Antibiotics Use in ICU

WK To
April 2010
Antibiotics resistance is inevitable & Total consumption is a critical factor in selecting resistance organisms

S. Pneumoniae: Resistant Rate

Source: HA, Hong Kong
Antibiotics are specialized drug!

- Effectiveness
  (Local epidemiology)
- Pharmaco-kinetic
- Resistance mechanism
- Action mechanism
- Adverse reaction
- Cost
Table 7. Recommended empirical antibiotics for community-acquired pneumonia.

<table>
<thead>
<tr>
<th>IDSA guideline, CID 2007:44 (Suppl 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outpatient treatment</strong></td>
</tr>
<tr>
<td>1. Previously healthy and no use of antimicrobials within the previous 3 months</td>
</tr>
<tr>
<td><strong>A macrolide (strong recommendation; level I evidence)</strong></td>
</tr>
<tr>
<td>Doxycycline (weak recommendation; level III evidence)</td>
</tr>
<tr>
<td>2. Presence of comorbidities such as chronic heart, lung, liver or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressing conditions or use of immunosuppressing drugs; or use of antimicrobials within the previous 3 months (in which case an alternative from a different class should be selected)</td>
</tr>
<tr>
<td>A respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin [750 mg]) (strong recommendation; level I evidence)</td>
</tr>
<tr>
<td>A β-lactam plus a macrolide (strong recommendation; level I evidence)</td>
</tr>
<tr>
<td>3. In regions with a high rate (&gt;25%) of infection with high-level (MIC ≥ 16 μg/mL) macrolide-resistant <em>Streptococcus pneumoniae</em>, consider use of alternative agents listed above in (2) for patients without comorbidities (moderate recommendation; level III evidence)</td>
</tr>
<tr>
<td><strong>Inpatients, non-ICU treatment</strong></td>
</tr>
<tr>
<td>A respiratory fluoroquinolone (strong recommendation; level I evidence)</td>
</tr>
<tr>
<td>A β-lactam plus a macrolide (strong recommendation; level I evidence)</td>
</tr>
</tbody>
</table>

**Local epidemiology**

**S. pneumonia:**

% sensitive (HA)

<table>
<thead>
<tr>
<th>Erythromycin</th>
<th>30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levofloxacin</td>
<td>96</td>
</tr>
</tbody>
</table>

IDSA guideline, CID 2007:44 (Suppl 2)
# Treatment of S. pneumoniae

## New CLSI interpretation:

| Penicillin MIC: | 
|-----------------|---------------------------------------------------|
| **≤ 0.06 – 2 µg/ml** | **“Sensitive”** |
| **MIC (µg/ml) ≤ 0.06** | Amoxil 250mg tds, Augmentin 375mg tds, other b-lactam |
| **MIC (µg/ml) = 0.12 – 1** | Amoxil 500mg tds, Augmentin 750mg tds |
| **MIC (µg/ml) = 2** | Amoxil 750mg-1g tds, Augmentin 1g tds |
| **MIC (µg/ml) = 4** | **“Intermediate”** |
| **“Intermediate”** | Amoxil 1g tds, Augmentin 2g BD |
| **MIC (µg/ml) > 8** | **“Resistant”** |
| **“Resistant”** | Quinolone / Vancomycin / Cefotoxime (depend on MIC) |

**Empirical Tx:**

a. Cover H. influenza, b. >50% MIC up to 1 µg/ml

**Choice:**

- **iv:** Augmentin 1.2g Q8H or Ceftriaxone 1g Q24H
- **Oral:** Augmentin 750mg tds or Augmentin 375mg tds + Amoxil 250mg tds
Pharmacokinetic

Some examples:

- **Quinolones, Linezolid, Metronidazole, Fluconazole**, etc have excellent oral bio-availability, therefore, PO=IV unless the patients cannot eat or are in shock.

- **Aminoglycosides** (if use as mono-therapy) have limited clinical effectiveness for certain infections:
  - Pneumonia: as they have poor penetration in infected airway;
  - Abscess: as activity is diminished in acid conditions.

- **Nitrofurantoin**: An excellent alternative for ESBL+ UTI, however, can be used for UTL only as only urine can achieve adequate drug level for clinical effectiveness.
Resistance mechanism: 1. What is ICBL/AmpC

Inducible Enterobacteriaceae

- Organisms with inducible Chromosomal β lactamases /AmpC β lactamases:
  Enterobacter, Serratia, Morganella morganii, Citrobacter freudii, Providencia
  Some Klebsiella, E.coli: Plasmid mediated AmpC β lactamases

- Points to notice:
  (1) AmpC BL are **NOT** inhibited by β lactamase inhibitor
  (2) AmpC BL has activity against Cephalosporins (1st, 2nd, 3rd gen but **NOT**
  Cefepime) & Penicillins
  (3) Enzyme is induced by an inducer
      In vitro test may appear sensitive, especially for weak inducer

<table>
<thead>
<tr>
<th>Inducer</th>
<th>Ampicillin, Clavulanic acid, Cefoxitin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weak inducer</td>
<td>2nd, 3rd gen Cephalosporins, Pipericillin</td>
</tr>
</tbody>
</table>

(4) Derepressed mutant can be selected during therapy even with weak inducer

- Treatment option:
  (1) β lactam: a) Carbapenems, b) Cefepime (4th gen.)
  (2) Non-β lactam : e.g. Quinolone, Aminoglycoside

Phenotypic test suggests presence of AmpC beta-lactamase. Resistance may develop during prolonged therapy with 3rd generation cephalosporins
2. **ESBL:** Do all infections caused by ESBL-producing organisms require carbapenems?

For **severe infection** with a high bacterial load, e.g. bacteremia, or in sequestered site, e.g. inadequately drained loculated intra-abdominal abscesses, **carbapenems are considered to be the treatment of choice**

**β lactam/β lactamase inhibitor combination drugs are excellent alternatives for most of the milder and uncomplicated infections.** e.g. Augmentin, it is highly concentrated in urine and its excellent bioavailability (~80%) allows outpatient treatment. In addition, with anaerobic coverage, it is particular useful to treat polymicrobial infections such as bite wounds and diabetic foot infections.

For deep seated infection or serious infections, although β lactam/ lactamase inhibitor combination drugs are generally not suggested as they may be subject to the inoculum effect in case of high bacterial load, we don’t have to step up to carbapenem in all cases if the clinical responses to the empirical treatment are good.
• **Fluoroquinolones**, similarly, have excellent bioavailability (70-90%), and in addition to attaining high level in urine, penetrate prostate tissue well. If being tested sensitive in-vitro, they are considered as alternatives in the treatment of bacteremia and pneumonia caused by ESBL producing organisms.

• Other options for uncomplicated UTI include **Septrin** and **Nitrofurantoin**. Considering that E coli remains highly susceptible to **Nitrofurantoin** (PMH data: over 95% sensitive) and its good bioavailability (80%), it should be given as first line empirical treatment for most uncomplicated UTI, except in patients with renal impairment as reduced urinary excretion would result in sub-therapeutic urine concentration.

• Concerning newer options, such as **tigecycline**, clinical data is still lacking. Moreover, bearing in mind of its low urinary excretion (only 10-15%), its bacteriostatic property and low serum concentration, its role in treating infections caused by ESBL producers is rather limited.
Meropenem (MER) Vs Imipenem (IMI)

Meropenem is the better choice as imipenem is less effective and has much greater chance of seizure?

FDA label: MER: Overall seizure rate being 0.7%.

IMI: Possibly, probably, or definitely related: 0.4%

Imipenem is the more cost effective choice of carbapenem with the following exceptions:

- Impair renal function: ≤20mL/min/1.73 m²
- Patients with CNS disorders (e.g., brain lesions or history of seizures)
- Patients on hemodialysis
- Patients (especially paediatric) with CNS infections

Remark: Close adherence to the dosing guidelines for Imipenem needed

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>MEM</th>
<th>IPM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ps. Aeruginosa</td>
<td>98</td>
<td>98</td>
</tr>
<tr>
<td>E-coli</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Klebsiella</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Proteus</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Enterobacter</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Acinetobacter</td>
<td>62</td>
<td>67</td>
</tr>
</tbody>
</table>

| Tienam | IV | 500 mg Q8H | 234 |
| IV | 500 mg Q6H | 312 |
| Meropenem | IV | 500 mg Q8H | 397.14 |
| IV | 1 g Q8H | 609.6 |
3. **Klebsiella Pneumoniae Carbapenemase (KPC)**

- KPC is a class A $\beta$-lactamase
  - Confers resistance to all $\beta$-lactams including extended-spectrum cephalosporins and **carbapenems**

- Occurs in Enterobacteriaceae
  - Most commonly in *Klebsiella pneumoniae*
  - Also reported in: *K. oxytoca, Citrobacter freundii, Enterobacter* spp., *Escherichia coli, Salmonella* spp., *Serratia* spp.,

- Also reported in *Pseudomonas aeruginosa* (Columbia)
- Treatment options: Colistin (nephrotoxic) and tigecycline (low blood level)
When to Suspect a KPC-Producer

• Enterobacteriaceae – especially *Klebsiella pneumoniae* that are resistant to extended-spectrum cephalosporins:
  
  – MIC range for 151 KPC-producing isolates
    
    • Ceftazidime $32$ to $>64 \mu g/ml$
    • Ceftriaxone $\geq 64 \mu g/ml$
    • Cefotaxime $\geq 64 \mu g/ml$
  
  – Variable susceptibility to cefoxitin and cefepime
Modified Hodge Test

Lawn of *E. coli* ATCC 25922
1:10 dilution of a 0.5 McFarland suspension

Test isolates

Imipenem disk

Described by Lee et al. CMI, 7, 88-102. 2001.
Common fallacies about use of antibiotics
Fallacy 1: Big guns are required for all cases of neutropenic fever

2002 Guidelines for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer

Table 3. Factors that favor a low risk for severe infection among patients with neutropenia.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute neutrophil count of $\geq 100$ cells/mm$^3$</td>
<td></td>
</tr>
<tr>
<td>Absolute monocyte count of $\geq 100$ cells/mm$^3$</td>
<td></td>
</tr>
<tr>
<td>Normal findings on a chest radiograph</td>
<td></td>
</tr>
<tr>
<td>Nearly normal results of hepatic and renal function tests</td>
<td></td>
</tr>
<tr>
<td>Duration of neutropenia of $&lt;7$ days</td>
<td></td>
</tr>
<tr>
<td>Resolution of neutropenia expected in $&lt;10$ days</td>
<td></td>
</tr>
<tr>
<td>No intravenous catheter-site infection</td>
<td></td>
</tr>
<tr>
<td>Early evidence of bone marrow recovery</td>
<td></td>
</tr>
<tr>
<td>Malignancy in remission</td>
<td></td>
</tr>
<tr>
<td>Peak temperature of $&lt;39.0^\circ C$</td>
<td></td>
</tr>
<tr>
<td>No neurological or mental changes</td>
<td></td>
</tr>
<tr>
<td>No appearance of illness</td>
<td></td>
</tr>
<tr>
<td>No abdominal pain</td>
<td></td>
</tr>
<tr>
<td>No comorbidity complications$^a$</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** Data are adapted from [4, 42–49, 51–53].

$^a$ Concomitant condition of significance (e.g., shock, hypoxia, pneumonia or other deep-organ infection, vomiting, or diarrhea).

Table 4. Scoring index for identification of low-risk febrile neutropenic patients at time of presentation with fever.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extent of illness$^a$</td>
<td></td>
</tr>
<tr>
<td>No symptoms</td>
<td>5</td>
</tr>
<tr>
<td>Mild symptoms</td>
<td>5</td>
</tr>
<tr>
<td>Moderate symptoms</td>
<td>3</td>
</tr>
<tr>
<td>No hypotension</td>
<td>5</td>
</tr>
<tr>
<td>No chronic obstructive pulmonary disease</td>
<td>4</td>
</tr>
<tr>
<td>Solid tumor or no fungal infection</td>
<td>4</td>
</tr>
<tr>
<td>No dehydration</td>
<td>3</td>
</tr>
<tr>
<td>Outpatient at onset of fever</td>
<td>3</td>
</tr>
<tr>
<td>Age $&lt;60$ years$^b$</td>
<td>2</td>
</tr>
</tbody>
</table>

**NOTE.** Highest theoretical score is 26. A risk index score of $\geq 21$ indicates that the patient is likely to be at low risk for complications and morbidity. The scoring system is derived from [50].

$^a$ Choose 1 item only.

$^b$ Does not apply to patients $\leq 16$ years of age. Initial monocyte count of $\geq 100$ cells/mm$^3$, no comorbidity, and normal chest radiograph findings indicate children at low risk for significant bacterial infections [46].
2002 Guidelines for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer

Figure 1. Algorithm for initial management of febrile neutropenic patients. See tables 3 and 4 for rating system for patients at low risk. Carbapenem, imipenem or meropenem.
Fallacy 2: Big guns are required for all cases of hospital acquired pneumonia

For patients with early-onset infections (fewer than 5 days following admission to hospital) who have not previously received antibiotics and in the absence of other risk factors, the use of co-amoxiclav or cefuroxime would be appropriate.

For patients with early-onset infections (fewer than 5 days following admission to hospital) who have recently received antibiotics and/or who have other risk factors, a third-generation cephalosporin (cefotaxime or ceftriaxone), a fluoroquinolone or piperacillin/tazobactam would be appropriate.

Percentage Resistance of Antibiotics to Klebsiella species against Time after Hospital Admission

- TIM
- SUL
- CXM
- CXO
- CTX
- TZC
- AMK
- LVX
- GEN
- AUG
- AMP
- SXT

* Day1-2  Day3-4  Day5-6  > 6 Days
Percentage Resistance of Antibiotics to Enterococci against Time after Hospital Admission

Percentage Resistance of Antibiotics to Pseudomonas aeruginosa against Time after Hospital Admission
% Enterobacter and Acinetobacter isolated against "Time after Hospital Admission"

Ratio of MRSA to MSSA against "Time after Hospital Admission"
In most instances:

- Early onset (within 4-5 days) HAP: Augmentin, Ceftriaxone
- Late onset HAP:
  - No recent antibiotics exposure and,
  - Clinically stable

◆ Consider Augmentin, Ceftriaxone
Fallacy 3: Don’t change a winning team & big guns are always more effective than 1\textsuperscript{st} line antibiotics

Streamline the antibiotics when laboratory result available

The patient should be reassessed at 48–72 h and antibiotic therapy should be de-escalated based on the microbiological results and clinical response. De-escalation includes changing from the broad-spectrum antibiotic to an agent with a narrow focus, based on the culture data; changing the focus from multiple antibiotics to a single drug; and shortening the course of therapy to 5 days in cases with negative culture results and $\geq$ 48 h without fever.
Forward stepwise logistic regression analysis (cut-off $P$ value of 0.05) was used to determine the relationship between mortality and independent baseline variables previously identified in univariate analyses ($P < 0.05$), including: age, mechanical ventilation, Acute Physiology, Age, and Chronic Health Evaluation (APACHE) II score, treatment group, and adequacy of initial empiric therapy. Group I, patients with an unknown etiology and unmodified therapy; Group II, patients with resistant organisms, who had unmodified therapy; Group III, patients with susceptible organisms, who had unmodified therapy; Group IV, patients who had susceptible organisms and whose therapy was modified accordingly; and Group V, patients who initially received inadequate antibiotic therapy, which was later modified on the basis of cultures.

**Table 3**

Effectiveness and mortality analyses for each treatment group as defined per bacteriologic documentation (visit 2)

<table>
<thead>
<tr>
<th></th>
<th>Group I ($n = 113$)</th>
<th>Group II ($n = 14$)</th>
<th>Group III ($n = 38$)</th>
<th>Group IV ($n = 56$)</th>
<th>Group V ($n = 23$)</th>
<th>Overall ($n = 244$)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Effectiveness response rates</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modified intention-to-treat population</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End of therapy (visit 3) (%)</td>
<td>81.4</td>
<td>78.6</td>
<td>68.4</td>
<td>75.0</td>
<td>56.5</td>
<td>75.4</td>
</tr>
<tr>
<td>Final evaluation (visit 4) (%)</td>
<td>54.0</td>
<td>64.3</td>
<td>44.7</td>
<td>50.0</td>
<td>34.8</td>
<td>50.4</td>
</tr>
<tr>
<td>Patient-evaluable population</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final evaluation (visit 4) (%)</td>
<td>61.0</td>
<td>81.8</td>
<td>47.2</td>
<td>58.3</td>
<td>44.4</td>
<td>57.7</td>
</tr>
<tr>
<td><strong>Mortality rates</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient-evaluable population</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall mortality (%)</td>
<td>19.0</td>
<td>18.2</td>
<td>25.0</td>
<td>14.6</td>
<td>33.3</td>
<td>20.2</td>
</tr>
<tr>
<td>Nosocomial pneumonia-attributable mortality (%)</td>
<td>15.0</td>
<td>9.1</td>
<td>8.3</td>
<td>8.3</td>
<td>33.3</td>
<td>13.6</td>
</tr>
</tbody>
</table>
### Spectrum VS Effectiveness

**Example 1: Cloxacillin VS Cefuroxime (Zinnat)**

<table>
<thead>
<tr>
<th>Coverage</th>
<th>Cloxacillin</th>
<th>Cefuroxime</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus</td>
<td></td>
<td>Strept., S. aureus, Gram negative bacilli</td>
</tr>
<tr>
<td>MIC 90 (S. aureus)</td>
<td>1 µg/ml</td>
<td>4 µg/ml</td>
</tr>
</tbody>
</table>

Spectrum: Cefuroxime > Cloxacillin  
Activity against S. aureus: Cefuroxime < cloxacillin

**Example 2: Augmentin vs Tazocin**

<table>
<thead>
<tr>
<th>Coverage</th>
<th>Augmentin</th>
<th>Tazocin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MSSA, enterobacteriacea,</td>
<td>MSSA, ESBL, enterobacteriacea,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pseudomonas</td>
</tr>
<tr>
<td>MIC50 (E.coli) (Break point)</td>
<td>2 µg/ml</td>
<td>4 µg/ml</td>
</tr>
<tr>
<td></td>
<td>8 µg/ml</td>
<td>16 µg/ml</td>
</tr>
</tbody>
</table>

Spectrum: Tazocin > Augmentin  
Activity against E.coli: Tazocin = Augmentin
Fallacy 4: Step up antibiotics immediately when there is no clinical response

Clinical response do take time!

“Receipt of antibiotic treatment for at least 3–5 days is usually required to determine efficacy of the initial regimen.” CID 2002:34 (15 March)

- Early switch in deteriorating life threatening diseases
- **Sepsis workup** before you step up your antibiotics!
Pathogen coverage is just one of the factors that determine the clinical response of a treatment regimen.

**Other causes of appearance failure**

- Treating colonization
- Inadequate tissue level
- Penetration problems: Undrained abscess; foreign bodies
- Non-infective diseases, e.g, adult still, SLE,…
- Non-bacterial infection: viral, fungal.
- Drug fever

We should determine the causes instead of routinely adding/changing antibiotics!
Colonization/contamination:

• Treatment are not required for colonization/contamination.
• Even in doubt, **sepsis work up** before empirical Tx.
• Duration/ Effectiveness of treatment should base on clinical response but not culture result for some infections as most antibiotics are not good for eradicating colonizers.

Fallacy 5: Culture report interpretation:

i: Treatment is required for all positive culture;
ii: Persistence positive culture = Treatment failure → Prolong treatment or stepping up antibiotics
Fact or Fallacy?
**Allergy means whole class of antibiotics cannot be used**

If the reaction is an allergy or side effect?  *Vancomycin: infusion related reaction*

If the rash is MP rash or urticaria rash?

For type I hypersensitivity:
1. Skin testing: Highly accurate for the identification of penicillin allergy but false negative result may be obtained for other antibiotics. (NA)
2. Whole class should be avoid unless in life threatening situation with no other alternatives.
3. Drug desensitization & ICU monitoring required when use of B-lactam.
   Oral desensitization appears to have fewer reactions and the starting dose should be very small, usually 1/10,000 of the therapeutic dose. The dose is then doubled every 15 minutes till the full therapeutic dose is achieved.

For non-type I allergy: May try cephalosporins with a test dose* with close monitoring and documentation when there is no alternatives.
   *Test dose challenge might be done by using 1/100 of the therapeutic dose followed by 1/10 of the dose and then the full therapeutic dose if there is no reaction.

Clearly describe the case whenever you label a drug allergy history of a patient
Treatment of specific organisms

- S. pneumoniae
- ICBL
- ESBL
- KPC
- MRSA
- Acinetobacter
**MRSA TREATMENT PROTOCOL**
(Modified from recommendations of the BSAC Guidelines 2005 & 2008 [www.bsac.org.uk](http://www.bsac.org.uk))

**Colonisation:** MRSA is present in or on a body site but no clinical signs or symptoms of illness or infection are present.

**Infection:** Isolation of an organism accompanied by clinical signs of illness or sepsis, eg fever, inflammation, increase WCC, etc.

**BACTERAEMIA**
- Look for primary focus
- If related to intravascular line, consider removing line urgently

- IV Vancomycin
  - Loading dose required (25mg/kg iv)
  - Keep Trough level at 15 – 20 mg/L (10.0 – 13.4 µmol/L)
- If Vancomycin is contraindicated or MIC >1µg/ml, consider alternate regimen*, seek advice from Microbiologist or ID physicians
- Duration of therapy: 2 weeks (Prolong if underlying infections require longer duration of treatment)

**NO BACTERAEMIA**

- **Respiratory**
  - **VAP**
    - IV Vancomycin
      - Keep Trough level at 15 – 20 mg/L (10.0 – 13.4 µmol/L)
      - If unfavorable clinical response, contact lab. For MIC and seek advice from Microbiologist or ID physicians
      - Duration of therapy: 2 weeks
  - **Pneumonia**
    - IV Vancomycin
      - Keep Trough level at 15 – 20 mg/L (10.0 – 13.4 µmol/L)
      - If unfavorable clinical response, contact lab. For MIC and seek advice from Microbiologist or ID physicians
      - Duration of therapy: 2 weeks

- **UTI, Skin or Soft Tissue Infection (including wound infection), infected ulcer**
  - Severe: IV Vancomycin
  - Oral (UTI): Doxycycline or Septrin or Nitrofurantoin
  - Oral (SSTIs) : Doxycycline or any 2 of Septrin, Rifampicin & Fusidic acid
  - Duration of therapy: 5-7 days then review

- **Bone & Joint Infection**
  - Seek advice from Microbiologist or ID physicians

**MRSA isolated from specimen**
- Contact pre-caution; Seek infection control advice
- Modify surgical prophylaxis regimen – cover MRSA

*Alternate regimens:*
- Linezolid, Daptomycin (Not for Pneumonia)
- Combination treatment: Vancomycin + Septrin/ Rifampicin / Fusidic acid
Use of vancomycin

Early reports of “vancomycin nephrotoxicity” were apparently related to the impurities in the solution and not to vancomycin per se. Therefore, **impaired renal function is not a contraindication of using vancomycin although we have to adjust the dose of vancomycin for patients with renal insufficiency.**

Common misconception: “step up” to vancomycin if the clinically response of MSSA is poor after treating with cloxacillin. However, if we compare the pharmacokinetic properties and bactericidal activities of these 2 drugs, **cloxacillin is the preferred drug than vancomycin for MSSA infection.** Therefore, if the clinical response of cloxacillin is not good, we may consider other reasons.
Drug Monitoring:

1. Vancomycin peaks have no clinical significance
2. Indications for vancomycin troughs: (Trough levels should be obtained within 30 minutes before 4th dose of a new regimen or dosage change):
   1. Patients on continuous or intermittent hemodialysis
   2. Patients with unusually high volumes of distribution (e.g. morbid obesity, significant edema, burns)
   3. Initial and definitive therapy of suspected central nervous system infections, endocarditis, ventilator-associated pneumonia, bacteremia or osteomyelitis (Higher trough level needed)

Dosing:
Because of its large molecular size, vancomycin does not penetrate well into many tissues such as lung and bone. Therefore, higher dose (15-20mg/kg Q8-12H) of vancomycin may be required to achieve the adequate trough level of 15 – 20 mg/L (10.0 – 13.4 μ mol/L)) for treating these infections. However, if the MIC of vancomycin is >2mcg/ml, we have to consider alternative therapy.
Acinetobacter

• Current guidelines for the treatment of *A. baumannii* VAP recommend combination therapy with a betalactam plus an aminoglycoside
• However, we start to see emergency of resistant.

2009 Hospital C

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>% sensitive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imipenem/meropenem</td>
<td>53</td>
</tr>
<tr>
<td>Tazocin</td>
<td>37</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>38</td>
</tr>
<tr>
<td>Septrin</td>
<td>50</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>61</td>
</tr>
<tr>
<td>Amikacin</td>
<td>83</td>
</tr>
<tr>
<td>Sulparzon/unasyn</td>
<td>58</td>
</tr>
</tbody>
</table>
Treatment of Multidrug or pan-drug resistant Acinetobacter baumanii

- No standard definition
- HA: concomitant resistant (not including Intermediate resistant) to all the following classes: Fluoroquinolones, Aminoglycosides, Cephalosporins, & Beta-lactam /beta-lactamase inhibitor combinations. Carbapenems are not included in the MDRA criteria.
- High dose of Sulbactam: 4g/day or even higher (8g/d (Pharmacotherapy. 2002;22(4)))
- Colistin +/- rifampicin or amikacin
  - main adverse effects of colistin are nephrotoxicity (acutetubular necrosis) and neurotoxicity
- Tigecycline
Rational use of antibiotics

Antibiotics stewardship program (ASP)

- **Administrative Control**
  1. Drug Formulary
  2. Restricted prescription
  3. Autostop system
  4. Restricted reporting

- **Surveillance**
  1. Antimicrobial susceptibility
  2. Antibiotics consumption

- **Audit: HA – 7 Big gun**
  1. Drug order form
  2. Immediate concurrent feedback

- **Guidelines**
  1. Update
  2. User agreement

- **Education**
  1. Talk
  2. Forum,
  3. Newsletter
Microbiology Lab. Support

- **Streptococcus pneumoniae, M.I.C. of Penicillin : 2 ug/ml**
  Suggested doses for adults with normal renal function:
  Amoxicillin 1g TDS or equivalent

- **ESBL producing strains are clinically resistant to all Cephalosporins and Aztreonam.**

- **Phenotypic test suggests presence of AmpC beta-lactamase.** Resistance may develop during prolonged therapy with 3rd generation cephalosporins.

- **For Enterococcal infection, cephalosporins, clindamycin and trimethoprim-sulfamethoxazole (Septrin) are not effective clinically.**

- **Coagulase negative Staphylococci is probably a contaminant.**

- **Oropharyngeal contamination. Suggest repeat if clinically indicated.**

- **For CSU, treatment needed only if patient has symptoms.**

- **Multi-resistant organism isolated, please perform "CONTACT ISOLATION" to prevent spreading of the organism."**
Conclusion

Aim: To optimize selection & use of antibiotics so that:

• Emergence and spread of antibiotic resistance can be controlled and hospital costs can be reduced
• To achieve best clinical outcomes, with minimal toxicity to the patient.
• NOT to restrict the autonomy of doctor-in-charge

Microbiology / ID consultation
Concurrent feedback
Thank You

Question?
Table 3. Number of cases and national estimates of the rate of emergency department (ED) visits for adverse events associated with a single systemic antibiotic class, by adverse event condition—United States, 2004–2006.

<table>
<thead>
<tr>
<th>Drug class&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Moderate-to-severe allergic reaction&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Neurologic and/or psychiatric</th>
<th>Gastrointestinal</th>
<th>Mild allergic reaction&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Other or unspecified effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases</td>
<td>Estimated no. of ED visits per 10,000 OPV (95% CI)</td>
<td>No. of cases</td>
<td>Estimated no. of ED visits per 10,000 OPV (95% CI)</td>
<td>No. of cases</td>
</tr>
<tr>
<td>Penicillins</td>
<td>420</td>
<td>2.2 (1.7–2.7)</td>
<td>66</td>
<td>0.4 (0.3–0.6)</td>
<td>212</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>184</td>
<td>1.3 (0.9–1.7)</td>
<td>39</td>
<td>0.3 (0.2–0.5)</td>
<td>88</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>212</td>
<td>2.4 (1.8–3.1)</td>
<td>100</td>
<td>1.2 (0.9–1.6)</td>
<td>83</td>
</tr>
<tr>
<td>Sulfonamides and trimethoprim</td>
<td>163</td>
<td>4.3 (2.9–5.8)</td>
<td>55</td>
<td>1.7 (0.9–2.4)</td>
<td>61</td>
</tr>
<tr>
<td>Macrolides and ketolides</td>
<td>120</td>
<td>1.1 (0.7–1.4)</td>
<td>39</td>
<td>0.3 (0.2–0.4)</td>
<td>111</td>
</tr>
<tr>
<td>Lincosamides (clindamycin)</td>
<td>32</td>
<td>2.8 (1.3–4.2)</td>
<td>11</td>
<td>...</td>
<td>34</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>38</td>
<td>1.2 (0.6–1.8)</td>
<td>11</td>
<td>...</td>
<td>28</td>
</tr>
<tr>
<td>All other antibiotic classes&lt;sup&gt;d&lt;/sup&gt;</td>
<td>80</td>
<td>1.9 (1.2–2.7)</td>
<td>52</td>
<td>1.4 (0.8–1.9)</td>
<td>66</td>
</tr>
</tbody>
</table>

**NOTE.** Estimates of the number of adverse events are based on the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance project (2004–2006). Estimates of the number of outpatient prescription visits (OPV) are based on the National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey (2004–2006). Adverse event categories were mutually exclusive and were assigned hierarchically (left to right). For example, a case in which a patient experienced both a severe allergic reaction and gastrointestinal effects would be categorized as a moderate-to-severe allergic reaction.

<sup>a</sup> Only cases in which drugs from a single systemic antibiotic class were implicated in the adverse event are included (5902 cases). Estimates with coefficient of variation >30% or based on <20 cases were not calculated.

<sup>b</sup> Includes anaphylaxis, angioedema, erythema multiforme, exfoliative dermatitis, facial-pharyngeal-genital edema, hypersensitivity vasculitis, red man syndrome, respiratory distress or arrest, serum sickness, and Stevens-Johnson syndrome.

<sup>c</sup> Includes dermatitis, drug eruption, erythema, flushing, localized edema, pruritus, rash, rash morbilliform, and urticaria.

<sup>d</sup> Includes metronidazole, nitrofurans, vancomycin, linezolid, unspecified, and other antibiotic classes.
Seizures and other adverse CNS experiences have been reported during treatment with MERREM I.V.

These experiences have occurred most commonly in patients with CNS disorders (e.g., brain lesions or history of seizures) or with bacterial meningitis and/or compromised renal function.

During clinical investigations, 2904 immunocompetent adult patients were treated for non-CNS infections with the overall seizure rate being 0.7% (based on 20 patients with this adverse event). All meropenem-treated patients with seizures had pre-existing contributing factors. Among these are included prior history of seizures or CNS abnormality and concomitant medications with seizure potential. Dosage adjustment is recommended in patients with advanced age and/or reduced renal function.

Close adherence to the recommended dosage regimens is urged, especially in patients with known factors that predispose to convulsive activity. Anticonvulsant therapy should be continued in patients with known seizure disorders. If focal tremors, myoclonus, or seizures occur, patients should be evaluated neurologically, placed on anticonvulsant therapy if not already instituted, and the dosage of MERREM I.V. re-examined to determine whether it should be decreased or the antibiotic discontinued.
FDA approved labelling – Imipenem-cilastatin

- **CNS adverse experiences** such as confusional states, myoclonic activity, and seizures have been reported during treatment with PRIMAXIN I.V., especially when recommended dosages were exceeded.
- These experiences have occurred most commonly in patients with CNS disorders (e.g., brain lesions or history of seizures) and/or compromised renal function.
- When recommended doses were exceeded, adult patients with creatinine clearances of ≤20mL/min/1.73 m², whether or not undergoing hemodialysis, had a higher risk of seizure activity than those without impairment of renal function. Therefore, close adherence to the dosing guidelines for these patients is recommended.
- Patients with creatinine clearances of ≤5mL/min/1.73 m² should not receive **PRIMAXIN I.V.** unless hemodialysis is instituted within 48 hours.
- For patients on hemodialysis, **PRIMAXIN I.V.** is recommended only when the benefit outweighs the potential risk of seizures.
- **PRIMAXIN I.V.** is not recommended in pediatric patients with CNS infections because of the risk of seizures.
- The most frequently reported systemic adverse clinical reactions that were reported as possibly, probably, or definitely related to **PRIMAXIN I.V.** were nausea (2.0%), diarrhea (1.8%), vomiting (1.5%), rash (0.9%), fever (0.5%), hypotension (0.4%), seizures (0.4%)