ANTIBIOTICS: Which Drugs for Which Bugs

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Objectives

- Present evidence-based guidelines for the antibiotic treatment of sepsis, meningitis, pneumonia, urinary infections, skin and soft tissue infections, and intra-abdominal infections
- Review bacterial resistance trends in Ontario to help guide the appropriate choice of antibiotics

Antibiotics: Bioavailability

- Low: not well absorbed
  - PO agent not for serious infection ➔ nitrofurantoin
- Good: [blood and tissue] < than if given IV
  - [Therapeutic] in excess of [effective] eg. cephalexin
- High: > 90% absorption orally
  - Ideal to treat serious infections
  - Uncommon to need iv administration
  - Quinolones, TMP/SMX, linezolid, doxycycline, metronidazole, clindamycin
Case 1

- 66 y.o. female
- PMH: hypertension, bronchitis, RA
- Meds: puffers, HCT, prednisone, acet
- Fever, cough, SOB, not eating x few days
- SH: nonsmoker

Case 1

- Px: drowsy, p 120, rr 24, bp 70/40, T 39°C
- O2 sats 90% R/A
- neck supple, no rash
- HS’s normal, chest clear
- moving all four limbs
- ECG: sinus tachycardia
- CXR: no clear consolidation
- Diagnosis = Septic Shock

Management
- Early goal directed therapy
- Antibiotics:
  - Broad-spectrum, second-line agents
  - Two or more classes
  - Target all major suspected bugs
- 7-15% mortality reduction if antibiotics started in ED within 1 hour (severe sepsis or shock)

Critical Care Medicine, 2012;41(2):580-637

Etiology of Pneumonia in Septic Shock Patients

- Streptococcus pneumoniae
- Klebsiella pneumoniae
- Staphylococcus aureus
  - Escherichia coli
  - Legionella species
  - Haemophilus species
  - Anaerobes
  - Other Gram-negative bacteria (pseudomonas)
  - Candida

**Aware of mixed infections**
Respiratory Pathogen Treatment for Septic Shock

*Use a big gun...*
- **Antipneumococcal/antipseudomonal:**
  - Imipenem 0.5-1 g iv q6-8h or
  - Piperacillin-tazobactam 4.5 g iv q8h or
  - Cefepime 2 g iv q8-12h

*Plus add a second agent(s)*
- Levofloxacin 750 mg iv q24h or
- Aminoglycoside + azithromycin
*Add Vancomycin 2 g iv if MRSA suspected or coexisting central line or medical device*

IDSA 2007 Guidelines

Etiology of Suspected Abdominal Infections in Septic Shock

- E coli
- K pneumonia
- Proteus species
- Pseudomonas species
  - Enterobacter species
  - Bacteroides fragilis
  - Gramnegative species
  - Streptococcus species
  - Staphylococcus species

**Often polymicrobial**

Treatment of Suspected Abdominal Infections in Septic Shock

- ampicillin + gentamycin + metronidazole*
- ampicillin + ceftriaxone + metronidazole
- piperacillin-tazobactam or levofloxacin or imipenem, plus metronidazole
- moxifloxacin plus metronidazole

*Avoid clindamycin*

Empiric Treatment of Septic Shock Without Known Infection Source

- **Vancomycin**
- plus
- **Imipenem or Piperacillin-tazobactam or Cefepime**
Case 2

- 49 y.o. male
- PMH: nil  Meds: nil  NKDA
- 5 day Hx: fever, dry cough, myalgias
  mild exertional dyspnoea
  no CP/SOA/GI Sx
- Px: p 120  rr 24  bp 130/70  T 38°C
  O2 sats 98% R/A
  nil findings

Choice of Antibiotics for CAP

Critical factors
- Co-morbidity: COPD, CHF, CRF, DM, cirrhosis, alcoholism, active malignancy, asplenism, immunosuppression
- Antibiotic use in previous 3 months
- Local antibiotic resistance
- Outpatient vs inpatient

Etiology of CAP

- Healthy “walking pneumonia”:
  - S. pneumoniae
  - M. pneumoniae
  - Chlamydia pneumoniae
- Co-morbidity: All the above plus
  - Haemophilus influenzae
  - Moraxella catarrhalis
  - Legionella
- NSG home patients: also consider
  - S. aureus
  - K. pneumoniae
- Pseudomonas aeruginosa more common in COPD, bronchiectasis, steroid use and ICU patients
Impact on Management

- Bacterial Meningitis
- CAP and cystitis
- Pyelonephritis
- SSTI
- People with CAP are not dropping dead because of resistance (host defenses)

Outpatient CAP Rx

- Previously healthy and no recent antibiotic use
  - Macrolide OR Doxycycline

- Presence of comorbidities or recent use of antibiotics
  - FQ alone
  - β-lactam plus a macrolide

2007 IDSA guidelines

Inpatient (Non-ICU) CAP Rx

- No recent antibiotic use
  - FQ alone OR β-lactam plus macrolide

- β-lactam or macrolide use
  - FQ use
  - β-lactam plus macrolide (if β-lactam allergy, use FQ)

2007 IDSA Guidelines

Community Acquired Pneumonia TC-LHIN ER Algorithm 2013
Antibiotic Resistance in Strep pneumoniae respiratory isolates (2010-2011)

- Penicillin G (non-meningitis): 0.4%
- Ceftriaxone: 0.7%
- Moxifloxacin: 1.0%
- Levofloxacin: 1.9%
- Amoxicillin: 4.5%
- Cefuroxime: 12%
- Doxycycline: 16%
- Azithromycin: 28%
- Clarithromycin: 28%

Percent of isolates Neumophtis influenzae resistant to ampicillin:

- Outpatients: 18%
- Inpatients: 22%

The decision for the antibiotics in the algorithm was made based on local data.

Antibiotic Selection

- Throughout the guideline, fluoroquinolones are second line
- Reason:
  - High association with C.difficile
  - They are broad spectrum:
    - May lead to higher gram negative resistance
    - Atypical coverage is infrequently necessary

Community Acquired Pneumonia

Duration of Treatment

- minimum 5 days, no fever x 48 hrs, normal vitals, adequate oxygen saturation
Case 3

- 21 y.o. female with dysuria, urin frequency x 3d
- Now presents with fever and vomiting
- Px: T 39°C p 120 bp 110/70
  - tender suprapubic, left CVA
- Urine: rbc, wbc, positive nitrites, neg BHCG
- Bloods: wbc 20, creatinine normal

Etiology:
- E. coli 70 – 90%
- Klebsiella
- Proteus
- Enterococcus

* Staphylococcus saprophyticus common in uncomplicated cystitis, but rare cause of pyelonephritis
Rx of Uncomplicated UTIs

- TMP/SMX (Septra DS® bid x 3 days = $1)*
- Ciprofloxacin (Cipro 250 mg bid x 3 days = $2)*
- Nitrofurantoin x 3-5 days
  (Macrobid 100 mg bid x 5 days = $7)*

*plus dispensing fee ($6-12)

ESBL E. coli

- Resistance to penicillin, cephalosporins, sulfa, quinolones, nitrofurantoin
- Rx options:
  - no treatment
  - fosfomycin 3g sachet x 48-72 hrs
    x 2-3 doses (Monurol)
  - amox/clav
  - gentamycin 5mg/kg iv x 1 dose
  - meropenem for pyelo, bacteremia

Impact of Resistance: Acute Pyelonephritis

<table>
<thead>
<tr>
<th>Drug</th>
<th>All pathogens</th>
<th>Bacteremia</th>
<th>E. coli</th>
<th>Clinical</th>
<th>Bacteriologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>1/255 (0.4%)</td>
<td>0/14</td>
<td>96</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>TMP / SMX</td>
<td>47/255 (18.4%)</td>
<td>4/14 (29%)</td>
<td>92 vs 35</td>
<td>96 vs 50</td>
<td>83 vs 89</td>
</tr>
</tbody>
</table>

p Value: <0.001 ---- <0.001 <0.001

JAMA, 2000;283(12):1583-90

Case 3: Pyelonephritis

Treatment

- Antibiotic: Ceftriaxone 1 – 2 g iv
  or Gentamicin 5mg/kg iv
  or Ciprofloxacin 400 mg iv

*Add ampicillin 1- 2 g iv if enterococcus suspected
Case 3: Pyelonephritis

Disposition

- Antibiotics:
  - Ciprofloxacin 500 mg q12h x 7 days
  - or
  - TMP/SMX DS one q12h x 10 – 14 days
  - (Not nitrofurantoin)**

**add amoxicillin 500 mg q8h if enterococcus suspected

Case 4

- 27 y.o. female
- 4 day Hx: vaginal discharge
- No fever, abd pain, vomiting
- New sexual partner

Pyelonephritis in Pregnancy

- Inpatient therapy
- Antibiotics: Ampicillin + Gentamicin
  - or
  - Ceftriaxone
  - (not fluoroquinolones)
- Oral Rx after discharge: TMP/SMX*
  - or
  - cephalexin

* Not for late third trimester due to risk of kernicterus

Urosepsis in the Elderly Patient

Antibiotic Choices

- Cipro 500 mg po or 400 mg iv q12h
- Ceftriaxone 1 g iv q24h
- Levofoxacin 500 mg po or iv q24h
  - (not moxifloxacin)
- Gentamycin 5 mg/kg iv q24h
**Canadian Guidelines on Sexual Transmitted Infections 2010-2013**

<table>
<thead>
<tr>
<th>Infection Type</th>
<th>Recommended Regimen</th>
<th>Pregnancy</th>
<th>Penicillin Allergy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlamydia [uncomplicated]</td>
<td>Azithromycin 1g po single dose or Doxycycline 100mg po bid X 7 days</td>
<td>Amoxicillin 500mg po tid X 7 days or Azithromycin 1g po or Erythromycin 2g/day po X 7 days</td>
<td>Azithromycin 1g po single dose or Doxycycline 100mg po bid X 7 days</td>
</tr>
<tr>
<td>Gonorrhea [uncomplicated]</td>
<td>Cefixime 800mg po or Ceftriaxone 250mg IM</td>
<td>Cefixime 800mg po or Ceftriaxone 250mg IM</td>
<td>Azithromycin 2g po or Spectinomycin 2g IM (special access)</td>
</tr>
<tr>
<td>PID [outpatient]</td>
<td>Ceftriaxone 250mg M PLUS Dory 100mg bid X 14 days +/- Metronidazole 500 mg bid X 14 days</td>
<td>Consider inpatient treatment</td>
<td>Levofloxacin 500 mg qd, PLUS metronidazole 500 mg po bid X 14 days</td>
</tr>
</tbody>
</table>

**STD: Treatment**

- Quinolone resistance is in Ontario:
  - 4% in 2002 ➔ 28% 2006 ➔ Cipro is out
- No single dose azithromycin for PID
- PID Inpatient:
  - IV cefoxitin 2 g q6h / doxycycline 100mg q12h
  - IV clindamycin 900mg q8h + IV gentamycin

**Case 5**

- 44 y.o. male
- Lives in shelter
- 6 day Hx of pain, swelling over left shin
- Rx with Keflex x last 3 days with no improvement
Case 5: Cellulitis

- Treatment options:
  - Keep on going with Keflex
  - Switch to a different PO antibiotic
  - PO probenecid/ IV cefazolin
  - Do we need a godzillacillin?

Prospective Observational study
March-June 2007
7 Toronto Area Hospitals
Swabbed all purulent SSTI

Of the 299 staph aureus positive
81% MSSA and 19% MRSA
Highest risk factor: homeless
(2003 Canadian surveillance data: 8% CA-MRSA)

Traditional Risk Factors CaMRSA

- Homeless
- IVDU
- Men who have sex with men
- Athletes (contact sports: football)
- Military personnel
- Inmates
- Veterinarians, pet owners, pig farmers
- Chronic skin disorder (eg. Psoriasis)
- Recurrent/recent Abx
Prevalence of MRSA as cause of Purulent Skin and Soft Tissue Infection in Adult ED Patients (n=422)

CA-MRSA Susceptible Antibiotics
- TMP/SMX
  - 100% susceptibility
  - Poor coverage for strep A
- Doxycyclines
  - > 90% susceptible
- Clindamycin
  - GI adverse effects
  - Covers strep/anaerobes
  - Increasing resistance
- Rifampin
  - Synergy
- Linezolid
  - $$$$
  - ID consult
- Fluoroquinolones/Macroildes
- Poor choices
- Vanco
  - 1st line IV therapy

Methicillin-Resistant S. aureus Infections among Patients in the Emergency Department

Susceptibilities:
- 90% Clindamycin
- 100% Rifampin/TMP/SMX
- 97% tetracycline
- 92% erythromycin

Nonpurulent SSTI:
- Cephalexin 500 mg q6h x 5-7 d (levo/moxi/clinda)

Purulent STTI:
- TMP/SMX-DS τ bid x 7 d (Doxycycline 100 mg bid)

Simple abscess:
- I&D + no antibiotics

Recurrent abscess, same location: I&D + culture + antibiotics

IDSA Guidelines, 2014
TC LHIN Guidelines, 2014
**Diabetic Foot Infections**

Minor Infection (ulcer < 2 cm)
- Staph, strep (CA-MRSA)
- Cephalexin (+ TMP/SMX)

Moderate to Severe Infection
- Staph, strep, gram negative, anaerobes
- Amox/clav + TMP/SMX; clinda + cipro
- Ceftriaxone + metronidazole; Pip-Tazo
  (Consider Vancomycin for CA-MRSA)

**Intra-abdominal Infections**

- Majority due to E coli and bacteroides
  (pseudomonas, enterococcus)
- Increasing clindamycin resistance: B fragilis

Diverticulitis
- Amox/clav 2g q12h
- TMP/SMX + metronidazole
- Cipro + metronidazole
- moxifloxacin

**Case 6**

- 28 y.o. male
- Fever, headache
- Px: neck stiffness, pain on flexion
- Preliminary diagnosis of meningitis
- Treatment prior to LP results

**Bacterial Meningitis (IDSA)**

Etiology (community-acquired)
- Streptococcus pneumonia 37%
- Neisseria meningitidis 13%
- Listeria monocytogenes 10%
- Haemophilus influenzae 4%
- Other gram negatives 3%

(gram negative, Staph more prevalent in hospital-acquired)
Bacterial Meningitis Treatment

- Dexamethasone: 0.15 mg/kg (10 mg) q6h x 2-4 days
- Vancomycin*: 2 g iv q12h
  - plus
  - Ceftriaxone 2 g iv q12h
- Add ampicillin 2 g iv q4h if possible Listeria: elderly, alcoholic, immunocompromised
  * > 5% high level pneumococcal resistance to penicillin

Clinical Infectious Diseases 2004:39;1267-84

Bacterial Meningitis (IDSA)

Penicillin “Allergy”:
Vancomycin + Neisseria/Haemophilus coverage:
- Meropenem 2 g iv over 3 hours if non-anaphylaxis reaction to penicillin
- Chloramphenicol 1-1.5 g iv if anaphylaxis to penicillin (Call ID!)
- Listeria coverage: TMP/SMX 15-20 mg/kg/day divided q6h
  * Add acyclovir if herpes meningoencephalitis suspected

CID 2004:39 (November)