4-1.0) in the combination therapy group and 0.8hrs (IQR, 0.5-1.4) in monotherapy group
- **Equal treatment of groups?** Yes, both groups received antimicrobial treatment and similar rates of concomitant treatment (activated protein C, low-dose hydrocortisone, selenium, >5mg prednisolone equivalent immunosuppression)
- **Did randomization work?** Yes
- **Conflicts of interest:** Authors received payments from pharmaceutical companies for travel, lectures, and research grants. Sponsors had no role in study design/conduct/analysis/ manuscript preparation or review.

Are the Results of the Trial important?
- **Size of treatment effect?** No statistically significant difference in primary outcome between the 2 groups
• **Precision of the estimate of the effect?** There is not effect. The sample population was selected to study to detect a difference of 1.1 points in mean SOFA score between the 2 interventions with a significance level of .05 and a power level of 90%

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<tr>
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<th>Result</th>
<th>Significance</th>
<th>ARR</th>
<th>NNT</th>
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| Mean SOFA score (degree of end-organ dysfunction) | Monotherapy: 7.9 (7.5-8.4)  
Combination: 8.3 (7.8-8.8)   | p=0.36        |     |     |
| % mortality @ 28d                             | Monotherapy: 21.9 (17.1-27.4)  
Combination: 23.9 (19.0-29.4)  | p=0.58        |     |     |
| % mortality @ 90d                             | Monotherapy: 32.1 (26.5-38.1)  
Combination: 35.3 (29.6-41.3)  | p=0.43        |     |     |
| Length of stay, median d in ICU                | Monotherapy: 11 (5-24)      
Combination: 12 (6-21)  | p=0.90        |     |     |
| Length of stay, median d in hospital           | Monotherapy: 29 (14-45)     
Combination: 26 (15-42)  | p==0.64       |     |     |
| % secondary infection                          | Monotherapy: 32.1 (28.2-36.1)  
Combination: 31.4 (26.0-37.2)  | p=0.95        |     |     |

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<th>NNH</th>
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| % study-related adverse event                 | Monotherapy: 3.8 (1.2-6.6)  
Combination: 8.6 (5.7-12.3)  | p=0.02        |     |     |

**Can I apply these results to my patient?**

• **Comparison of my patient to trial patients:** Based on the inclusion criteria of this study, my patient would not qualify for this study. Although she fulfilled the requirements for severe sepsis and does not have any of the exclusion criteria for the study, the onset of her symptoms per history was over 24hrs before presentation to the ED. Additionally, generalization of this study is difficult as it looks at a specific combination of antimicrobial treatments for empiric treatment. However, it still offers a general proof of principle analysis of whether combination therapy is necessarily better than monotherapy.

• **All clinically important outcomes considered.** Yes, the most important outcomes for the patient are end-organ dysfunction, which can lead to debilitating long-term sequelae as well as mortality.

• **Likely benefits outweigh potential harms and cost?** No, there are no benefits to combination therapy and increased adverse effects based on this trial. Moreover, dual-therapy is more expensive than monotherapy. However, again, this study is limited to a specific patient population with a specific combination of antimicrobials.

**Other references:**


