Therapeutic Review of Cephalosporins

Role of Cephalosporins in Multi Drug Resistance (MDR) Era.

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Problem of Bacterial Resistance in Thailand
1. Multi-drug-resistant GNB (MDR-GNB)
   [Resist > 2 classes antibiotics]
   - Acinetobacter sp.
   - Pseudomonas aeruginosa
   - Klebsiella, E. coli, Enterobacter

2. MDR-GPB
   - MRSA (methicillin resistant S. aureus)
   - DRSP (drug resist S. pneumoniae)

MDR-Gm-Neg Infections
1. Nosocomial Infections
2. Infection in Cancer Patient
3. Septic Patient with Recent/Frequent antibiotic Use

Cephalosporins : 5. Generations

<table>
<thead>
<tr>
<th>First</th>
<th>Second</th>
<th>Third</th>
<th>Fourth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefazolin</td>
<td>Cefuroxime</td>
<td>Cefotaxime</td>
<td>Cefpirome</td>
</tr>
<tr>
<td>Cephalaxin</td>
<td>Cefamandole</td>
<td>Ceftriaxone</td>
<td>Cefepime</td>
</tr>
<tr>
<td>Cefaclor</td>
<td>Cefotaxime</td>
<td>Cefotaxime</td>
<td>Cefpirome</td>
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<tr>
<td>Cefpodoxime</td>
<td>Cefpirome</td>
<td>Cefpodoxime</td>
<td>Cefpirome</td>
</tr>
</tbody>
</table>

Vitro-activity of parenteral cephalosporins

<table>
<thead>
<tr>
<th>Cephalosporin generation</th>
<th>Bacterial activity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gram positive</td>
</tr>
<tr>
<td>First</td>
<td>+++ +++++</td>
</tr>
<tr>
<td>Second</td>
<td>+++ +++++</td>
</tr>
<tr>
<td>Third</td>
<td>++ + +++++</td>
</tr>
<tr>
<td>Fourth</td>
<td>+++ + ++++++++</td>
</tr>
<tr>
<td>Fifth</td>
<td>++++ &amp; MRSA</td>
</tr>
</tbody>
</table>

Antibacterial activity of parenteral cephalosporins

<table>
<thead>
<tr>
<th>Cephalosporins</th>
<th>Gram positive</th>
<th>Gram negative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Strep</td>
<td>Stap</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Cefamandole</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Cefepirome</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Cefepine</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>
63 year old female, HT, DM, admitted because of fever, diagnosed acute pyelonephritis. She was given antibiotic IV, Day 3rd. Better.

Urine and blood culture grew E.coli.

How long to give antibiotic ??

Parenteral... days

Oral ??

She became afebrile on day 4th

What is your plan for antibiotic?

1. Duration of antibiotic?
2. Should IV ceftriaxone be continued?
   2.1 yes?
   2.2 No : what agent should be switched to?

IDSA Uncomplicated UTI Treatment Guidelines

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Category or grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 d of antimicrobial therapy is appropriate</td>
<td>A, I</td>
</tr>
<tr>
<td>Courses of highly active agents as short as 7 d may be sufficient for mild or moderate cases</td>
<td>B, I</td>
</tr>
<tr>
<td>Mild cases can be managed with oral medications</td>
<td>A, II</td>
</tr>
<tr>
<td>An oral fluoroquinolone is recommended</td>
<td>A, II</td>
</tr>
<tr>
<td>or</td>
<td>Not rated</td>
</tr>
<tr>
<td>If the organism is known to be susceptible, TMP-SMX</td>
<td>B, II</td>
</tr>
<tr>
<td>Patients with more severe cases of acute pyelonephritis should be hospitalized and treated with a parenteral fluoroquinolone, an aminoglycoside, an ampicillin, or an extended-spectrum cephalosporin-amoxicillin</td>
<td>B, III</td>
</tr>
<tr>
<td>or</td>
<td>Not rated</td>
</tr>
<tr>
<td>With improvement, can change to an oral antimicrobial to which the organism is susceptible to complete the course of therapy</td>
<td>B, II</td>
</tr>
</tbody>
</table>

IDSA Uncomplicated UTI Treatment Guidelines

Bacterial etiology of urinary tract infection

<table>
<thead>
<tr>
<th>% Uncomplicated</th>
<th>%Complicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-negative</td>
<td>70-95</td>
</tr>
<tr>
<td>E.coli</td>
<td>1-2</td>
</tr>
<tr>
<td>P mirabilis</td>
<td>1-2</td>
</tr>
<tr>
<td>Klebsiella sp</td>
<td>1-2</td>
</tr>
<tr>
<td>Citrobacter sp</td>
<td>1-2</td>
</tr>
<tr>
<td>Enterobacter sp</td>
<td>1-2</td>
</tr>
<tr>
<td>P aeruginosa</td>
<td>1-2</td>
</tr>
<tr>
<td>Other</td>
<td>1-2</td>
</tr>
<tr>
<td>Gram-positive</td>
<td>5-10</td>
</tr>
<tr>
<td>Coagulase-negative staphylococci</td>
<td>5-10</td>
</tr>
<tr>
<td>Enterococci</td>
<td>1-2</td>
</tr>
<tr>
<td>Group B streptococci</td>
<td>1-4</td>
</tr>
<tr>
<td>S. aureus</td>
<td>1-4</td>
</tr>
<tr>
<td>Other</td>
<td>1-2</td>
</tr>
</tbody>
</table>

Bacterial etiology of urinary tract infection


*10% of S saprophyticus
**Management of Urinary Tract Infections**

**Evidence-based Clinical Practice Guideline**

To promote best practice linked to

OUTCOME and COST EFFECTIVENESS

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**Acute Uncomplicated Cystitis**

Women 15-55 yrs, non pregnant

1. **1st UTI**
   - No recent antibiotic
   - Ciproflox, Ofloxacin, Levoflox
   - x 3 days
   - FU-Urinalysis

2. **Recurrent UTI**
   - Previous UTI due to R pathogen
   - Recent Antibiotic
   - + Urine culture
   - then Ciprofloxacin, Ofloxacin or Levoflox
   - or
   - 3rd cephalosporins

*NO URINE CULTURE

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**LUTI in non Pregnant Women age 16-55 yrs**

can be treated with antibiotic without any testing

- Identifying Barriers and Tailoring Intervention
  to improve the management of UTI
  : a pragmatic study using qualitative methods

  BMC Health Service Research 2003;3
  BMJ 2002;325:367

*No need for Urine culture in 1st episode acute uncomplicated cystitis in women

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**Why not TMP-SMX (Co-trimoxazole)**

(gold standard antibiotic in many countries)

Uropathogen in Thailand

TMP-SMX Resistance >20%

(Many Guideline, US, EUR. If, Resistance > 10 - 20% not appropriate)

Why ??

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**Aim / Objective of LUTI Management**

1. Prompt relieve of Symptoms
2. Cure as LUTI

So... is Norfloxacin appropriate as

1st line empiric in 1st episode Cystitis
Impact of Resistance on the treatment of UTI

PK : High Urine Concentration

Resistant Uropathogen - ≤ 50 % Cure
Susceptible Uropathogen ≥ 90% Cure

Clin Therapeutic 2002;24:2088
Urology 1997;157

Acute Pyelonephritis : Moderate to Severe
High fever, severe flank pain
CVA tenderness
Systemic S/S Sepsis
Nausea - vomiting
Hospitalization
UA - Urine C/S
Blood Culture
Parenteral
48-72 hr.

Uropathogen in Community-acquired UTI in Thailand:
Increasing 2nd generation Quinolone - Resistant - E.coli
(Resistant to Oflox / Ciproflox)
More common in UUTI than LUTI
Severity of UUTI > LUTI

What is antibiotic of choice in case with resistance
1 : 3rd or advanced generation cephalosporins
2 : 3rd and 4th generation Quinolones

ESBL – producing Bacteria
(extended spectrum beta lactamase)
Found in complicated UTIs, healthcare asso-infections
• Klebsiella spp esp K. pneumoniae
• E. coli
Therefore do not test ESBL in others Bacteria
When to suspect ESBL producing Klebsiella & E.coli
• Ceftazidime-resistant Klebsiella or E.coli
esp with co-resistant to gentamicin/amikacin
may be resistant to Fluoroquinolone

Problems of ESBL even in Klebsiella or E. coli
• Clinical dilemma
  • Frequently resistant to many agents
  • Mostly treated with carbapenems..resulted in
  • more MDR-GNB

Problems posed by ESBLs

• Clinical dilemma
• Carbapenem always recommended
  • Combination of β-lactam/β-lactamase inhibitors may be useful
    (cefoperazone-sulbactam)

Treatment options for infections Caused by ESBL-producing organism

• Serious infections
  • Carbapenems, Tigecycline
• UTI, not serious/severe
  • β-lactam/β-lactamase inhibitor
  • Cefoperazone/sulbactam, piperacillin/tazobactam
  • 4th Cephalosporin + Aminoglycoside

Implication for Antimicrobial Dosing

α PK/PD Principles

$T > MIC$ (% of dosing interval)

<table>
<thead>
<tr>
<th>Infection Type</th>
<th>$T &gt; MIC$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal, mild-moderate</td>
<td>40-60</td>
</tr>
<tr>
<td>Severe infections</td>
<td>&gt;60</td>
</tr>
<tr>
<td>Neutropenic host</td>
<td>90-100</td>
</tr>
<tr>
<td><em>P. aeruginosa</em> infections</td>
<td>100</td>
</tr>
</tbody>
</table>

Bacterial-killing activities of antibiotics : B-lactams Carbapenems

Advantage of cephalosporins?

1. Broad spectrum
2. Stability to β-lactamase
3. Oral and parenteral preparations
4. High safety profile similar to amoxicillin
5. Reasonable costs

Cost Of Treatment

Direct Cost
- Drug Cost
- Drug Administration - Monitoring

Indirect Cost
- Hospitalization
- Investigation ..., etc.

Intangible Cost
- Time - Income Cost
- Family Visit
- Revisit
- etc
Good oral antibiotics

1. Optimal PK-PD properties
   (excellent oral absorption, good penetration to infection sites, 
   long terminal disposition half-life, and stability in serum)
2. Low adverse effect
3. Convenience (OD or BID dosing)

Why Oral Beta-lactams?
When amoxicillin?
When Amoxicillin-clavulanate?
When Cephalosporins?

Classification Of Oral Cephalosporins:
I. 1st generation
   - Cephalexin
   - Cefadroxil
   - Cefaclor
II. 2nd generation
   - Cefuroxime axetil
   - Cefpodoxime
III. 3rd generation
   - Cefixime
   - Cefdinir
   - Cefditoren

Relative Activities Of Oral Cephalosporins
(PK/PD based)

The Comparative MIC_{50} (µg/ml) between Gram Negative
For Oral Third and Advanced Generation Cephalosporins

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>S. pneumoniae</th>
<th>Staphylococcus aureus</th>
<th>S. pyogenes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PSSP</td>
<td>PRSR</td>
<td>MSSA</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>2-4</td>
<td>16-32</td>
<td>4-16</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>0.03-0.06</td>
<td>4-8</td>
<td>1-2</td>
</tr>
<tr>
<td>Cefpodoxime</td>
<td>0.03-0.06</td>
<td>1-4</td>
<td>1-4</td>
</tr>
<tr>
<td>Cefdinir</td>
<td>0.03-0.5</td>
<td>1-4</td>
<td>0.015-0.1</td>
</tr>
<tr>
<td>Cefixime</td>
<td>0.03-0.5</td>
<td>8-32</td>
<td>0.125-1</td>
</tr>
<tr>
<td>Cefditoren</td>
<td>0.02-0.03</td>
<td>0.5-4</td>
<td>0.5-3.13</td>
</tr>
</tbody>
</table>

MIC_{90} (µg/ml) of oral cephalosporins against Some gram positive species*

Drugs: Cefditoren, Cefdinir, Cefixime, Cefpodoxime

Organism | Cefditoren | Cefdinir | Cefixime | Cefpodoxime |
----------|------------|----------|----------|-------------|
Escherichia coli | 1.56 | 3.13 | 12.5 | 6.25 |
Klebsiella pneumonia | 0.2 | 0.2 | 0.05 | 0.2 |
Klebsiella oxytoca | 0.39 | 0.2 | 0.1 | 0.2 |
Proteus mirabilis | 0.39 | 0.1 | 0.025 | 0.2 |
Proteus vulgaris | 0.78 | 12.5 | 0.05 | 0.78 |
Morganella morganii | 0.2 | 25 | 0.78 | 3.13 |

*Adapted from Pathology of Infectious Diseases/ (Clinical Practice), Kazunori Sano et al., Drug 2002;62(2):245-241

Kazunori Sano et al.
Strategy to Deliver Antibiotic with Novel Drug

<table>
<thead>
<tr>
<th>% T &gt; MIC</th>
<th>% T &gt; MIC&lt;sub&gt;90&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PSSP</td>
</tr>
<tr>
<td></td>
<td>H. Influenzae</td>
</tr>
<tr>
<td>Cefdinir  200 mg q 12 hr</td>
<td>50</td>
</tr>
<tr>
<td>Cefditoren 200 mg q 12 hr</td>
<td>60</td>
</tr>
<tr>
<td>Cefdinir 300 mg q 12 hr</td>
<td>65</td>
</tr>
<tr>
<td>Cefpodoxime p. 200/400 mg q 12 hr</td>
<td>98/100</td>
</tr>
<tr>
<td>Cefixime 400 mg qd</td>
<td>41</td>
</tr>
<tr>
<td>Cefitibuten 400 mg qd</td>
<td>11</td>
</tr>
</tbody>
</table>

Role of Oral Cephalosporins In Rx of infection

- Community acquired infections

Clinical Use of oral cephalosporins

1. Skin and Skin Structure Infections; cellulitis, abscess...
2. UTI (Urinary Tract Infection) Pyelonephritis, Cystitis
3. Switch Therapy after parenteral cephalosporins
4. Some RTIs: sinusitis, otitis media, bronchitis community-acquire pneumonia

Need For Novel Antibiotics

1. For resistant pathogen
2. Better PK-PD

- amoxicillin > pen V / ampicillin
- azithromycin / clarithro > erythromycin
- cefdinir > cephalaxin

Approaches to minimize cost of treatment is to know the real cost of treatment

Total Cost of treatment

- Direct Cost
  - Drug
  - Drug monitoring

- Indirect Cost
  - Investigation
  - Hospitalization Cost

- Intangible Cost
  - Cost of Revisit
  - Lose of / from work
  - Family visit

Approaches to minimize cost of treatment eg. with moderate to severe infection

- Therapy are Switch Therapy or Out patient Antibiotic Therapy or IPD Antibiotic Therapy OPD Therapy

- Oral antibiotic (Switch Therapy)
- Parenteral antibiotic (OPAT)
  - OPD
  - Day Care
  - Home
The single most important step in reducing hospital antibiotic costs is to initiate an outpatient-antibiotic therapy. Conventional belief to the contrary, many infections can be treated orally or parenterally-OPD with the same therapeutic effectiveness

Ramirez 1992
A Tice 1993-2005
BA Cunha 1997
Williams DN, Tice AD, Craig WA: Practice guideline

To start with oral antibiotic

- Localized infection eg. some CAP, UUTI...
- Mild-Moderate severity systemic infection
  Enteric fever, Ac.pyelonephritis

Sequential, Step down from parenteral antibiotic

- After (During) improvement

Good Oral Antibiotics

- Good Bioavailability vs pathogen (PK-PD based)
- OD, BID (For Good Compliance)
- Tolerable

Good Oral Antibiotics:

- Amoxicillin
- Amoxicillin – Clavulanate, ampi-sulbactam
- Co-trimoxazole
- Advanced Macrolides (Roxithromycin, Azithromycin, Clarithro)
- Metronidazole
- Some Cephalosporin
  1st Generation: Cefadroxil
  2nd Generation: Cefuroxime
  3rd or advanced generation: Cefdinir, Cefditoren, Cefixime
- Fluoroquinolones
  2nd - Ofloxacin, Ciprofloxacin.
  3rd - Levofloxacin, Gatiflox
  4th - Moxifloxacin, Gemiflox
- Doxycycline, Minocycline

Clinical Experience with Switch Therapy

INFECTIONS

- Community-acquired pneumonia (CAP)
- Acute Pyelonephritis, Complicated UTI
- Skin/Soft-tissue infection
- Septic arthritis
- Osteomyelitis
- Pyogenic liver abscess
- Melioidosis

Switch Therapy/Out Patient Parenteral Therapy

General Rules of Guidelines

Should be applied wisely with respect to

- Individual variations
- Type of infections
- Antimicrobial susceptibility pattern
- Underlying disease

62 y/o female HT, DM, admitted because of septic arthritis of right knee joint, treated with cefazolin 3 gm daily and became afebrile on day 6th. She was continued on cefazolin for one more week. What should be her choice?

1. continue on IV cefazolin for total of 4 weeks
2. discharge on
   2.1 oral dicloxacillin 500 mg QID
   2.2 oral amoxi-clavulanate 1 g TID
   2.3 oral cephalaxin 500 mg QID
   2.4 oral cefdinir 200 mg BID
   2.5 oral cefditoren 200 mg BID
Switch Therapy For Septic Arthritis

I. Parenteral antibiotic 10-14 days:
- Cloxacillin or Cefazolin (Strep, Stap)
  or PGS (if culture grew streptococci)

II. After D 10 or 14 – oral antibiotic:
- Dicloxacillin
- Cefadroxil or Cefdinir

Penicillin allergic: Clindamycin

Outpatient Antibiotic Therapy For Osteomyelitis

Pioneer or First treated OPAT
Ceftriaxone 2 gm OD

- Hospital-based OPD programmed
  (popular in Europe)
- Doctor office-based programmed
  (popular in USA)
- Home-based programmed

CID 2000;30:205

Outpatient Therapy for Soft Tissue Infection

Uncomplicated Cellulitis
- Mostly Oral Antibiotic or One dose of IM Cefazolin or Clindamycin
  then Oral antibiotic

Underlying Disease
- Evaluate Patients

Complicated severe
- Hospitalize

Good Oral Antibiotic For Soft Tissue Infection

- Bioavailability ≥ 70%
- OD or BID dosing
- Tolerable

Streptococci: Amoxicillin
Staphylococci: Cefadroxil, Cefdinir, Clindamycin
Dicloxacillin
Mixed Streptococci + Staphylococci + Anaerobes
  - Amoxicillin – clavulanate
  - Clindamycin + oral 3rd Ceph or Quinolone

Community acquired pneumonia

No Comorbidity
- Oral antibiotic
  1. Amoxicillin
  2. Amoxy-clavulanate (failed 1)
  3. 3rd Gen. cephalosporin

With Comorbidity or Sever CAP
- Improved switch to Oral antibiotic
  - 1st Amoxy-clavulanate + macrolide
  - 2nd Choice 3rd-4th gen Quinolone

64 y/o male admitted with diagnosis of AECOPD
Treated with ceftriaxone, with improvement sputum
Grew S. pneumoniae, resist to penicillin, sensitive
Ceftriaxone. He asked for discharge what would be
Oral antibiotic of choice
Antibiotic In Pyogenic Liver Abscess:

Common Pathogen: GNB > 70%
Anaerobes 1-20%

Initial Empiric Antibiotic

I. Not Severe – Ceftriaxone+Metronidazole
or – B-lactamase Inhibitor

II. Severe sepsis
   - Add Gentamicin
   or – Metronidazole+Cefazidime (Northeast)

10-14 Days then switch to oral Antibiotic

Oral Antibiotic In Pyogenic Liver Abscess:

1st: BL-BI

2nd : 3rd Ceph* + Metronidazole
   or Clindamycin

* Any oral 3rd ceph

29 year old female came in because of dysuria & burning for 1 day.
No fever, not sick.
Urinalysis: numerous WBC,
Appropriate antibiotic should be.
1. Co-trimoxazole
2. Norfloxacin
3. Ciprofloxacin
4. Cefdinir

45 yo female, DM, HT., came in due to fever.
BT 37.8 c.
Urinalysis: WBC >200 /HPF
Appropriate antibiotic should be;
1. Oral cefixime or cefdinir
2. Oral levofloxacin
3. Cefazidime
4. Ceftriaxone

12 yo male c cellulitis lt. foot, no fever.
Appropriate antibiotic should be.
1. IV Cloxacillin
2. Oral dicloxacillin
3. Oral cefdinir
4. Oral cefixime
Ceftriaxone for UTI should be given;
1. Once daily
2. Twice daily
3. Thrice daily
4. QID

Dose of cefdinir for UTI should be.
1. 100 mg tid
2. 200 mg bid
3. 300 mg od
4. 300 mg bid