Infections of Trauma Patients

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Professor of Public Health in Medicine
Weill Cornell Medicine
New York, USA

- The estimated incidence of infection following trauma is 15-25%
  – (Now, perhaps as high as 35% for combat casualties)

- Among those who survive > 24° (resuscitation and surgery), infection is the leading cause of death

Stillwell and Caplan
ID Clin North Am 1993
Epidemiology of Trauma Deaths

<table>
<thead>
<tr>
<th></th>
<th>Acute (&lt; 24h)</th>
<th>Early (24h-7d)</th>
<th>Late (&gt;7d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS</td>
<td>40%</td>
<td>64%</td>
<td>39%</td>
</tr>
<tr>
<td>Blood loss</td>
<td>55%</td>
<td>9%</td>
<td>0</td>
</tr>
<tr>
<td>MODS</td>
<td>&lt; 1%</td>
<td>18%</td>
<td>61%</td>
</tr>
</tbody>
</table>

Asensio, et al.

Incidence of Infection in Trauma Patients

Results from Abdominal Antibiotic Prophylaxis Trials

<table>
<thead>
<tr>
<th>Reviews</th>
<th>Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hooker, 1991</td>
<td>Nichols, 1984</td>
</tr>
<tr>
<td>Dellinger, 1991</td>
<td>Hofstetter, 1984</td>
</tr>
<tr>
<td></td>
<td>Jones, 1985</td>
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<tr>
<td></td>
<td>Dellinger, 1986</td>
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<td></td>
<td>Mbawa, 1993</td>
</tr>
<tr>
<td></td>
<td>Griswold, 1993</td>
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<tr>
<td></td>
<td>Tyburski, 1998</td>
</tr>
<tr>
<td></td>
<td>Borogozadeh, 1999</td>
</tr>
<tr>
<td></td>
<td>Kirton, 2000</td>
</tr>
</tbody>
</table>
Penetrating Colon Injuries
Risk Factor for Infection


- 350 patients
  - 33 stab wounds
- Mortality: 311 patients survived 48 hours
  - 25% incidence of infection
  - 152 infections in 78 patients
- 46% traumatic infections
- 54% nosocomial infections

Are Trauma Patients Different?


- Review of 3,715 cases
  - 1,272 trauma/ 2,443 surgical
- Outcome: all infection
  - CDC definitions
- Infection rates higher after trauma
  - 12% vs. 6%, p <0.001
- Significantly more pneumonia after trauma
  - 23.9 vs. 16.7 cases/1,000 days of intubation
  - p <0.0005
Combat Casualty Care

- World War I
  - “Gas gangrene” 5%, mortality 28%
- World War II
  - “Gas gangrene” 0.3%-1.5%, mortality 15%
- Vietnam
  - Sepsis the third leading cause of death
- Iraq and Afghanistan
  - 52,000 wounded in action
  - Highest percentage ever who survived initial injuries

Weintrob et al. Surg Infect 2018;19:286-297

Combat Casualty Care

- Initial survival:
  - Forward surgical assets
  - Tourniquets
  - Rapid evacuation
  - Improved body armor
    - Fewer, less severe torso trauma
- Survivors:
  - Massive blood loss
  - Bone/soft tissue injuries
  - Multiple operations

Weintrob et al. Surg Infect 2018;19:286-297
Combat Casualty Care

– Landstuhl Regional Medical Center, Germany
– 3,304 admissions with combat-related injuries
  • 79% blast injuries
  • 16% ≥ 10 U blood/first 24 h
  • 1% in-hospital mortality
– Incidence of infection 34%
  • Two or more infections 57%
  • SSTI 45% (median, day 9)
  • Pneumonia 15% (median, day 4)
  • BSI 15% (median, day 5)
  • Osteomyelitis 8% (median, day 16)

Weintrob et al. Surg Infect 2018;19:286-297

<table>
<thead>
<tr>
<th>Type of Infection</th>
<th>% Gram-positive</th>
<th>% Gram-negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood stream</td>
<td>48</td>
<td>42</td>
</tr>
<tr>
<td>Skin/soft tissue</td>
<td>27</td>
<td>47</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>23</td>
<td>47</td>
</tr>
</tbody>
</table>

Weintrob et al. Surg Infect 2018;19:286-297
– Blast injury (non-IED) 0.69 (0.49-0.97)
– Proximal amputation 1.57 (1.23-2.01)
– ISS
  • 16-24 (moderate) 1.46 (1.06-2.00)
  • > 25 (life-threatening) 1.79 (1.29-2.49)
– Blood transfusion
  • 1-9 U 1.80 (1.40-2.33)
  • 10-20 U 2.00 (1.48-2.70)
  • > 20 U 3.19 (2.30-4.42)
– Mech vent @ LRMC 2.12 (1.70-2.65)

“Failure to Rescue”

• Death following a complication
• Trauma registry data, Pennsylvania 2011-2014
  • 95,806 patients
    – At least one complication 11%
    – Infection as first complication 34%
• Mortality
  – Overall 3.7%
  – No complication 2.8%
  – Infection 7.2%
  – Non-infectious complication 13.5%
Risk Factors for Infection
Multivariable Analysis

- Male gender
- Stab wound
- Higher ISS (injury site not relevant)
- Lower GCS
- Any post-ED destination other than ward
- Drug abuse
- Cirrhosis
- Dementia
- Stroke
- Previous TBI


Risk Factors for Failure to Rescue from Infection
Multivariable Analysis

- Male gender
- Older age
- Motor vehicle collision
- Higher ISS
- Lower GCS
- Cirrhosis
- Anticoagulation
- Chronic kidney disease
- Steroids

Infection Risk of Traumatic Wounds Based on Wound Classification

• Retrospective study of 1,436 wounds
  – 1,054 abdominal
  – 382 extremity

• Wound infection risk
  – 331 clean wounds: 3.2%
  – 855 clean-contaminated wounds: 10.5%
  – 250 contaminated wounds: 24.8%

Overview of Human Immunity
Innate Immunity: Common Recognition Pathways (DAMPs and PAMPs)

<table>
<thead>
<tr>
<th>Innate Immune Recognition Strategy</th>
<th>Receptor Families</th>
<th>Specific examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Detecting ‘microbial non-self’ (i.e. pathogen-associated molecular patterns (PAMPs))</td>
<td>Toll-like receptors</td>
<td>TLR4, TLR5</td>
</tr>
<tr>
<td></td>
<td>NOD-like receptors</td>
<td>NOD2, IPAF</td>
</tr>
<tr>
<td></td>
<td>Cofolin family</td>
<td>MBP</td>
</tr>
<tr>
<td>2. Detecting common metabolic consequences of cell infection or injury (i.e. damage-associated molecular patterns (DAMPs))</td>
<td>NOD-like receptors</td>
<td>NLRC4 (or NALP3)</td>
</tr>
<tr>
<td></td>
<td>RAGE (receptor of advanced glycation and product) family</td>
<td>RAGE</td>
</tr>
<tr>
<td>3. Detecting ‘missing self’</td>
<td>MHC-class-I-specific inhibitory receptors</td>
<td>KIR, CD94-NKG2A, NKG2C</td>
</tr>
</tbody>
</table>

Immune Dysfunction in Trauma

- Immediate activation of coagulation
- Immediate up-regulation of innate immunity
  - Mononuclear cell activation
  - Release of pro-and anti-inflammatory cytokines
- Immediate up-regulation of adaptive immunity
  - Immunosuppressive phenotype
Immune Dysfunction in Trauma

- Lymphopenia
- CD4:CD8<1
- Downregulated:
  - T, B cell proliferation
  - NK cell activity
  - IL-2 receptor expression
  - IL-4, -10 production
  - HLA-DR expression
  - DTH skin test response

- Monocytosis
- Upregulated:
  - Acute-phase proteins
  - TNFα, IL-6 production
  - Eicosanoid production
- Downregulated:
  - Neutrophil function

Expression Profiling of Genes Responsive to Injury: Principal Component Analysis

Nathens et al.
Gender Difference and Outcome of Trauma

**Maybe No**
Napolitano, 2001
- 18,892 patients
- No effect of gender on mortality without pneumonia
- Males more likely to develop pneumonia
- Females more likely to die of pneumonia

**Maybe Yes**
Offner, 1999
- 545 patients
- ISS > 15
- Survival > 48 hours
- Male gender an independent risk for infection (RR 1.58)
- No difference in mortality
Infection After Penetrating Abdominal Trauma

- 145 Patients
- Cefoxitin vs. clindamycin/gentamicin
- Intraoperative randomization
  - 619 patients randomized

Risks for infections
RR (95% CI)

- Left colon injury 5.66 (2.24 - 14.29)
- ≥4 organs injured 10.50 (2.35 - 46.87)
- Shock on presentation 3.58 (1.44 - 8.90)
- Blood products given 1.05 (1.03 - 1.12)

Infections After Trauma Multivariable Analysis
Papia et al. J Trauma 1999; 47: 923-927

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Odds Ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical ventilation</td>
<td>2.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Multiple operations</td>
<td>2.8</td>
<td>0.02</td>
</tr>
<tr>
<td>Multiple blood transfusions</td>
<td>2.3</td>
<td>0.04</td>
</tr>
<tr>
<td>Spinal cord injury</td>
<td>5.0</td>
<td>0.002</td>
</tr>
<tr>
<td>First operation &lt; 24°</td>
<td>0.4</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Transfusions Correlate with Infections in a Dose-Dependent Manner

![Graph showing the correlation between transfusions and infection incidence.](image)

\[ Y = 0.1375e^{0.1187x} \]

\[ R^2 = 0.7566 \]


Allogeneic Blood Transfusion and Risk of Postoperative Infection

*Hill et al. J Trauma 2003;54:908-914*

- 20 Trials 1986-2000
  - > 13,000 patients
  - Trauma patient sub-analysis

- Overall infection 3.45 (1.43-15.15)
  - Trauma patients 5.26 (5.03-5.43)
**Why are Transfusions Immunosuppressive?**

- Induced by leukocyte antigens (?)
- Cell-mediated immunity decreased
  - Shift to Th2 (immunosuppressive) response
- Disruption of microcirculation

**Genetic Response to Massive Transfusion at 12 Hours**

<table>
<thead>
<tr>
<th></th>
<th>&lt; 6 Units</th>
<th>&gt;6 Units</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
Gene Profiling in Massive Transfusion  
Nathens et al. “Glue Grant”

~2000 probe sets significant at 5% FDR

Poor Efficacy of Blood Tx

- RBCs stored > 15 days lose deformability and ATP
- Altered capillary lumen size (decreased cross-sectional diameter) in critically ill patients
- Increased “stickiness” (adherence) of RBCs to altered endothelium in the microcirculation of critically ill pts.
- Depletion of 2,3-DPG means NO improvement in DO₂
Hyperglycemia and Dysfunction of Immune Cells

- Decreased respiratory burst - alveolar macrophages
- Decreased insulin-stimulated chemokinesis
  - Glucose-induced PKC activation
- Increased adherence
  - Increased adhesion molecule generation
- Spontaneous activation of neutrophils

Tight Glycemic Control in Critical Surgical Illness

- RCT of 1,548 SICU patients
- Glucose 80-110 mg/dL vs. 180-220 mg/dL
- Mortality 4.6% vs. 8.0% (p=0.04)
  - ICU stay > 5 days 10.6% vs. 20.2%
- Reductions of:
  - Bloodstream infection 46%
  - Need for renal replacement therapy 41%
  - Red blood cell transfusion 50%
  - Critical illness polyneuropathy 44%

Acute Glucose Elevation (AGE) Portends Infection After Trauma

• Prospective study 2,200 patients
• AGE score 0-7 points
  – Class IV (6-7 points)
    • Increase of baseline glucose > 50% (3 pts).
    • Increase of baseline glucose > 75% (4 pts).
    • Variability (48h) 20-50% (2 pts).
    • Variability (48 h) > 50% (3 pts).

• Area under ROC curve 0.912


Risk ratios of mortality in clinical trials comparing intensive insulin therapy (IIT) to conventional glycemic control stratified by type of ICU

Surgical ICU:
RR 0.63
95% CI 0.44-0.91

Griesdale et al. CMAJ 2009;180:821-827
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### Glycemic Control Meta-Analysis

<table>
<thead>
<tr>
<th>Type of ICU</th>
<th>Relative Risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pooled (all studies)*</td>
<td>0.93</td>
<td>0.83–1.04</td>
</tr>
<tr>
<td>Surgical ICU**</td>
<td>0.63</td>
<td>0.44–0.91</td>
</tr>
<tr>
<td>Medical ICU</td>
<td>1.00</td>
<td>0.78–1.28</td>
</tr>
<tr>
<td>Mixed Medical-Surgical ICU</td>
<td>0.99</td>
<td>0.86–1.12</td>
</tr>
</tbody>
</table>

*Significant heterogeneity between studies (Q statistic = 46.7, \( p = 0.005 \))

**No significant heterogeneity (Q statistic = 2.8, \( p = 0.60 \))


### Glycemic Variability

- Retrospective study of 3,252 consecutive patients
- Relationship of glycemic variability to mortality strongest in euglycemic range (70-99 mg/dL)
  - Six-fold increased mortality quartile 4 (30% vs. quartile 1 (6%)

**Glycemic Variability**

Krinsley J. Crit Care Med 2008;36:3008-3013

**Early Enteral Nutrition in Trauma Meta-Analysis**

Marik and Zaloga. Crit Care Med 2001;29:2264-2270

- 15 randomized trials
  - All postoperative, trauma, or burn studies
- **Reduced infections**
  - RR 0.45 (0.30-0.66)
- Reduced hospital stay
  - Mean, 2.2 days (0.81-3.63 days)
- No effect on mortality
- No effect on non-infectious complications
Appropriate Antibiotic Prophylaxis

- Shortest duration with equivalent efficacy
- Dosing at correct interval
- Narrowest spectrum with equivalent efficacy
- Good safety profile

Pharmacokinetics and Trauma Surgery Points to Consider

- Vasoconstriction
  - Poor tissue penetration
- Blood loss
  - Antibiotic loss
- Tissue edema
  - Changing volume of distribution
- Hypoalbuminemia
  - More free drug
- Increased GFR
  - More-rapid excretion

DO TRAUMA PATIENTS NEED HIGHER DOSES?
**DURATION OF ANTIBIOTIC THERAPY IN PENETRATING TRAUMA**


- 300 Patients
- Cefoxitin 1g IV q6h
  - 24 hours vs. 5 days
- 58% gunshot trauma
- Overall infection 25%
- Abdominal infection 6%

**Antibiotics for Penetrating Abdominal Trauma Multivariate Analysis**


<table>
<thead>
<tr>
<th>Predictor</th>
<th>Any Infection</th>
<th>IAI</th>
<th>LOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative shock</td>
<td>0.003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraoperative shock</td>
<td></td>
<td>0.021</td>
<td></td>
</tr>
<tr>
<td>Colon injury</td>
<td>0.004</td>
<td>0.0031</td>
<td>0.0008</td>
</tr>
<tr>
<td>Chest injury</td>
<td></td>
<td></td>
<td>0.0006</td>
</tr>
<tr>
<td>CNS injury</td>
<td>0.031</td>
<td></td>
<td>0.0001</td>
</tr>
<tr>
<td># abdominal organs injured</td>
<td>0.026</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Eastern Association for the Surgery of Trauma
Guidelines for Antibiotic Prophylaxis

PENETRATING ABDOMINAL TRAUMA

• Level I:
  – Single-dose prophylaxis if no hollow viscus injury

• Level II:
  – Continue antibiotics < 24 h with hollow viscus injury

• Level III:
  – Increase the dose in the presence of shock

Effect of Duration of Prophylaxis on Infections

<table>
<thead>
<tr>
<th>Duration of prophylaxis</th>
<th>All patients</th>
<th>Non-transplant patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;1 day</td>
<td>&gt;4 days</td>
</tr>
<tr>
<td>No. of patients</td>
<td>180</td>
<td>94</td>
</tr>
<tr>
<td>No. of patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>developing bacteremia (%)</td>
<td>6 (3%)</td>
<td>16 (17%) P&lt;0.0001</td>
</tr>
<tr>
<td>No. of line infections (%)</td>
<td>4 (2%)</td>
<td>14 (15%) P&lt;0.0001</td>
</tr>
</tbody>
</table>

“Severe Trauma is Not an Excuse for Prolonged Antibiotic Prophylaxis”

Velmahos et al. Arch Surg 2002;137:537-541

- Prospective observational trial
  - Surgical ICU, level I trauma center
- 250 Multiple trauma patients
  - 54% Penetrating trauma
  - Mean ISS 22 ± 10
  - 74% Underwent chest or abdominal surgery
  - All with SICU LOS > 3 days
  - Antibiotic prophylaxis < 24 h. (n=133) vs. > 24 h

- Hollow viscus injury 23%
- Blood transfusion 6 ± 7 U
- Sepsis 43%
- Organ failure 41%
- Mortality 6%
“Severe Trauma is Not an Excuse for Prolonged Antibiotic Prophylaxis”
Multivariable Analysis of Drug-Resistant Infection
Velmahos et al. Arch Surg 2002;137:537-541

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head AIS &gt; 3</td>
<td>4.27</td>
<td>1.94-10.03</td>
</tr>
<tr>
<td>Age &gt; 55 years</td>
<td>3.62</td>
<td>1.25-11.51</td>
</tr>
<tr>
<td>Transfusion &gt; 2 U</td>
<td>2.62</td>
<td>1.42-4.99</td>
</tr>
<tr>
<td>Prophylaxis &gt; 24 h</td>
<td>2.13</td>
<td>1.22-3.74</td>
</tr>
</tbody>
</table>

Antibiotic Prophylaxis of Dog Bite Wounds: Meta Analysis

- 8 randomized, placebo controlled trials
  - 783 patients
- A penicillin or macrolide used in 7/8 trials
- Control infection rate: 16%
- Antibiotic treatment
  - RR 0.56 (0.38 - 0.82)
- Hand wounds
  - RR 0.23 (0.05 - 0.95)

? Duration of Prophylaxis
Antibiotic Prophylaxis of Open Fractures: Systematic Review

- 4 RCTs, 472 patients:
  - Lower infection rate with prophylaxis
  - 0.37 (0.21-0.66)
- 3 studies, 1,104 patients
  - No difference in infection rate with 1 day vs > 3 days of prophylaxis
  - 0.97 (0.69-1.37)

Chang et al. JBJS Rev 2015;3(6).

Infection and Intracranial Pressure Monitors
Risk Factors and Antibiotic Prophylaxis


- Review of 215 patients
- Infection rate 7.5%
  - Not influenced by prophylaxis
- Risk Factors (RR, 95% CI)
  - Monitoring > 5 days 4.4 (1.3 - 11.9)
  - Ventriculostomy 3.4 (1.0 - 10.7)
  - CSF leak 6.3 (1.5 - 27.4)
  - Concurrent infection 3.4 (1.2 - 9.5)
  - Serial device placement 4.9 (1.7 - 13.8)
Antibiotic Prophylaxis for Basilar Skull Fracture?  
Meta Analysis 

- 12 studies, 1,241 patients  
- 58% received antibiotics  
- Antibiotics did not prevent meningitis  
  - RR 1.15 (0.68 - 1.94) p=0.68  
- CSF leakage subset  
  - RR 1.34 (0.75 - 2.41) p=0.36  
- Pediatric subset  
  - RR 1.04 (0.07 - 14.90) p=1.0

CVC-Associated BSI-NHSN  
Unit-Specific Incidence, 2006-2008

<table>
<thead>
<tr>
<th>Type of ICU</th>
<th>1999</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean/Median</td>
<td></td>
</tr>
<tr>
<td>Medical</td>
<td>6.1/5.4</td>
<td>2.6/2.3</td>
</tr>
<tr>
<td>Pediatric</td>
<td>7.9/6.9</td>
<td>3.0/2.5</td>
</tr>
<tr>
<td>Surgical</td>
<td>5.6/5.0</td>
<td>2.3/1.7</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>2.9/2.3</td>
<td>1.4/0.8</td>
</tr>
<tr>
<td>Neurosurgical</td>
<td>5.6/4.5</td>
<td>2.5/1.9</td>
</tr>
<tr>
<td>Trauma</td>
<td>7.3/6.4</td>
<td>3.6/3.0</td>
</tr>
</tbody>
</table>

Ventilator-Associated Pneumonia -NHSN
Unit-Specific Incidence, 2006-2008

<table>
<thead>
<tr>
<th>Type of ICU</th>
<th>1999</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical</td>
<td>8.2-7.3</td>
<td>2.4/2.2</td>
</tr>
<tr>
<td>Pediatric</td>
<td>5.7/4.6</td>
<td>1.8/0.7</td>
</tr>
<tr>
<td>Surgical</td>
<td>14.6/12.3</td>
<td>4.9/3.8</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>17.6/11.0</td>
<td>3.9/2.6</td>
</tr>
<tr>
<td>Neurosurgical</td>
<td>17.1/12.7</td>
<td>5.3/4.0</td>
</tr>
<tr>
<td>Trauma</td>
<td>16.9/14.7</td>
<td>8.1/5.2</td>
</tr>
</tbody>
</table>


Changing Definitions of Pneumonia

• Changed by CDC/NHSN in 2013
  – “Ventilator-associated events”
• Retrospective study 2013-2014
  – 1,165 trauma patients received ≥ 2 d mech vent
• Proportion of patients meeting definitions
  – Old: 361 patients (31%)
  – New: 78 patients (7%) k=0.22 for old v. new
  – Both: 68 patients (6%)
• NO DIFFERENCES IN MORTALITY

Thank You!

NewYork-Presbyterian Hospital/Weill Cornell Medical Center, New York, USA