Limiting the Attributable Mortality of Healthcare-Associated Infection & Multidrug Resistance

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Disclosures

• Nothing to disclose
Introduction

Healthcare associated infection (HAI)

- Point-prevalence study (n=10,038 ICU patients)
  - Infected: n=4,501 (44.8%)
  - ICU-acquired: n=2,046 (20.6%)

Vincent et al. JAMA 1995
Introduction

Healthcare associated infection (HAI)

• Risk profile:
  ➔ severity of acute illness
  ➔ underlying conditions
  ➔ aging population
  ➔ immunosuppressive agents
  ➔ invasive devices

• Medical progress ➔ growing pool of high-risk patients
Introduction

Healthcare associated infection (HAI)

• 1980s – 1990s perception of HAI in ICUs:
  ➔ generally unavoidable
  ➔ high mortality
Introduction

Relationship HAI and Mortality

- ICUs → highest rates of HAI
  → highest disease severity

- ICU patients → high risk for HAI and death

→ discriminate attributable from associated mortality
Introduction

Relationship HA-BSI and Mortality

• Bacteremia in ICU patients
  → associated mortality: 50%
  → attributable mortality: 35%

• Candidemia ICU/general ward patients
  → associated mortality: 57%
  → attributable mortality: 38%

Pittet D, et al. JAMA 1994
Introduction

Relationship Candidemia and Mortality

- Outcome perception in ICU patients with candidemia in the 1990s

1/3 Survival

1/3 Death due to candidemia (attributable)

1/3 Death due to general disease severity

Introduction

Attributable mortality of candidemia

“Matched cohort” study design

Candidemia → Matching (1:2 ratio) → No candidemia

- Based on risk factors for mortality & candidemia
- Exposure time
- APACHE II score (severity of acute illness & underlying disease)
- Admission diagnosis

Equal ‘a priori’ risk for death for cases and matched controls

Introduction

Attributable mortality of candidemia

Methodological concept

\[ \text{attributable mort.} = 20\% \]

\[ \text{mortality due to severity of underlying disease} = 40\% \]
Introduction

Attributable mortality of candidemia

In-hospital mortality:

Cases: 47.9%
Controls: 42.5% (P=0.44)

➔ attributable mortality: 5.4% (95% CI: -8 – 19%)

Introduction

Relationship MDR & Mortality

Gram-negative bacteremia in ICU patients

In-hospital mortality:

- AB-S: 41.8%
- AB-R: 45.0% (P=0.58)

→ No difference in mortality

Introduction

Relationship MDR & Mortality

**MSSA** bacteremia in ICU patients

In-hospital mortality:

- MSSA bacteremia: 23.7%
- Uninfected controls: 22.4% (P=0.94)

**→ attributable mortality: 1.3% (95% CI: -15 – 18)**

Introduction

Relationship MDR & Mortality

**MRSA** bacteremia in ICU patients

In-hospital mortality:
- MRSA bacteremia: 63.8%
- Uninfected controls: 40.4% (P=0.02)

➔ attributable mortality: 23.4% (95% CI: 7 – 40)

# Introduction

## Attributable mortality of Bloodstream infection

<table>
<thead>
<tr>
<th>Author, journal, year</th>
<th>Focus</th>
<th>Mortality cases</th>
<th>Mortality controls</th>
<th>Attributable mortality, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blot S, et al. Eur J Clin Microb Infect Dis 2002</td>
<td><em>Klebsiella</em></td>
<td>36%</td>
<td>37%</td>
<td>0%</td>
</tr>
<tr>
<td>Blot S, et al. J Hosp Infect 2003</td>
<td><em>P. aeruginosa</em></td>
<td>62%</td>
<td>47%</td>
<td>15% (-1–31)</td>
</tr>
<tr>
<td>Blot S, et al. Intensive Care Med 2003</td>
<td><em>A. baumannii</em></td>
<td>42%</td>
<td>34%</td>
<td>8% (-10–25)</td>
</tr>
<tr>
<td>Blot S, et al. Chest 2003</td>
<td><em>Enterobacter</em></td>
<td>34%</td>
<td>38%</td>
<td>0%</td>
</tr>
<tr>
<td>Blot S, et al. Infect Control Hosp Epidem 2003</td>
<td><em>E. coli</em></td>
<td>44%</td>
<td>45%</td>
<td>0%</td>
</tr>
<tr>
<td>Hoste E, et al. J Am Soc Nephrol 2004</td>
<td>RRT pts.</td>
<td>70%</td>
<td>63%</td>
<td>7% (-9–21)</td>
</tr>
<tr>
<td>Brusselaers N, et al. Burns 2010</td>
<td>Burn pts.</td>
<td>12%</td>
<td>17%</td>
<td>0%</td>
</tr>
</tbody>
</table>
## Introduction

Mortality of healthcare-associated infections

<table>
<thead>
<tr>
<th>Author, journal, year</th>
<th>Focus</th>
<th>Mortality compared with unexposed patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vandewoude K, et al. J Hosp Infect 2004</td>
<td>Invasive aspergillosis</td>
<td>HR 1.9 (95% CI 1.2-3.0)</td>
</tr>
<tr>
<td>Agbath K, et al. Crit Care Med 2006</td>
<td>Bacteremic vs. non-bacteremic VAP</td>
<td>RR 2.9 (95% CI 1.1-7.5)</td>
</tr>
<tr>
<td>De Waele J, et al. Pancreas 2004</td>
<td>BSI after surgery for acute pancreatitis</td>
<td>57% vs. 35% (NS)</td>
</tr>
<tr>
<td>De Waele J, et al. Clin Infect Dis 2003</td>
<td><em>Candida</em> infection in necrotizing pancreatitis</td>
<td>35% vs. 28% (p=0.41)</td>
</tr>
<tr>
<td>Benoit D, et al. Intensive Care Med 2005</td>
<td>Bacterial vs. non-bacterial compl. in hemato-pts.</td>
<td>OR 0.2 (95% CI 0.1-0.6)</td>
</tr>
<tr>
<td>Myny D, et al. Acta Clin Belg 2005</td>
<td>VAP</td>
<td>OR 0.8 (95% CI 0.4-1.5)</td>
</tr>
<tr>
<td>Blot S, et al. Crit Care Med 2009</td>
<td>BSI in old ICU pts. BSI in very old ICU pts.</td>
<td>HR 1.2 (95% CI 1.0-1.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HR 1.8 (95% CI 1.4-2.4)</td>
</tr>
<tr>
<td>De Waele J, et al. Surg Infect 2008</td>
<td>BSI + intra-abd. infections</td>
<td>62% vs. 42% (p&lt;0.001)</td>
</tr>
</tbody>
</table>
## Introduction

Low attributable mortality rates are not for free!

### Matched cohort studies on Central Line-Associated Bloodstream Infection

<table>
<thead>
<tr>
<th>Author</th>
<th>Source year</th>
<th>Number of cases</th>
<th>Number of controls</th>
<th>Attributable mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soufir</td>
<td>ICHE 1999</td>
<td>n=38</td>
<td>n=76</td>
<td>26% (NS)*</td>
</tr>
<tr>
<td>Rello</td>
<td>AJRCCM 2000</td>
<td>n=49</td>
<td>n=49</td>
<td>0% (NS)</td>
</tr>
<tr>
<td>Renaud</td>
<td>AJRCCM 2001</td>
<td>n=26</td>
<td>n=26</td>
<td>12% (NS)</td>
</tr>
<tr>
<td>Rosenthal</td>
<td>Am J Infect Control 2003</td>
<td>n=142</td>
<td>n=142</td>
<td>25% (14 – 36%)</td>
</tr>
<tr>
<td>Blot</td>
<td>Clin Infect Dis 2005</td>
<td>n=176</td>
<td>n=315</td>
<td>2% (NS)</td>
</tr>
<tr>
<td>Garrouste-Orgeas</td>
<td>CID 2006</td>
<td>n=47</td>
<td>n=207</td>
<td>3% (NS)</td>
</tr>
<tr>
<td>Higuera</td>
<td>ICHE 2007</td>
<td>n=55</td>
<td>n=55</td>
<td>20% (p=0.06)</td>
</tr>
</tbody>
</table>

* NS after adjustment for covariates
Introduction

Determinants of Mortality in Severe HAI

Mortality - genetic predisposition
  ~ age
  ~ underlying disease
  ~ site of infection
  ~ micro-organism + resistance pattern
  ~ anti-infective management

only “manageable” factor
Essentials in Anti-Infective Management

1. Early recognition of sepsis
2. First shot antimicrobial therapy: asap
3. Coverage of causative etiology
4. Adequate dosing
5. Infection prevention
1. Early recognition of sepsis
2. First shot antimicrobial therapy: asap
3. Coverage of causative etiology
4. Adequate dosing
5. Infection prevention
Early recognition of sepsis

- **Sepsis alert scores**
  - Checklist, regular bedside control
  - High NPV, Low PPV
  - Advantage: not diagnosing sepsis at a very late stage of the disease
Early recognition of sepsis

- **Task: detect discrete variations in vital signs**
  - Central vital sign = art. blood pressure
  - Decreasing ABP / hypotension = too late
  - Human body will do everything to keep ABP up
  - IC nurse must (also) focus on the mechanisms that precede overt ABP variation
  - E.g. heart rate
Arterial pressure

High pressure receptors (A. carotis)

Cardiovascular centra

Low pressure receptors (V. cava)

Venous return

Blood volume

Diastolic compliance

α: tonus arteriols

β1: extr. inotropism

intr. inotropism

β1: pos. chronotropism

neg. chronotropism

Venous capacity

α: tonus venules

Heart frequency

Preload

Inotropism

Stroke volume

Systolic work

E.F. (%)

Afterload

Total vascular resistance

Ventricular volume

Preload

Cardiac output

Arterial pressure

Blot S. 2009; all rights reserved.
Observations prior to septic shock

Hypotension = late symptom of shock
Challenge = to sense compensation mechanisms and to prevent shock (and damage to vital organs).

<table>
<thead>
<tr>
<th>Observation</th>
<th>Possible meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ urine output</td>
<td>Peripheral vasoconstriction, Saving circulating blood volume for vital organs</td>
</tr>
<tr>
<td>Pallor, mottling, cold skin, cold extremities,…</td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>Reflex triggered by ↓ venous return</td>
</tr>
<tr>
<td>↓ filling pressures (CVP, PCWP)</td>
<td>↓ blood volume (absolute hypovolemia) ↑ venous capacity (relative hypovolemia)</td>
</tr>
<tr>
<td>↑ cardiac output (C.O.)</td>
<td>may be early signal for evolving sepsis</td>
</tr>
<tr>
<td>Restlessness, confusion</td>
<td>Pending shock</td>
</tr>
<tr>
<td>Tachypnea</td>
<td>Compensation pending metabolic acidosis</td>
</tr>
</tbody>
</table>
1. Early recognition of sepsis
2. First shot antimicrobial therapy: asap
3. Coverage of causative etiology
4. Adequate dosing
5. Infection prevention
Basic conditions for optimal antibiotic therapy

First antibiotic dose without delay

• Start empiric antibiotic therapy asap (take relevant cultures first!)

• Surviving Sepsis Guidelines: <1 hr in septic shock / severe sepsis

• Strongly related to processes of care targetting mechanisms to detect sepsis at an early stage!

How to decrease time to 1st shot of antibiotic therapy in severe community-acquired pneumonia?

Effects of delayed oxygenation assessment on time to antibiotic delivery and mortality in patients with severe community-acquired pneumonia*

<table>
<thead>
<tr>
<th>Delay in Oxygenation Assessment</th>
<th>Time (hrs) to First Antibiotic Dose&lt;sup&gt;a&lt;/sup&gt;</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1 hr (n = 84)</td>
<td>6 (3–9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>≤1 hr (n = 269)</td>
<td>3 (2–5)</td>
<td></td>
</tr>
</tbody>
</table>
Effects of delayed oxygenation assessment on time to antibiotic delivery and mortality in patients with severe community-acquired pneumonia*

Figure 2. Mortality according to delay in oxygenation assessment. *Relative risk of death, 2.24 (95% confidence interval, 1.17 to 4.30).
1. Early recognition of sepsis
2. First shot antimicrobial therapy: asap
3. Coverage of causative etiology
4. Adequate dosing
5. Infection prevention
Impact of Delayed Appropriate Antimicrobial Therapy in Severe Infections

Critical time frame to start appropriate therapy: ≤24-48 hrs

Kollef et al. Chest 1999
Empiric coverage of causative etiology

• At onset of sepsis the causative pathogens are unknown

• Culture results are generally available in 48 hrs

• Empiric ("blind") antimicrobial therapy must be started

• MD has to make an estimate of the most probable pathogens
Most important reason of empiric inappropriate antimicrobial therapy...

Multidrug resistance!

Inappropriate empiric therapy

Mortality
Relationship MDR & Mortality

Gram-negative bacteremia in ICU patients

Cumulative Percent Surviving

Days from onset of the bacteremia

In-hospital mortality:

AB-S: 41.8%
AB-R: 45.0% (P=0.58)

→ No difference in mortality

Rate of appropriate therapy:
AB-S: 93%
AB-R: 91% (p=0.55)

Strategies for appropriate empiric therapy

- “Last-line” antibiotics up front
  - Very broad empiric coverage
  - De-escalate to narrow spectrum once culture results are available
  - Concept proved to be save
  - Average % appropriate therapy 70-80%
  - Very often: not de-escalated
  - Triggers MDR development…
Strategies for appropriate empiric therapy

• “Risk factor” –based
  o Use “last-line” antibiotics in case of overt risk profile for MDR
  o Major risk factors for MDR:
    ➢ Recent antibiotic exposure
    ➢ Length of hospital stay >7 day
  o Rates of appropriate empiric therapy: 60-80%
  o Problem: classic risk factors for MDR have lost their predictive value
Strategies for appropriate empiric therapy

• “Surveillance culture-assisted”
  o Combines
    ➢ risk profile for MDR
    ➢ Colonization status of the patient
  o Results from routine surveillance cultures
    ➢ Typical body sites screened in ICUs
      ✦ Tracheal aspirates
      ✦ Urine cultures
      ✦ Rectal swab
      ✦ Nasal swab
    ➢ Initially used to detect and cohort/isolate MDR carriers
Can surveillance cultures predict MDR involvement in HAI (bacteremia/pneumonia)?

**Fagan plot:**
Pre- and post-test likelihood for VAP to be caused by MDR pathogens

## Sensitivity & Specificity of Surveillance Cultures to Predict MDR in Ventilator-Associated Pneumonia

<table>
<thead>
<tr>
<th>Study</th>
<th>Sensitivity (95% CI)</th>
<th>Study</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Latorre (1995)</td>
<td>0.43 [0.10 - 0.82]</td>
<td>de Latorre (1995)</td>
<td>0.80 [0.28 - 0.99]</td>
</tr>
<tr>
<td>Ewig (1999)</td>
<td>0.75 [0.19 - 0.99]</td>
<td>Ewig (1999)</td>
<td>1.00 [0.59 - 1.00]</td>
</tr>
<tr>
<td>Cendrero (1999)</td>
<td>0.83 [0.36 - 1.00]</td>
<td>Cendrero (1999)</td>
<td>1.00 [0.82 - 1.00]</td>
</tr>
<tr>
<td>Flanagan (2000)</td>
<td>0.50 [0.25 - 0.75]</td>
<td>Flanagan (2000)</td>
<td>0.95 [0.77 - 1.00]</td>
</tr>
<tr>
<td>Nair (2008)</td>
<td>0.70 [0.35 - 0.93]</td>
<td>Nair (2008)</td>
<td>1.00 [0.75 - 1.00]</td>
</tr>
<tr>
<td>Depuydt (2008)</td>
<td>0.66 [0.55 - 0.76]</td>
<td>Depuydt (2008)</td>
<td>0.95 [0.87 - 0.99]</td>
</tr>
<tr>
<td>Lampati (2009)</td>
<td>0.66 [0.51 - 0.79]</td>
<td>Lampati (2009)</td>
<td>0.91 [0.80 - 0.97]</td>
</tr>
<tr>
<td>Joseph (2010)</td>
<td>0.68 [0.43 - 0.87]</td>
<td>Joseph (2010)</td>
<td>0.94 [0.81 - 0.99]</td>
</tr>
<tr>
<td>Brusselaers (2011)</td>
<td>0.83 [0.63 - 0.95]</td>
<td>Brusselaers (2011)</td>
<td>0.93 [0.82 - 0.99]</td>
</tr>
<tr>
<td>Combined</td>
<td><strong>0.75 [0.65 - 0.83]</strong></td>
<td>Combined</td>
<td><strong>0.92 [0.85 - 0.96]</strong></td>
</tr>
</tbody>
</table>

### Pooled Sensitivity: 0.75 (95% CI 0.65 – 0.83)

### Pooled Specificity: 0.92 (95% CI 0.85 – 0.96)
“Surveillance culture”–assisted empiric therapy increases the likelihood of appropriateness

<table>
<thead>
<tr>
<th>Author ,y (infection)</th>
<th>Comparator guideline</th>
<th>Appropriate empiric therapy</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Strict empiric scheme</td>
<td>Surveillance culture assisted</td>
</tr>
<tr>
<td>Jung B, 2008 (VAP)</td>
<td>ATS 2005</td>
<td>71%</td>
<td>85%</td>
</tr>
<tr>
<td>Depuydt P, 2006 (Bacteremic pneumonia)</td>
<td>IDAB 2002</td>
<td>75%</td>
<td>90%</td>
</tr>
<tr>
<td>Michel F, 2002 (VAP)</td>
<td>ATS 1996 Trouillet 1998</td>
<td>68%</td>
<td>95%</td>
</tr>
<tr>
<td>Depuydt P, 2008 (MDR VAP)</td>
<td>Carbapenem (ATS 2005) B-lact.+QUI (Trouillet 1998) B-lact.+aminoside (Trouillet ‘98)</td>
<td>81% 56% 68%</td>
<td>77%</td>
</tr>
</tbody>
</table>
Assumption

Surveillance culture-assisted empiric therapy → High rates of appropriate empiric therapy → Low attributable mortality in HAI → Limited impact of MDR
High NPV... “Surveillance culture”–assisted empiric therapy decreases antibiotic consumption

<table>
<thead>
<tr>
<th>Antibiotic class</th>
<th>% of observed prescriptions (SC assisted)</th>
<th>Hypothetical prescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbapenems, Antipseudomonal cephalosporins, Antipseudomonal penicillins</td>
<td>45%</td>
<td>ATS (1996) 80% (p=0.002)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trouillet (1998) 76% (p=0.01)</td>
</tr>
</tbody>
</table>

Michel F, Chest 2005
High NPV... “Surveillance culture”–assisted empiric therapy decreases antibiotic consumption

1. Depuydt P, CCM 2006
2. Michel F, Chest 2005

Higher rate of appropriate empiric therapy

AND

Less antibiotic consumption
Essentials in Anti-Inflective Management

1. Early recognition of sepsis
2. First shot antimicrobial therapy: asap
3. Coverage of causative etiology
4. Adequate dosing
5. Infection prevention
Basic conditions for optimal antibiotic therapy

Adequate dosing

- Maximize of “Bacterial killing capacity”
- Minimize risk of resistance development (caused by underdosing)
- Minimize adverse effects (caused by overdosing)
Pharmacokinetics (PK)

- Concentration
- Time (hours)
- $C_{\text{max}}$
- AUC
- $C_{\text{min}}$
Pharmacokinetics (PK)

• PK only describes concentration-time curve

• PK does not provide information on antibiotic activity (i.e. “bacterial killing”)
Pharmacodynamics (PD)

PD \rightarrow \text{relation between AB concentration and effect on pathogen}

- (!) **MIC**, minimal inhibitory concentration

- Three classes of antibiotics:
  - Time-dependent
  - Concentration-dependent
  - Concentration-dependent with time-effect
Pharmacodynamics (PD)

- Time-dependent antibiotics

Objective:
- Optimizing time period in which concentration AB > MIC
- T>MIC (% of dosing interval):
  - ~50% for penicillins
  - ~60-70% for cephalo’s
  - ~40% for carbapenems
- Optimal bacterial killing at AB concentrations = 4-5 x MIC
Pharmacodynamics (PD)

• Concentration-dependent antibiotics

Objective:
• Antibiotic effect determined by \( C_{\text{max}} \)
• Optimal bacterial killing at AB concentrations = 8-10 x MIC
Mechanisms leading to PK of an antibiotic agent

- Absorption
  - Non-critically ill patients
    - Stable processes
    - PK = predictable
    - Standard doses → desired [AB]

- Distribution

- Metabolism

- Elimination

PK
Mechanisms leading to PK of an antibiotic agent

- Δ Absorption
- Δ Distribution
- Δ Metabolism
- Δ Elimination

Sepsis: pathophysiological alterations

Δ PK

Δ response on standard dosing
The effect of pathophysiology on pharmacokinetics in the critically ill patient — Concepts appraised by the example of antimicrobial agents

PK of antibiotics in severe sepsis...

- Overdosing and toxicity is possible in context of organ failure

- Plenty of other factors (sometimes in the same patient) might cause underdosing through ↑Vd and ↑clearance.

- Risk of underdosing (with hydrophilic antibiotics) is a greater threat than risk of overdosing

- Errors in the administration of ABs (might) ↑risk of underdosing
Nursing point of interest

(!) Do not postpone start new AB in case of switch

- Culture & antibiogram: MDR bacteria
- Switch to adequate AB therapy
Nursing point of interest

(!) Do not postpone start new AB in case of switch

• Culture & antibiogram: MDR bacteria
• Switch to adequate AB therapy
Nursing point of interest

(!) Do not postpone start new AB in case of switch

• Culture & antibiogram: MDR bacteria
• Switch to adequate AB therapy

Limit the time period of inappropriate therapy

Consider accumulated risk of toxicity!
Nursing point of interest

(!) Avoid too slow infusion rate of conc.-dep. AB

- Use an infusion pump

- Concentration

- Time (hours)

- $C_{\text{max}}$/MIC (optimal if 8-10 x MIC)

- Too long infusion time

- Insufficiently high $C_{\text{max}}$

- T>MIC
Nursing point of interest

(!) Do not increase time interval of time-dep. AB

Danger zone (T<MIC)
Nursing point of interest

(!) Do not increase time interval of time-dep. AB

Danger zone (T<MIC) ↑↑
- bad bacterial killing
- resistance development

Concentration

09:00 17:00 20:00 01:00 04:00
T>MIC T>MIC T>MIC

Time (hours)
Nursing point of interest - **Continuous infusion**

(!) No time between loading dose and C.I.
Nursing point of interest - Continuous infusion

(!) No time between loading dose and C.I.

Loading dose

Start continuous infusion immediately after the loading dose

Concentration

08:00  16:00  00:00

T>MIC  T>MIC  T>MIC

MIC

Time (hours)
Nursing point of interest - Continuous infusion

(!) No time between loading dose and C.I.

Loading dose

Start continuous infusion immediately after the loading dose

T>MIC = 100%

08:00  16:00  00:00

Time (hours)
Nursing point of interest - **Continuous infusion**

(!) No time between loading dose and C.I.

**Loading dose**

**Start Continuous infusion**

**T>MIC=100%**

**BUT... insufficient bacterial killing:**

\[ [AB] < 4-5 \times \text{MIC} \]

**Time (hours)**

<table>
<thead>
<tr>
<th>08:00</th>
<th>16:00</th>
<th>00:00</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**MIC**

**Concentration**

**T>MIC = 100%**
Nursing point of interest - Continuous infusion

(!) No time between loading dose and C.I.

Loading dose

Start Continuous infusion

T>MIC=0%!
No bacterial kill
Ideal scenario for resistance-development
Nursing point of interest - **Continuous infusion**

(!!) **No time between loading dose and C.I.**

- Failure to initiate continuous infusion immediately after the loading dose...
  - Inform physician
  - Await a second intermittent dose to start C.I.
  - Idea: start C.I. together with loading dose
Essentials in Anti-Infective Management

1. Early recognition of sepsis
2. First shot antimicrobial therapy: asap
3. Coverage of causative etiology
4. Adequate dosing
5. Infection prevention
Infection prevention

↓ infections

Limiting infections to high-risk patients

↓ cross-transmission

↓ involvement of MDR microorganisms

↓ antimicrobial consumption

↓ emergence of MDR

↓ attributable mortality

↓ inappropriate antimicrobial therapy

Blot S. Clin Microbiol Infect 2008
Conclusion

1. HAI are associated with high morbidity and mortality

2. Attributable mortality can be limited
   • Early recognition of sepsis
   • 3 basic conditions for optimal antibiotic therapy

3. HAI prevention remains pivotal