

Antibiotics in Acute Care

Fredrick M. Abrahamian, D.O., FACEP, FIDSA
Clinical Professor of Medicine
UCLA School of Medicine
Director of Education
Department of Emergency Medicine
Olive View-UCLA Medical Center
Sylmar, California

Decisions in Selecting Antibiotics



- Knowledge of causative organism(s)
- Resistance patterns
- Spectrum of activity



- Patient factors
 - ❖ Community vs healthcare
 - ❖ Age, co-morbidities, pregnancy



- Side-effects
- Drug-drug interactions
- Availability of drug & cost

Discussion Points

- Skin & soft-tissue infections
- Gonococcal infections
- Intra-abdominal infections
- Febrile neutropenia
- Urinary tract infections
- *Clostridium difficile* infection

Warfarin & Antibiotics

■ Interactions with Warfarin:

- ❖ TMP/SMX
- ❖ Metronidazole
- ❖ Fluoroquinolones (dysglycemia)
- ❖ Doxycycline (minor)
- ❖ Dicloxacillin (reduces INR)



Arch Intern Med. 2010;170:617-21. [TMP/SMX & warfarin]
Clin Infect Dis. 2013;57:971-80. [Fluoroquinolones & blood glucose]
JAMA. 2015;314:296-7. [Dicloxacillin & INR]

Rifampin & Drug Interactions

- Inducer of cytochrome-P450 system
- Decreases the effect or levels of:
 - ❖ β -blockers, digoxin, ACE-inhibitors
 - ❖ Diltiazem, nifedipine
 - ❖ Corticosteroids, methadone
 - ❖ Oral anticoagulants
 - ❖ Phenytoin, sulfonylureas
 - ❖ Oral contraceptives



Obstet Gynecol. 2001;98:853-60. [OCs & antibiotics]

Vancomycin 1 gram IV q12h	❖ Concern for emergence of VRE, VISA, VRSA ❖ Slow bactericidal activity; poor tissue penetration
Linezolid 600 mg IV/PO q12h	❖ Oral form 100% bioavailable ❖ Different pharmacokinetics compared to Vanco ❖ Inhibits toxin production
Daptomycin 4-6 mg/kg IV q24h	❖ Complicated SSTIs, <i>S. aureus</i> bacteremia, right sided endocarditis due to MSSA & MRSA ❖ Binds surfactant and gets inactivated
Tigecycline 1 st dose 100 mg IV then 50 mg IV q12h	❖ Also covers Gram-negatives & anaerobes ❖ Does not cover <i>Pseudomonas</i> ; \pm <i>Proteus</i> ❖ Complicated SSTIs, intra-abdominal infections, CAP (not for DRSP)

Other FDA-Approved Antimicrobial Therapies for MRSA SSTIs

Telavancin	IV	❖ Lipoglycopeptide ❖ 10 mg/kg qd (given over 60 min)
Ceftaroline	IV	❖ Cephalosporins with MRSA activity ❖ 600 mg q12 hrs (over 5-60 min)

Other Antimicrobials for MRSA SSTIs

Tedizolid	PO/IV	❖ Oxazolidinone ❖ 200 mg once daily for 6 days ❖ IV infusion over 1 hr
Dalbavancin	IV	❖ Lipoglycopeptide ❖ 1500 mg over 30 min
Oritavancin	IV	❖ Lipoglycopeptide ❖ Single dose of 1200 mg over 3 hrs

JAMA. 2013;309:559-69. [Tedizolid vs linezolid]
N Engl J Med. 2014;370:2169-79. [Dalbavancin vs vancomycin]
N Engl J Med. 2014;370:2180-90. [Oritavancin vs vancomycin]



Cellulitis & MRSA

- Randomized, multicenter, double-blind, placebo-controlled trial
- Cellulitis, no abscess, Sxs for <1 week
- Cephalexin & TMP/SMX vs. Cephalexin
- 153 enrolled / 146 with outcome data
- Clinical cure:
 - ❖ Cephalexin & TMP/SMX: 85%
 - ❖ Cephalexin & placebo: 82%

Clin Infect Dis. 2013;56:1754-62. [Cellulitis & Non-MRSA therapy]

Drug	Streptococci, Group A (B,C,G)	MSSA	MRSA
Penicillin	+	-	-
Dicloxacillin ☆	+	+	-
Amoxicillin	+	-	-
Amox/clav ☆	+	+	-
Cephalexin ☆	+	+	-
Erythromycin	+/-	+/-	-
Azithromycin	+/-	+	-
Doxycycline	+/-	+/-	+
Minocycline ☆	+	+	+
TMP/SMX	-	+	+
Clindamycin ☆	+	+	+
Ciprofloxacin	+/-	+	-
Levo / Moxifloxacin	+	+	-

Complicated Infections

- More likely mixed aerobic & anaerobic infections
- Consider in patients with:
 - ❖ Chronic infections
 - ❖ Peri-rectal infections
 - ❖ Wounds involving lower extremities
 - ❖ Vascular insufficiency (venous stasis ulcers)
 - ❖ Immunocompromising conditions
 - ❖ Bite-related wounds
 - ❖ Post-operative wounds, infected burns

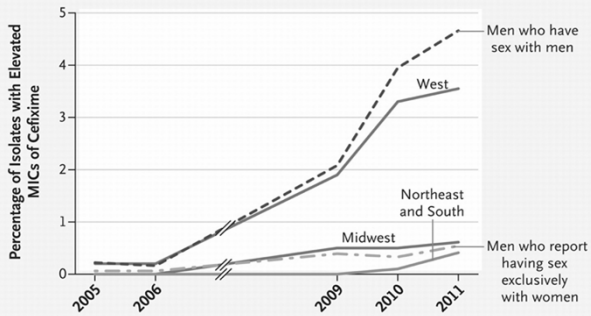
Infect Dis Clin North Am. 2008;22:89-116.

Complicated Infections

- Knowledge of emerging resistance & spectrum of activity of antimicrobials

Vancomycin	No Gram neg. & anaerobic coverage
Ceftaroline	Does not cover <i>Pseudomonas</i>
Clindamycin	No Gram neg. coverage
Ertapenem	Does not cover <i>Pseudomonas</i>
Linezolid	No Gram neg. & anaerobic coverage
Daptomycin	No Gram neg. & anaerobic coverage
Tigecycline	Does not cover <i>Pseudomonas</i>

% Cefixime MIC ≥ 0.25 , 2005–2011



N Engl J Med. 2012;366:485-7.

Cefixime MICs & Outcomes

- Retrospective cohort study
- Culture-positive *N. gonorrhoea* infections
- Reduced susceptibility MIC ≥ 0.12 $\mu\text{g/mL}$
- 291 culture-positive cases; 133 returned
- 6.77% overall rate of clinical failure
- 25% clinical failure with cefixime MIC ≥ 0.12
- 1.9% clinical failure with cefixime MIC < 0.12
- Relative risk of 13.13

JAMA. 2013;309:163-170.

Treatment of Uncomplicated Gonococcal Infections of the Cervix, Urethra, & Rectum

- Ceftriaxone 250 mg IM x 1 **PLUS**
- Azithromycin 1 gram PO x 1 **or**
- Doxycycline 100 mg PO bid x 7 days
- Azithromycin preferred over doxycycline

MMWR. 2012;61:590-4.
MMWR. 2015;64:1-137. [Practice guidelines]

Gonorrhea Treatment

- Dose ceftriaxone at 250 mg
 - ❖ Safeguard against decreased susceptibility
 - ❖ Effective against pharyngeal infection; often asymptomatic, difficult to detect, & eradicate
- Dual treatment recommended whether or not chlamydial infection has been ruled out

MMWR. 2012;61:590-4.
MMWR. 2015;64:1-137. [Practice guidelines]

Gonorrhea Treatment Regimens

- If ceftriaxone not available:
 - ❖ Cefixime 400 mg PO x 1
- If severe cephalosporin allergy:
 - ❖ Gentamicin 240 mg IM x 1 **or**
 - ❖ Gemifloxacin 320 mg PO x 1 **PLUS**
 - ❖ Azithromycin 2 grams PO x 1
- Monotherapy with azithromycin is no longer recommended

ClinicalTrials.gov Identifier: NCT00926796
MMWR. 2015;64:1-137. [Practice guidelines]

Intra-Abdominal Infections

- In general, direct empiric therapy towards:
 - ❖ Enterobacteriaceae & anaerobes
- Anaerobic therapy not indicated for acute uncomplicated cholecystitis
- Reserve anti-pseudomonal coverage for:
 - ❖ Severe infections, immunocompromised, or advanced age
- No need for routine MRSA coverage

Clin Infect Dis. 2010;50:133-64. [2010 IDSA guidelines]

Intra-Abdominal Infections

- Ampicillin-sulbactam not recommended
 - ❖ High rates of resistance among *E. coli*
- Cefotetan & clindamycin **not** recommended
 - ❖ High rates of resistance among *B. fragilis*
- Reserve aminoglycosides for patients allergic to β -lactams & quinolones

Clin Infect Dis. 2010;50:133-64. [2010 IDSA guidelines]

Intra-Abdominal Infections

- Mild diverticulitis, drained peri-rectal abscess
 - ❖ TMP/SMX DS **plus** Metronidazole
 - ❖ Amoxicillin/clavulanate (2 grams bid)
 - ❖ Cipro or Levofloxacin **plus** Metronidazole
 - ❖ Moxifloxacin
- Treat for 7-10 days
- 4-day course of therapy with source control for complicated infections has been advocated

Antimicrob Agents Chemother. 2007;51:1649-55. [Anaerobes susceptibility trends]
N Engl J Med. 2015;372:1996-2005. [Shorter course of therapy]

Community-Acquired Intra-Abdominal Infections in Adults Mild-to-Moderate Severity	
Cefoxitin	Ertapenem
Moxifloxacin	Tigecycline
Ticarcillin / clavulanic acid	
Cefazolin, cefuroxime, ceftriaxone, or cefotaxime plus metronidazole	
Ciprofloxacin or levofloxacin plus metronidazole	

Clin Infect Dis. 2010;50:133-64. [2010 IDSA guidelines]

Community-Acquired Intra-Abdominal Infections in Adults High Risk or Severe	
Imipenem-cilastatin	
Meropenem	Doripenem
Piperacillin-tazobactam	
Cefepime or ceftazidime plus metronidazole	
Ciprofloxacin or levofloxacin plus metronidazole	

Clin Infect Dis. 2010;50:133-64. [2010 IDSA guidelines]

Empiric Rx of Neutropenic Fever

- Piperacillin-tazobactam
- Imipenem; Meropenem; Doripenem
- Cefepime
- Ceftazidime
 - ❖ Poor activity against many gram-positives
- Penicillin-allergy:
 - ❖ Ciprofloxacin **plus** Clindamycin
 - ❖ Aztreonam **plus** Vancomycin

Clin Infect Dis. 2011;52:e56-e93. [IDSA guidelines]



Additional Antibiotics

- Add vancomycin if:
 - ❖ Severe sepsis / septic shock
 - ❖ Pneumonia
 - ❖ Catheter-related infection
 - ❖ Skin & soft-tissue infection
 - ❖ Known history of MRSA
- Add metronidazole if using cefepime/ceftazidime:
 - ❖ Oral mucositis
 - ❖ Perirectal & intra-abdominal infections

Clin Infect Dis. 2011;52:e56-e93. [IDSA guidelines]

Oral β -Lactams & Cystitis

- Amoxicillin & ampicillin
 - ❖ High rates of *E. coli* resistance
 - ❖ Short half-life; rapidly excreted
 - ❖ Lower eradication rates
- Amox-clavu (58%) vs. Ciprofloxacin (77%)
- Cefpodoxime (82%) vs. Ciprofloxacin (93%)
- Not very effective in clearing vaginal *E. coli*

JAMA. 2012;307:583-89. [Cefpodoxime for cystitis]
J Clin Microbiol. 2015;53:2686-92.

Acute Cystitis

- Nitrofurantoin 100 mg bid x 5 days
- TMP/SMX DS bid x 3 days
- Fosfomycin 3 grams single dose
- Avoid fluoroquinolones as first-line agents
- Avoid oral β -lactams as first-line agents
- Avoid amoxicillin & ampicillin

Arch Intern Med. 2007;167:2207-12. [Short course nitrofurantoin]
Clin Infect Dis. 2011;52:e103-e20. [IDSA UTI guidelines]
JAMA. 2012;307:583-89. [Cefpodoxime for cystitis]
Antimicrob Agents Chemother. 2012;56:2181-3. [Resistance trends]

Nitrofurantoin

- 100 mg PO bid x 5 days
- Efficacy compared to TMP/SMX x 3 days
- Not for *Proteus* or *Pseudomonas*; ± *Klebsiella*
- Category B; not near term (hemolytic anemia)
- Not in children ≤ 12 years
- Not for pyelonephritis
- Interaction with Mg-containing antacids

Arch Intern Med. 2007;167:2207-12. [TMP/SMX vs. Nitrofurantoin]

Acute Pyelonephritis

- Oral fluoroquinolones x 5-7 days
- May give initial IV dose in ED:
 - ❖ Fluoroquinolones; Ceftriaxone
- Aminoglycosides; Carbapenems
- TMP/SMX DS bid x 14 days
- Avoid oral β-lactams as first-line agents
- Obtain urine culture & susceptibility test

Clin Infect Dis. 2011;52:e103-e20. [IDSA UTI guidelines]
Emerg Infect Dis. 2016;22:1594-1603. [Resistant *E. coli* & pyelonephritis]

C. difficile: Assessing Severity

- Mild-moderate
 - ❖ Diarrhea without meeting severe criteria
- Severe
 - ❖ Serum albumin <3 g/dl
 - ❖ Leukocyte count ≥15,000 cells/mm³
 - ❖ Creatinine ≥1.5 times the baseline
- Severe & complicated
 - ❖ Hypotension, shock, ileus, megacolon

Am J Gastroenterol. 2013;108:478-98. [Practice guidelines]
Infect Control Hosp Epidemiol. 2010;31:431-55. [Practice guidelines]

C. difficile Antimicrobial Therapy

Initial episode, mild-moderate	Metronidazole, 500 mg PO tid for 10-14 days
Initial episode, severe	Vancomycin, 125 mg PO qid for 10-14 days
Initial episode, severe, complicated	Vancomycin, 500 mg PO and PR qid plus metronidazole, 500 mg IV tid

Am J Gastroenterol. 2013;108:478-98. [Practice guidelines]
Infect Control Hosp Epidemiol. 2010;31:431-55. [Practice guidelines]

C. difficile Antimicrobial Therapy

- Chance of 1st recurrence: 10-20%
- Chance of recurrence after 1st: 40-65%
- Fidaxomicin
 - ❖ FDA-approved in adults
 - ❖ Minimal systemic absorption
 - ❖ Lower recurrence rate

Clin Infect Dis. 2012;55(S2):S154-61. [*C. diff* & fidaxomicin]
Lancet Infect Dis. 2012;12:281-9. [*C. diff* & fidaxomicin]
N Engl J Med. 2011;364:422-31. [*C. diff* & fidaxomicin]

Take Home Points

- TMP/SMX: Increases activity of warfarin
- Utilize dual therapy for treatment of gonorrhea
- Anti-pseudomonal agents:
 - ❖ Avoid routine use for intra-abdominal infections
 - ❖ Initiate in febrile neutropenic patients
- Do not use nitrofurantoin for pyelonephritis
- Severity assessment of *C. difficile* infection:
 - ❖ Utilize WBC count, albumin, & creatinine
