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Disclosures

• Unrestricted Grants: Lilly, Pfizer, Wyeth, Merck, BMS, Astellas, Bayer, Astra-Zeneca, Roche

• Commercial Studies: Novartis, GSK, Circe, Eisai, Takeda, Roche

• Speaker: Merck, BMS, Pfizer, Wyeth, Lilly, Astellas

• Advisory Boards: Wyeth, BMS, Pfizer, Lilly, Ikaria, Roche
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Relationship of SIRS, Sepsis and Infection

Sepsis and Septic Shock: An Intensivist’s Immunologic View

van der Poll T, van Deventer SJH. Infect Dis Clin N Am
Sepsis and Septic Shock: An ID-Microbiologic View

TIME

Microbial load

Toxic burden

Inflammatory response

Cellular dysfunction/tissue injury
Shock is a syndrome resulting from depression of many functions, but in which reduction of the effective circulating volume and blood pressure are of basic importance, and in which impairment of circulation steadily progresses until it eventuates in a state of irreversible circulatory failure.
An Injury Paradigm of Septic Shock: The Golden Hours

- Microbial load
- Inflammatory response
- Toxic burden
- Cellular dysfunction/tissue injury

TIME

DEATH

Shock Threshold
An Injury Paradigm of Sepsis and Septic Shock

- Microbial load
- Inflammatory response
- Toxic burden
- Cellular dysfunction/tissue injury
- Antimicrobial therapy

TIME

Shock Threshold
An Injury Paradigm of Sepsis and Septic Shock

TIME

earlier antimicrobial therapy

Shock Threshold

Cellular dysfunction/tissue injury
Inflammatory response
Toxic burden
Microbial load
Impact of Appropriateness of Initial Antimicrobial Therapy on Survival from Septic Shock

Kumar et al, Chest 2009; 136:1237–1248
Cumulative Initiation of Effective Antimicrobial Therapy and Survival in Septic Shock

![Graph showing the cumulative initiation of antibiotic therapy and survival fraction over time from hypotension onset (hrs)]

- Survival fraction
- Cumulative antibiotic initiation

Antimicrobial Delay vs Survival (2001-07)

- Survival vs Delay (hrs)
- Academic
- Community
Case Study

Case Study: A 76 year old woman with a history of COPD, paroxysmal atrial fibrillation and ischemic heart disease is seen on the medical ward. She is recovering from a relatively minor stroke. She was last seen by a nurse at 10 pm am who noted a blood pressure of 90/55 mm Hg. However, her blood pressure has been a little low for the last several days and the patient was sleeping at the time. She is reassessed an hour later by the next nurse on shift. The nurse’s notes indicate the patient is moderately emaciated, pale, mildly lethargic and somewhat confused. She is slightly short of breath and has a productive sounding cough but has difficulty coughing up her sputum. Her heart rate is 95, respiratory rate 23/min, tympanic membrane temp 35.9°C and blood pressure 88/50 mm Hg. Oximeter shows a saturation of 94% on 50% face mask. Medications include digoxin, hydrochlorothiazide and metoprolol. She is assessed over 30 minutes by an intern who notes that her jugular venous pressure is decreased. He orders a bolus of 250 mL saline while awaiting the resident. Blood pressure initially increases to 104/62 mm Hg. However, when reassessed 30 minutes later, it is decreased again to 87/52 Hg. A repeat assessment 10 minutes later shows similar results. The resident assesses the patient and orders an immediate 500 mL saline bolus over 30 minutes, institution of bronchodilator therapy and a chest radiograph. Blood pressure again increases transiently but is again decreased to 86/50 when assessed 20 minutes after the saline bolus. The resident reviews the chest radiograph and notes evidence of a possible right lower lobe infiltrate. He orders sputum and blood cultures to be drawn prior to initiation of antimicrobials (cefepime, vancomycin and metronidazole). The blood technician is backed up and takes 50 minutes to arrive. In the meantime additional fluid boluses have been given and a modest dose of dopamine initiated through a central line.
Case study (continued)

• Broad spectrum antimicrobials at this academic hospital are restricted. As vancomycin is not restricted and is easily available in the ED, this drug is infused first (over 1 hour). Metronidazole follows over 40 minutes. The nurse informs the resident that pharmacy is unable to release cefepime without ID approval. After unsuccessfully attempting to contact the ID intern on call for 30 minutes, the resident calls the on-duty pharmacist and (unknown to Dr. Kumar, the Infectious Diseases staff) informs him that Dr. Kumar has approved the use of cefepime. Cefepime is released and begins infusing at 6 am, 8 hours after first documentation of hypotension. While awaiting transfer to the ICU, the patient’s blood pressure deteriorates further and she requires emergent intubation for airway protection. Dopamine is replaced by norepinephrine and the patient is emergently moved to ICU. Serum lactate there is found to be 3.2 mmol/L. White cell count is 3.8 X 10^9/L.

• Both sputum and blood cultures grow an E. coli resistant to ampicillin and ciprofloxacin. The patient does poorly with the development of acute tubular necrosis and thrombocytopenia. Despite the application of CVVH, she develops additional organ failures and is unable to be liberated from ventilatory support. Life support is withdrawn 14 days after admission.
What affects delays?

• Med ward > surg ward > ER
• Nosocomial vs community acquired
• Normal WBC/temp
• Older, more comorbidities
• Sicker (APACHE II)? More OF
• Certain types of infection site/organisms
Causes for Delays

- Failure to recognize that hypotension represents septic shock
- Effect of inappropriate antibiotic initiation
- Failure to appreciate risk of resistant organisms in certain scenarios (e.g. immunocompromised vs immunosuppressed; antecedent antimicrobial use)
- Wait for blood cultures from IV techs
- Two nurse check on antibiotic initiation
- Transfer from ER before antibiotics given
- Failure to use “stat” orders
- Failure to recognize that presence of inappropriate antimicrobials = no antimicrobials when responding to clinical failure
- No specified order with multiple drug regimens
- Administrative/logistic delays (nursing/pharmacy/ward clerk)
Solutions for Delays

• The presence of hypotension in a patient with known or suspected infection should be considered to be septic shock in the absence of a definitive alternate explanation
• No transfer from ER before antibiotics given
• All initial orders for any IV antibiotic automatically “stat”
• Syndrome-based, algorithm-driven guidelines similar to meningitis and neutropenic sepsis with designated broad spectrum antimicrobial regimen at each center
• Antibiotic order to include sequence and time limit (i.e. initiate “cefacurall” by within 30 minutes of order)
• First IV dose of most broad-spectrum agents (i.e. #lactam/carbapenems) “push” by physician
Door to balloon time and mortality in AMI

Adapted from Cannon et al. *JAMA* 2000; 283; 2941-7
Door to balloon time and mortality in AMI

By getting door-to-balloon times of <2h for ALL STEMI patients, we would save 4775 lives per year.

Adapted from Cannon et al. *JAMA* 2000; 283; 2941-7
Hypotension to effective antibiotic time and mortality in septic shock

Adapted from Kumar et al. *Crit Care Med* 2006; 34:1589-96
Hypotension to effective antibiotic time and mortality in septic shock

By getting shock-to-antibiotic times of <2h for ALL septic shock patients, we would save 32,360 lives per year.

<table>
<thead>
<tr>
<th>Time</th>
<th>Preventable Deaths</th>
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<tbody>
<tr>
<td>0-2h</td>
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<tr>
<td>&gt;2-3h</td>
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<tr>
<td>&gt;12h</td>
<td>18239</td>
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</tbody>
</table>

Adapted from Kumar et al. Crit Care Med 2006; 34: 1589-96
Survival vs Year

Year

Survival (%)

HSC  STB
GRA  CON
OAK  VIC