Antimicrobial Therapy

Whole Hospital Meeting
Wednesday 4th November 2015
Jeremy Gardner
Consultant Medical Microbiologist and Infection Control Doctor
Comparison With Other Major Diseases

Incidence of Severe Sepsis

Mortality of Severe Sepsis

SURVIVING SEPSIS CAMPAIGN BUNDLES

TO BE COMPLETED WITHIN 3 HOURS:

1) Measure lactate level
2) Obtain blood cultures prior to administration of antibiotics
3) Administer broad spectrum antibiotics
4) Administer 30 mL/kg crystalloid for hypotension or lactate 4 mmol/L

TO BE COMPLETED WITHIN 6 HOURS:

5) Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation to maintain a mean arterial pressure [MAP] 65 mm Hg)
6) In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥ 4 mmol/L (36 mg/dL):
   - Measure central venous pressure (CVP)*
   - Measure central venous oxygen saturation (ScvO2)*
7) Remeasure lactate if initial lactate was elevated*

*Targets for quantitative resuscitation included in the guidelines are CVP of 8 mm Hg, ScvO2 of 70%, and normalization of lactate
“Time Zero”

• Time Zero = time of presentation
  – ED, Medical Floors, ICU
• Both bundles time based
• Most important time based elements:
  – Antibiotic timing
  – Resuscitation timing (EGDT)
## Change in Mortality Over Time

<table>
<thead>
<tr>
<th>Site quarter</th>
<th>Hospital mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>37.0%</td>
</tr>
<tr>
<td>2</td>
<td>36.1%</td>
</tr>
<tr>
<td>3</td>
<td>36.8%</td>
</tr>
<tr>
<td>4</td>
<td>33.2%</td>
</tr>
<tr>
<td>5</td>
<td>34.7%</td>
</tr>
<tr>
<td>6</td>
<td>30.6%</td>
</tr>
<tr>
<td>7</td>
<td>34.1%</td>
</tr>
<tr>
<td>8</td>
<td>30.0%</td>
</tr>
</tbody>
</table>

**Mortality Benefit:**

- **7% ARR**
- **19% RRR**

P < .001

## Perspective

<table>
<thead>
<tr>
<th></th>
<th>Severe Sepsis</th>
<th>Acute coronary syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. cases per 100,000 per annum</td>
<td>127</td>
<td>200</td>
</tr>
<tr>
<td>NNT ‘basic’ care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis Six (our data)</td>
<td>6</td>
<td>Clopidogrel 48</td>
</tr>
<tr>
<td>First hour antibiotics</td>
<td>5</td>
<td>β-blockade 42</td>
</tr>
<tr>
<td>β-blockade</td>
<td></td>
<td>Aspirin 26</td>
</tr>
<tr>
<td>Aspirin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NNT invasive care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGDT (Rivers)</td>
<td>6</td>
<td>Thrombolysis 15</td>
</tr>
<tr>
<td>Resusc Bundle (SSC)</td>
<td>18</td>
<td>PCI over thrombolysis 33</td>
</tr>
</tbody>
</table>
Antibiotic Therapy

• We recommend that intravenous antibiotic therapy be started as early as possible and within the first hour of recognition of septic shock (1B) and severe sepsis without septic shock (1C).

(Best Practice versus Stand of Care)
Antibiotics

- Multiple large, observational studies have shown the time to administration of antibiotics to be strongly associated with improve survival.

- Not aware of a single physician that recommends withholding or slowing down the time to antibiotics in a patient with severe sepsis.

- “time to needle” or “door to balloon” metric.
Antibiotics

- No randomized-controlled data

Gailieski DF, Mikkelsen ME, Band RA, et al. Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department*. Critical Care Medicine 2010;38(4):1045-53.

Time to Antibiotics Following Onset Septic Shock

Running average survival in septic shock based on antibiotic delay (n=4195)
Increased Mortality With Inadequate Therapy Among ICU Patients With Bloodstream Infections\textsuperscript{1,a}

Prospective, single-center, cohort study (1997-1999)

Mortality in ICU Patients (%)

- Inadequate Therapy (N=147): 62%
- Adequate Therapy (N=345): 28%

\(P < .001\)

ICU=intensive care unit.

\textsuperscript{a}Major isolates: coagulase-negative staphylococci, \textit{Staphyloccus aureus}, and \textit{Candida} species.

Source Control

- No randomized-controlled data

In necrotizing fasciitis, multiple case series have shown improvement with an aggressive operative approach.


Expert opinion supports identifying the source of infection and aggressively managing it when possible.

Source Control

- Don’t be satisfied with a diagnosis of sepsis and no source.

- If a source exists and is potentially removable, get the ball rolling.
Antibiotic Therapy

- Initial empiric anti-infective therapy – activity against all likely pathogens and adequate concentrations into suspected or potential sources of infection (1B)

- Reassess antibiotic regimen daily for de-escalation (1B)
Difficult diagnosis

• Not all patients have classic SIRS
• Clinical diagnosis requiring experience and high index of suspicion for interpretation of history/symptoms/signs
• Signs often subtle
• Some groups at special risk eg infants, age > 65, neutropenia, haemodialysis, diabetes mellitus, alcoholism, lung disease, patients with invasive devices

Laupland et al Crit Care Med 2004
Common signs & symptoms of sepsis

- **Tachypnoea** 99%
- Tachycardia 97%
- **Fever > 38 degrees** 70%
- Hypothermia 13%
- Metabolic acidosis 38%
- Acute oliguria 54%
- Acute encephalopathy 35%


Accurate and routine measurement of respiratory rate is essential
# Diagnosis

## Table 4—Noninfectious Etiology of Fever in the ICU

<table>
<thead>
<tr>
<th>Category</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Hematoma, IM injections, Burns</td>
</tr>
<tr>
<td>CNS</td>
<td>Hemorrhage (intracerebral, subdural, subarachnoid), Infarction, Seizures</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Myocardial infarction, Dressler syndrome, Aortic dissection, Pericarditis</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Pulmonary embolus, Aspiration or chemical pneumonitis, Fat embolus, ARDS</td>
</tr>
<tr>
<td>GI</td>
<td>Pancreatitis, Acute cholecystitis, Inflammatory bowel disease, Ischemic colitis, Nonviral hepatitis, Retroperitoneal or GI hemorrhage</td>
</tr>
<tr>
<td>Metabolic/endocrinologic</td>
<td>Alcohol or other drug withdrawal, Hyperthyroidism, Adrenal insufficiency, Malignant hyperthermia, Heat stroke</td>
</tr>
<tr>
<td>Rheumatologic/inflammatory</td>
<td>Collagen vascular disease, Gout/pseudogout, Vasculitis</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Drug fever, Neoplasm, Deep venous thrombosis</td>
</tr>
</tbody>
</table>
C-Reactive Protein

- Acute phase protein produced by the liver

- Raised in
  - Infection
  - Immune disorders
    - Auto-immune disease
    - Inflammatory syndromes
  - Tissue destruction
    - Haemolysis
    - Pancreatitis
    - Surgery
    - Crush injury
    - Rhabdomyolysis
    - Ischaemia
  - Transfusion related
  - Neoplastic disease especially haematological malignancy
  - Metabolic disturbance e.g. gout, porphyria
  - Thrombo-embolic events
C-Reactive Protein

Increase of PCT after 3-4 hours versus > 12 hours for CRP
• The ‘right’ antibiotic is crucial
• Take blood cultures before antibiotics but do not delay antibiotics to undertake investigations or await results
• Start antibiotic therapy within 60 minutes
• Use bolus administration where possible
• REMEMBER: one dose is safer than not treating at all

PREScribe IT...

GET IT...

GIVE IT...

NOW!!!
Antibiotics

**Loading dose** high to start with

\[ LD = V \times C_p \]

**Volume of distribution (V):**
- hydrophillic \( \rightarrow \) increase in sepsis
- lipophillic \( \rightarrow \) increase in obese

**Required plasma concentration (C_p):** MICs

**Renal function plays NO ROLE in calculation of loading dose**

Antibiotics

SEPSIS

- Increased cardiac output
  - Increased clearance
    - Low plasma concentrations

- Leaky capillaries
  - Increased volume of distribution

- Multi-organ failure
  - Decreased clearance
    - High plasma concentrations

Adequate initial dosing important
Reassess and adjust

Blood Cultures
Commonly used classification of bacteremias into 3 categories: transient (bacteremia lasts for a short amount of time and can be caused by actions such as brushing of teeth or after gastrointestinal biopsy), intermittent (recurring bacteremia due to discontinuous seeding of the same organisms, which can be caused by infections such as abscesses), and persistent or sustained (bacteremia occurring over a prolonged period that is usually associated with infections such as infective endocarditis).
Diagnosis

1. To optimize identification of causative organisms, we recommend at least two blood cultures be obtained before antimicrobial therapy is administered as long as such cultures do not cause significant delay (>45 minutes) in antimicrobial administration, with at least one drawn percutaneously and one drawn through each vascular access device, unless the device was recently (<48 hr.) inserted (Grade 1C).
Blood cultures

2. Obtain Blood Cultures Prior to Administration of Antibiotics

Related Measures
Timing of Blood Cultures

Background
The incidence of sepsis and bacteremia in critically ill patients has been increasing in the past two decades.[8,9] Thirty percent to 50 percent of patients presenting with a clinical syndrome of severe sepsis or shock have positive blood cultures. Therefore, blood should be obtained for culture in any critically ill septic patient.

Collecting blood cultures prior to antibiotic administration offers the best hope of identifying the organism that caused severe sepsis in an individual patient. Failure to check blood cultures prior to antibiotic infusion will perhaps affect the growth of any blood borne bacteria and prevent a culture from becoming positive later.
2. Blood cultures

- Take blood cultures **BEFORE** starting antibiotics
- Take two blood cultures from separate sites if possible
- Obtain other cultures: urine, CSF, faeces, wound swabs, sputum, other fluids from within cavities,
- Consult specialty teams **early** for source control
BLOOD CULTURE SAMPLING GUIDELINE - ADULT

Released September 2014

Overview
This guideline outlines evidence-based practice for obtaining blood cultures which should be taken for all patients:

- who meet criteria for commencement on the sepsis pathway
- with severe pneumonia as scored by CORB/SMARTCOP
- with fever or history of fever and suspected or proven neutropenia
- with fever and immunocompromised
- with fever or evidence of infection and a vascular access device or recent surgery
- with fever and recent overseas travel
- with suspected bacterial endocarditis (take 3 sets or 6 sets if the patient has received antibiotics within the last 30 days)
- with delirium.

Selected patients with fever of unknown origin who appear unwell or are at risk of sudden deterioration, such as the elderly (age ≥ 65) or chronically ill, but do not meet criteria for the sepsis pathway may benefit from blood cultures. Discuss these patients with the Staff Specialist or senior doctor in charge of the department/overseeing care of the patient.
Blood cultures

Introduction

The taking of blood cultures to detect bacteraemia is an important medical investigation affecting the diagnosis and treatment of our patients. Their value will be maximised by taking the cultures for the appropriate indications and with the correct technique in order to reduce the risk of contamination.

Indications for taking a blood culture

Blood cultures are taken to identify patients with bacteraemia. There are many clinical signs and symptoms which may suggest bacteraemia and clinical judgement is required, but the following indicators should be taken into account when assessing a patient for signs of bacteraemia or sepsis:

- Core temperature out of normal range (there is no absolute temperature below which blood cultures are not required)
- Focal signs of infection
- Signs of sepsis
- Chills or rigors
- Raised or very low peripheral blood white cell count
- New or worsening confusion

NB Signs of sepsis may be minimal or absent in the very young and the elderly.

Blood cultures should be taken before starting antibiotics. If the patient is already on antibiotics the cultures should be taken immediately before the next dose.

Blood cultures should not routinely be performed to ensure that a previously positive culture is now negative. Do not take blood cultures in instances where the patient is for palliative care only and where further investigations have been deemed inappropriate.
ABSTRACT

Bloodstream infections are an important cause of morbidity and mortality. Physician orders for blood cultures often specify that blood specimens be collected at or around the time of a temperature elevation, presumably as a means of enhancing the likelihood of detecting significant bacteremia. In a multicenter study, which utilized retrospective patient chart reviews as a means of collecting data, we evaluated the timing of blood culture collection in relation to temperature elevations in 1,436 patients with bacteremia and fungemia. The likelihood of documenting bloodstream infections was not significantly enhanced by collecting blood specimens for culture at the time that patients experienced temperature spikes. A subset analysis based on patient age, gender, white blood cell count and specific cause of bacteremia generally also failed to reveal any associations.
Usefulness of Blood Culture for Hospitalized Patients Who Are Receiving Antibiotic Therapy

Christopher J. Grace¹,², John Lieberman¹,a, Kristen Pierce², and Benjamin Littenberg¹,²

Abstract

We conducted a retrospective study to determine the yield of blood samples drawn for culture during the initial 72 h of antibiotic therapy given to 139 patients who were admitted to the hospital for community-acquired infections or fever. The yield of these blood cultures was predictable and rarely (in only 1 patient [0.72%]) isolated new pathogens.
## Blood cultures

### Table 3. Contamination versus True Infection Rates for Specific Organisms.

<table>
<thead>
<tr>
<th>Organism</th>
<th>False positives</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Bacillus</em> spp.</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>Coag-negative <em>Staphylococcus</em> ssp.</td>
<td>&gt;90%</td>
</tr>
<tr>
<td><em>Propionibacterium</em> ssp.</td>
<td>&gt;90%</td>
</tr>
<tr>
<td><em>Corynebacterium</em> ssp.</td>
<td>&gt;80%</td>
</tr>
<tr>
<td>Viridans streptococci</td>
<td>50%</td>
</tr>
<tr>
<td><em>Clostridium</em> ssp.</td>
<td>40%</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em> ssp.</td>
<td>25%</td>
</tr>
<tr>
<td><em>Enterococcus</em> ssp.</td>
<td>15%</td>
</tr>
</tbody>
</table>

Source: From a presentation by Dr. Patric Murray, University of Maryland School of Medicine. Microbiology for the Millennium Conference. Feb. 17-19, 1999. Baltimore, MD
## Blood cultures

### Table 6: Risk Factors for Gram Negative Bacilli Bacteremia

- Hematopoietic stem cell transplant
- Liver failure
- Serum albumin <3 mg/dL
- Solid organ transplant
- Diabetes
- Pulmonary disease
- Hypotension
- Hemodialysis
- HIV
- Hematologic malignancy
- Steroids
- Elderly
Blood cultures

- Blood culture reported ‘GPC likely staph.’
  - Significant? Contaminant?
  - Coagulase positive or negative

- Significant bacteraemia:
  - Local and/or systemic signs of infection or sepsis
  - Both BC bottles positive
  - Early detection – BC pos < 14 hrs
  - Previous *S. aureus* colonisation or isolation from BC < 3 months

Blood cultures

Blood Culture Interpretation

CDC Recommendations
Venipuncture sample - treat as positive infection if:

• One positive blood culture with a recognized pathogen

• Two positive cultures with same organism drawn on separate occasions and the patient is symptomatic

Lining Up to Infuse Excellence
Factors to consider when choosing antibiotics

- patient's recent antibiotic therapy
- Hospital flora
- presence of underlying diseases
- available culture data – current AND past
- risk for drug resistant pathogens:
  - receipt of antibiotics within the preceding 90 days
  - current hospitalization of ≥5 days
  - antibiotic resistance in the community
  - immunosuppressive disease and/or therapy
  - presence of risk factors for resistance
Choosing an antibiotic:

- Think about **Location**:  
  - Where did the patient become ill? Travel? Exposure?  
  - Where did the infection anatomically originate?  
  - Where in the body, has or will the infection spread to?  
- Think about **the bug you are treating**: 
Resistance & prescribing

- MRSA – consider vancomycin (or linezolid or teicoplanin)

- VRE – consider linezolid or daptomycin

- ESBL – consider carbapenem or alternative agent e.g. cipro or gent if sensitivities are known

- CPE – d/w Microbiology re tigecycline, colistin, fosfomycin etc

- Group A strep – consider high dose clinda
Mortality & Multidrug-Resistant Organisms

• Association between development of antimicrobial resistance in *Staphylococcus aureus*, enterococci, and Gram-negative bacilli and mortality\(^1\)

• *Pseudomonas aeruginosa* is increasingly resistant to fluoroquinolones, with a number of consequences, including infection-related mortality\(^2\)

• Enterococcal infections have been associated with mortality rates exceeding 30%\(^3\)

Mortality associated with carbapenem resistant (CR) vs susceptible (CS) Klebsiella pneumoniae (KP)

Overall Mortality

CRKP  OR 3.71 (1.97-7.01)

CSKP  OR 4.5 (2.16-9.35)

Attributable Mortality

Figure 1. Predicted mortality for patients with and without antimicrobial-resistant infection (ARI). APACHE, Acute Physiology and Chronic Health Evaluation.
Impact of Previous Therapy on Outcome of Gram-Negative Severe Sepsis

![Graph showing hospital mortality rates with APACHE II scores and the impact of prior antibiotic exposure.](image)

*Crit Care Med 2011; 39:1859*
Mortality Associated with Initial Inappropriate Therapy – Serious Infections

Guideline recommendations

- Combination empirical therapy for the following patients (grade 2B):
  - Neutropenic with severe sepsis and for patients with difficult-to-treat, multidrug-resistant bacterial pathogens (*Acinetobacter* or *Pseudomonas* bacteremia)
  - Severe infections associated with respiratory failure and septic shock (*Pseudomonas* bacteremia)
  - Septic shock from bacteremic *Streptococcus pneumoniae*
Combination therapy vs. monotherapy for septic shock

<table>
<thead>
<tr>
<th>Mortality rate *</th>
<th>Monotherapy (n=1223)</th>
<th>Combination Rx (n=1223)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>28-Day, %</td>
<td>36.3</td>
<td>29</td>
<td>0.77 (0.67 – 0.88)</td>
</tr>
<tr>
<td>ICU, %</td>
<td>35.7</td>
<td>28.8</td>
<td>0.75 (0.63 – 0.88)</td>
</tr>
<tr>
<td>Hospital, %</td>
<td>47.8</td>
<td>37.4</td>
<td>0.69 (0.59 – 0.81)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th># deaths</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>All Gram + , %</td>
<td>39.9</td>
<td>30.7</td>
<td>0.73 (0.58 – 0.92)</td>
</tr>
<tr>
<td>All Gram - , %</td>
<td>34.5</td>
<td>28.2</td>
<td>0.79 (0.67 – 0.94)</td>
</tr>
</tbody>
</table>

* Propensity score adjusted
Barriers to timely antibiotics

- Delayed recognition of sepsis and septic shock
  - Infection
  - Hypotension

- Inappropriate antimicrobial therapy
  - Failure to use stat order
  - Unrecognized risk factors for MDR pathogens
  - No specifications for order of administration
  - Logistical delays
Identification and Susceptibility Determination by Rapid Molecular Identification Allows Earlier Initiation of Optimal Therapy\textsuperscript{1-4}

Skin Infection

- Rapid molecular identification methods; identification and susceptibility results to physician (1-5 h)

Positive Blood Culture

- Rapid molecular identification methods; identification and susceptibility results to physician (additional 1-5 h)
- Culture results (18-48 h)
- AST results (additional 8-48 h)

Specimen collected

Final culture and AST report to physician

Limited impact on therapy

Time (hours)

0 24 48 72 96

PCR=polymerase chain reaction; AST=antimicrobial susceptibility testing.

Survive SEPSIS

the official training programme of the Surviving Sepsis Campaign

2nd Edition
2009 - 2010

Heart of England Sepsis Screening Tool (wards)

Apply if MEWS is 4 or more, or if infection suspected

- Are any 2 of the following SIRS criteria present and new to your patient?
  - Temperature <35 or > 38.3°C
  - Respiratory rate > 20/min
  - Heart rate > 90 bpm
  - Acutely altered mental state
  - Blood: WCC < 4 x 10^9/l or > 12 x 10^9/l
  - Glucose > 7.7 mmol/l
  - (Patient is not diabetic)

If patient is haemodynamically and any 1 present, follow 'yes' and call Consultant

- Call FY or CT doctor using SDAR Situation: Suspected Sepsis

Patient has SIRS: Think SEPSIS!!!

- Is this likely to be due to an infection?
  - Cough/ sputum/ chest pain
  - Abdominal pain/ distension/ diarrhoea
  - Line infection
  - Septicaemia

For example:
  - Osteomyelitis
  - Headache with neck stiffness
  - Septicaemia/ wound infection/ arthritis

If yes:
- This patient has SEPSIS
- Ensure Doctor present within 30 mins
- Immediately start Sepsis Six Pathway

Time of SDAR call:

Doctor's name:
Referring staff name:

(“SIRS = Systemic Inflammatory Response Syndrome”)
**Antibiotic allergy**

<table>
<thead>
<tr>
<th>Definitions of penicillin hypersensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immediate hypersensitivity</strong> involves the development of urticaria, angioedema, bronchospasm or anaphylaxis within one to two hours of drug administration.</td>
</tr>
<tr>
<td><strong>Severe prior reaction</strong> involves a history of drug rash eosinophilia and systemic symptoms (DRESS) or Stevens-Johnson Syndrome following administration of a penicillin or cephalosporin.</td>
</tr>
<tr>
<td>All penicillin and cephalosporin class antibiotics are contraindicated in patients with history of drug rash eosinophilia and systemic symptoms (DRESS), Stevens-Johnson Syndrome or IgE-mediated immediate penicillin or cephalosporin allergy.</td>
</tr>
<tr>
<td>Refer to <em>Therapeutic Guidelines: Antibiotic</em> for more information</td>
</tr>
</tbody>
</table>
Antibiotic allergy

In the setting of severe sepsis / septic shock carbapenems (e.g. meropenem) can be used in those with a history of penicillin allergy provided:

- No features of immediate hypersensitivity
- No severe prior reaction
- i.e. a prior history of a non-severe, delayed rash does not preclude the use of meropenem
Penicillin allergy

If history of immediate hypersensitivity or severe prior reaction

- d/w Microbiology
- Reasonable approach would be:
  - Vancomycin + cipro + metro + single dose of gentamicin
  - Review / rationalise and deescalate with progress and results of investigations
### Penicillins (β-lactams)

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Gram Positive</th>
<th>Gram Negative</th>
<th>Atypicals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MRSA</td>
<td>Staph</td>
<td>Strept pneumo</td>
</tr>
<tr>
<td>Benzylpenicillin / Penicillin V</td>
<td>R</td>
<td>R</td>
<td>G</td>
</tr>
<tr>
<td>Flucloxacillin</td>
<td>R</td>
<td>G</td>
<td>G</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>R</td>
<td>R</td>
<td>G</td>
</tr>
<tr>
<td>Co-amoxiclav</td>
<td>R</td>
<td>G</td>
<td>G</td>
</tr>
<tr>
<td>Anti-pseudomonal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tazocin</td>
<td>R</td>
<td>G</td>
<td>G</td>
</tr>
<tr>
<td>Carbapenems</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ertapenem</td>
<td>R</td>
<td>G</td>
<td>G</td>
</tr>
<tr>
<td>Imipenem</td>
<td>R</td>
<td>G</td>
<td>G</td>
</tr>
<tr>
<td>Meropenem</td>
<td>R</td>
<td>G</td>
<td>G</td>
</tr>
</tbody>
</table>
# Cephalosporins (β-lactams)

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>1st generation</th>
<th>2nd generation</th>
<th>3rd generation</th>
<th>Antipseudomonal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gram Positive</td>
<td>Gram Negative</td>
<td>Atypicals</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MRSA</td>
<td>Staph</td>
<td>Strept pneumo</td>
<td>Streptocoeci</td>
</tr>
<tr>
<td>Cefalexin</td>
<td>R</td>
<td>G</td>
<td>G</td>
<td>G</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>R</td>
<td>G</td>
<td>G</td>
<td>G</td>
</tr>
<tr>
<td>Ceftriaxone &amp; Cefotaxime</td>
<td>R</td>
<td>G</td>
<td>G</td>
<td>G</td>
</tr>
<tr>
<td>Cefixime</td>
<td>R</td>
<td>R</td>
<td>G</td>
<td>G</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>R</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
</tbody>
</table>

- **R**: Resistant
- **G**: Sensitive
- **A**: Active
Other cell wall antibiotics

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Gram Positive</th>
<th>Gram Negative</th>
<th>Atypicals</th>
</tr>
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</tr>
<tr>
<td>Glycopeptides</td>
<td>G</td>
<td>G</td>
<td>G</td>
</tr>
<tr>
<td>Vancocycin &amp; Teicoplanin</td>
<td>G</td>
<td>G</td>
<td>G</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>G</td>
<td>G</td>
<td>R*</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Colisin</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
</tbody>
</table>

*Inactive in the lung
• Total spend
  – 2010/2011: £1.9 million
  – 2011/2012: £2.15 million
  – 2012/2013: £2.2 million
  – 2013/2014 £2.3 million
• Percent on antibiotics
  – 29-41 on point prevalence audits (2011 -2014)
• Tazocin dose units
  – 2010/2011: 30,000 ➔ 2013/2014: 50,000
Antimicrobial Stewardship

- Optimize clinical outcomes
- Minimize Toxicity Resistance
- Potential for cost reduction

Kaplan-Meier Estimates of the Probability of Survival Probability of survival is for the 60 days after ventilator-assisted pneumonia onset as a function of the duration of antibiotics

No excess mortality
No more recurrent infections
More antibiotic-free days

Chastre, J. et al. JAMA 2003;290:2588-2598
De-escalation of empirical therapy is associated with lower mortality in patients with severe sepsis and septic shock


Original Article

Volume 40, Issue 1 / January , 2014

Pages 32 - 40
Antimicrobial Prescribing

Empiric

- Initial administration of a broad-spectrum antibiotic regimen that attempts to improve outcomes and minimize resistance.

Defined or Targeted

- Modification of antimicrobial therapy once the cause of infection is identified. Therapy may also be discontinued if the diagnosis of infection becomes unlikely.¹

- Focus on de-escalation of antibiotic therapy with the goal of minimizing resistance and toxicity, and improving cost-effectiveness.²,³

References:
What about risk?

• Meta-analysis of 24 studies in Critical Care

Antibiotic stewardship was not associated with increases in nosocomial infection rates, length of stay or mortality.

UK: Start Smart - Then Focus

Department of Health
Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI)

ANTIMICROBIAL STEWARDSHIP:
“START SMART - THEN FOCUS”

Guidance for antimicrobial stewardship in hospitals (England)
UK: Start Smart - Then Focus

Department of Health
Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI)

Antimicrobial stewardship
Right Drug, Right Dose, Right Time, Right Duration...
..... Every patient.

START SMART

THEN FOCUS

Do not start antibiotics in the absence of evidence of bacterial infection

- Take history of relevant allergies
- Initiate prompt effective antibiotic treatment within one hour of diagnosis (or as soon as possible) in patients with life threatening infections
- Comply with local prescribing guidance
- Document clinical indication and dose on drug chart and in clinical notes
- Include review/stop date or duration
- Ensure relevant microbiological specimens taken

CLINICAL REVIEW & DECISION#
AT 48 HOURS

Clinical review, check microbiology, make and document decision#

1. STOP
2. IV/oral switch
3. Change: to narrow spectrum agent
4. Continue and review again after a further 24 hours
5. OPAT*

DOCUMENT DECISION

# Antimicrobial Prescribing Decision
*Outpatient Parenteral Therapy

Figure 1: Antimicrobial Stewardship (AMS) – treatment algorithm

Advocating patient safety and auditing of antimicrobial stewardship in hospitals should be based around the principles stated in this AMS algorithm. Examples of audit tools are shared in Appendix 1
Take home messages

- Go hard / go early with antibiotics in severe sepsis/septic shock
- Blood (and other cultures)
- Source control
- Consider risk for multi-drug resistant organisms
- Start smart, Then focus
- De-escalate!
Sepsis is a medical emergency—and our second biggest killer

Awareness and recognition are the key

Reliable, early antibiotics and fluids will save more lives than Critical Care will..... even if CC were infinitely resourced
Any questions
## Hospital Mortality by Time to Antibiotics

<table>
<thead>
<tr>
<th>Time to ABX(^1), hrs</th>
<th>OR(^2)</th>
<th>95% CI</th>
<th>p-value</th>
<th>Probability of mortality(^3)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (ref)</td>
<td>1.00</td>
<td>---</td>
<td>---</td>
<td>18.7</td>
<td>17.5</td>
</tr>
<tr>
<td>1</td>
<td>1.05</td>
<td>1.02</td>
<td>1.07</td>
<td>&lt; 0.001</td>
<td>19.3</td>
</tr>
<tr>
<td>2</td>
<td>1.09</td>
<td>1.04</td>
<td>1.15</td>
<td>&lt; 0.001</td>
<td>20.0</td>
</tr>
<tr>
<td>3</td>
<td>1.14</td>
<td>1.06</td>
<td>1.23</td>
<td>&lt; 0.001</td>
<td>20.8</td>
</tr>
<tr>
<td>4</td>
<td>1.19</td>
<td>1.08</td>
<td>1.32</td>
<td>&lt; 0.001</td>
<td>21.5</td>
</tr>
<tr>
<td>5</td>
<td>1.25</td>
<td>1.11</td>
<td>1.41</td>
<td>&lt; 0.001</td>
<td>22.3</td>
</tr>
<tr>
<td>6</td>
<td>1.31</td>
<td>1.13</td>
<td>1.51</td>
<td>&lt; 0.001</td>
<td>23.1</td>
</tr>
</tbody>
</table>

\(^1\)Time to ABX is based on 15,948 observations that are greater than or equal to zero
\(^2\)Hospital mortality odds ratio referent group is 0 hours for the time to ABX and is adjusted by the number of baseline organ failures, infection type (community vs. nosocomial), and geographic region (Europe, North America, and South America)
Hospital Mortality by Time to Antibiotics

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\(^2\)Hospital mortality odds ratio referent group is 0 hours for the time to ABX and is adjusted by the number of baseline organ failures, infection type (community vs. nosocomial), and geographic region (Europe, North America, and South America)
Antibiotic Therapy

We recommend that intravenous antibiotic therapy be started as early as possible and within the first hour of recognition of septic shock (1B) and severe sepsis without septic shock (1C).

Remark: Although the weight of evidence supports prompt administration of antibiotics following the recognition of severe sepsis and septic shock, the feasibility with which clinicians may achieve this ideal state has not been scientifically validated.
Definitions

- A continuum of severity describing the host systemic inflammatory response

---

SIRS

- SIRS – systemic inflammatory response syndrome
- Must have at least 2 of the following:
  - Temperature >38.5°C or <36°C
  - Heart rate >90 beats/min
  - Respiratory rate >20 breaths/min or PaCO2 <32 mmHg
  - WBC >12,000 cells/mm³, <4000 cells/mm³, or >10 % immature (band) forms
- SIRS is the body’s response to infection, inflammation, stress.
Sepsis and Severe Sepsis

- **Sepsis** – SIRS + suspected or confirmed infection (documented via cultures or visualized via physical exam/imaging)
- **Severe Sepsis** – Sepsis + at least one sign of organ hypo-perfusion or dysfunction

<table>
<thead>
<tr>
<th>Area</th>
<th>Sign</th>
</tr>
</thead>
<tbody>
<tr>
<td>Areas of mottled skin</td>
<td>Disseminated intravascular coagulation</td>
</tr>
<tr>
<td>Capillary refill &gt; 3 secs</td>
<td>AKI</td>
</tr>
<tr>
<td>UOP &lt; 0.5cc/kg/hr</td>
<td>ARDS or acute lung injury (ALI)</td>
</tr>
<tr>
<td>Lactate &gt; 2mmol/L</td>
<td>Cardiac dysfunction on echo</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>Plt &lt; 100</td>
</tr>
<tr>
<td>Abnormal EEG</td>
<td>Troponin Leak</td>
</tr>
</tbody>
</table>
## Mortality by antibiotics

<table>
<thead>
<tr>
<th></th>
<th>Cohort size</th>
<th>Mortality %</th>
<th>RRR % (NNT)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>567 (100%)</td>
<td>34.7</td>
<td>-</td>
</tr>
<tr>
<td><strong>Delayed Antibiotics</strong></td>
<td>217 (38.4%)</td>
<td>45.4</td>
<td></td>
</tr>
<tr>
<td><strong>Antibiotics within 1 h</strong></td>
<td>350 (61.6%)</td>
<td>28.1</td>
<td>38.1 (5.77)</td>
</tr>
</tbody>
</table>

© Ron Daniels 2010
Indications

Fever, chills, hypothermia, leukocytosis, left shift of neutrophils, neutropenia, and the development of otherwise unexplained organ dysfunction (e.g., renal failure or signs of hemodynamic compromise) are specific indications for obtaining blood for culture. Blood cultures should be taken as soon as possible after the onset of fever or chills.

While it remains difficult to predict bacteremia in patients with sepsis[5], a number of clinical and laboratory parameters are independently correlated with the presence of bacteria in the blood of patients when infection is suspected. These include chills, hypoalbuminemia, the development of renal failure, and a diagnosis of urinary tract infection[5,6]; other criteria are new fever, hypothermia, leukocytosis and left shift of neutrophils, neutropenia, and signs of hemodynamic compromise[7]. Peaking fever appears to be more sensitive than leukocytosis to predict bacteremia[8]; however, fever and low-grade bacteremia can be continuous, such as in endocarditis.
Collection Strategy

Two or more blood cultures are recommended with at least one drawn percutaneously and one drawn through each vascular access device, unless the device was recently inserted (<48 hours).[1,2] In patients with suspected catheter-related infection, a pair of blood cultures obtained through the catheter hub and a peripheral site should be obtained simultaneously. Cultures of other sites (preferably quantitative, where appropriate), such as urine, cerebrospinal fluid, wounds, respiratory secretions, or other body fluids that may be the source of infection should also be obtained before antimicrobial therapy.[2] If the same organism is recovered from both cultures, the likelihood that the organism is causing the severe sepsis is enhanced. In addition, if the culture drawn through the vascular access device is positive much earlier than the peripheral blood culture (i.e., >2 hours earlier), it may offer support that the vascular access device is the source of the infection.[3] Volume of blood may also be important.[4]
Table 1. Organisms Associated with Nosocomial Catheter-Related Blood Stream Infections (CR-BSI).

<table>
<thead>
<tr>
<th>Organism</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulase-negative <em>Staphylococci</em></td>
<td>Most common pathogen in CR-BSI</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>Increasing prevalence of MRSA strains</td>
</tr>
<tr>
<td>Gram-negative bacilli</td>
<td>Among the resistant gram negative bacilli, <em>Acinetobacter baumannii</em> predominates in Europe. In USA <em>Pseudomonas aeruginosa</em> seems to be more prevalent</td>
</tr>
<tr>
<td><em>Enterococcus spp.</em></td>
<td><em>E. faecalis</em> is more common than <em>e. faecium</em></td>
</tr>
<tr>
<td><em>Candida spp.</em></td>
<td><em>C. albicans</em> is the most common species</td>
</tr>
<tr>
<td>Other bacteria including diphteroids, viridans streptococci</td>
<td>Micrococcus, and more rarely, fungi other than Candida spp.</td>
</tr>
</tbody>
</table>

The organisms are listed in order of decreasing frequency. From multiple sources (6, 9, 11, 20, 21)
<table>
<thead>
<tr>
<th>Table 2: Risk Factors for Bacteremia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced age</td>
</tr>
<tr>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Immunosuppressing medications (transplant patients, rheumatologic diseases, etc)</td>
</tr>
<tr>
<td>Chronic liver disease</td>
</tr>
<tr>
<td>Chronic renal failure (especially if on hemodialysis)</td>
</tr>
<tr>
<td>Hematological malignancies</td>
</tr>
<tr>
<td>HIV infection</td>
</tr>
<tr>
<td>Intravenous catheters</td>
</tr>
<tr>
<td>Intravenous drug use</td>
</tr>
<tr>
<td>Loss of skin integrity</td>
</tr>
<tr>
<td>Malnutrition and hypoalbuminemia</td>
</tr>
<tr>
<td>Neutropenia</td>
</tr>
<tr>
<td>Parenteral nutrition</td>
</tr>
<tr>
<td>Organism</td>
</tr>
<tr>
<td>----------------------------------</td>
</tr>
<tr>
<td>Coagulase-negative <em>Staphylococcal</em> spp.</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td><em>Enterococcus</em> spp.</td>
</tr>
<tr>
<td><em>Candida</em> spp.</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
</tr>
<tr>
<td><em>Klebsiella</em> spp.</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
</tr>
<tr>
<td><em>Enterobacter</em> spp.</td>
</tr>
<tr>
<td><em>Serratia</em> spp.</td>
</tr>
<tr>
<td><em>Acinetobacter baumannii</em></td>
</tr>
</tbody>
</table>
### Standardized order sets

<table>
<thead>
<tr>
<th></th>
<th>Before (n=60)</th>
<th>After (n=60)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appropriate antibiotics, %</td>
<td>71.7</td>
<td>86.7</td>
<td>0.043</td>
</tr>
<tr>
<td>28-day mortality, %</td>
<td>48.3</td>
<td>30</td>
<td>0.04</td>
</tr>
</tbody>
</table>
Empiric Antibiotic Treatment Reduces Mortality in Severe Sepsis and Septic Shock From the First Hour: Results From a Guideline-Based Performance Improvement Program*

Ferrer, Ricard MD, PhD¹; Martin-Loeches, Ignacio MD, PhD²; Phillips, Gary MAS³; Osborn, Tiffany M. MD, MPH⁴; Townsend, Sean MD⁵; Dellinger, R. Phillip MD, FCCP, FCCM⁶; Artigas, Antonio MD, PhD²; Schorr, Christa RN, MSN⁶; Levy, Mitchell M. MD, FCCP, FCCM⁷
Site of Infection

- Most important factor to consider in antimicrobial selection

- Defines the most likely organisms
  - Especially helpful in empiric antimicrobial selection

- Determines the dose and route of administration of antimicrobial
  - Efficacy determined by adequate concentrations of antimicrobial at site of infection
  - Serum concentrations vs. tissue concentrations and relationship to MIC
Streptococcus pneumoniae
“Pneumococcus”
Gram positive cocci looking like Staphylococci
Gram positive cocci looking like Streptococci
Gram positive bacilli
Gram negative bacilli
Gram negative cocci
Strep not Staph!
Prophylaxis

CMV: 3 months of antiviral (valganciclovir [valcyte], valacyclovir [valtrex]) for D+R- and R+

PCP: 6-12 mo TMP/SMX (or dapsone, pentamidine)

UTI: 1-3 mo TMP/SMX (or quinolone) for K txp

Candida: all KP, selected liver transplant recipients

1-3 mo fluconazole
Evaluation of the Patient

Baseline patient data critical for appropriate work-up

- Donor/recipient serologies (CMV, EBV, HSV, VZV, Toxoplasma)
- Underlying disease
- Time post-transplant
- Allograft function
- Prophylactic medications
- Rejection (and its treatment)
• Early and aggressive diagnostic investigation
  - adequate tissue
  - routine “staging”

• Appropriate notification and coordination with pathology and microbiology laboratories
“Timetable” of Infections After Organ Transplantation

- General guidelines, NOT absolute
- Epidemiology altered by prophylaxis
- Unusual timing may be a clue to unusual exposure
**Early Period** (first post-transplant month)

- Nosocomial/”surgical” infections
- Multi-drug resistant organisms (e.g., GNR, MRSA, VRE)
- Importance of adjunctive therapy (anatomical problems, adequate drainage)
- Opportunistic infections are uncommon (except Aspergillus, Candida, HSV— in absence of prophylaxis)
Middle Period (from post-transplant months 2-6)

- Greatest risk period for “classic” opportunists (e.g., PCP, Aspergillus, Toxoplasma, Cryptococcus, etc.)

- Immunomodulating viruses (e.g., CMV, EBV, HHV-6)
Late Period (after the 6th post-transplant month)

- “Typical” community-acquired infections in patients with good allograft function

- Continued risk of opportunistic infections in patients with poor allograft infection and/or chronic rejection
• Signs and symptoms of infection are muted by immunosuppression

• Specific, predictable risk periods for specific pathogens (unusual timing may be a clue to exposure)

• Link between immunosuppression and infection risk

• Consider the possibility of donor-derived infection (viral, fungal, bacterial, mycobacterial, etc.)
Fig. 1 Schematic outlining a practice of antimicrobial de-escalation. $FiO_2$ inspired oxygen fraction, $PaO_2$ partial pressure (or tension) of arterial oxygen, DRPs drug-resistant pathogens
Empirical therapy
- Early therapy
- Broad spectrum agents
- Consider combination therapy
- Optimization of dose schedule

Appropriate cultures
- Blood
- Site of infection

De-escalation therapy

Streamlining of empirical therapy
- Stopping of antibiotics
- Agents with narrower spectrum
- Low impact on microbiota
- Optimization of dose schedule
- Use oral route if possible
- Consider cost
Importance of Initial, Appropriate Antibiotic Therapy

“...selection of initial appropriate antibiotic therapy (ie, getting the antibiotic treatment right the first time) is an important aspect of care for hospitalized patients with serious infections.”

– ATS/IDSA Guidelines

A Study by Kollef and Colleagues Evaluating the Impact of Inadequate Antimicrobial Therapy on Mortality

ATS=American Thoracic Society; IDSA=Infectious Diseases Society of America.

Increased Mortality Associated With Inadequate Empirical Antibiotic Therapy in Patients With Pneumonia

Retrospective\(^1\) and prospective,\(^2\) single-center, cohort analyses

Among patients with healthcare-associated pneumonia, subsequent escalation\(^a\) of antibiotic therapy among patients who received inadequate initial therapy did not result in decreased risk of mortality\(^1\)

---

\(^a\)Escalation was defined as the switch to or addition of antibiotics with a broader spectrum.

Stewardship optimizes patient safety: decreased patient-level resistance

<table>
<thead>
<tr>
<th></th>
<th>Cipro</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic duration</td>
<td>3 days</td>
<td>10 days</td>
</tr>
<tr>
<td>LOS ICU</td>
<td>9 days</td>
<td>15 days</td>
</tr>
<tr>
<td>Antibiotic resistance/ superinfection</td>
<td>14%</td>
<td>38%</td>
</tr>
</tbody>
</table>

Study terminated early because attending physicians began to treat standard care group with 3 days of therapy

“Spiralling Empiricism”

Diagnostic Uncertainty → Broad-Spectrum Coverage → Rise in MDRO HAIs → MDRO Selection → Diagnostic Uncertainty