UWTASP tele-antimicrobial stewardship program | echo

March 4th, 2025

Agenda

- Sydney Kruse, PharmD: *The Chronicles of Oral Cephalosporin Antibiotics*
- Case Discussions
- Open Discussion

Background

Oral Cephalosporins are commonly used antibiotics

Have a wide variety of clinical uses

Have important differences in spectrum of activity and pharmacokinetics

Not routinely recommended as a first line treatment option

Main Objective

Using pharmacokinetics, pharmacodynamics, and clinical data become more comfortable using oral cephalosporins for common indications

- Cystitis
- Community acquired pneumonia (CAP)
- Oral step-down for *Streptococcus pneumoniae* bacteremia
- Skin and Soft Tissue Infections (SSTI)

Focused Oral Cephalosporin Review

Cephalexin	Cefadroxil	Cefuroxime	Cefdinir	Cefpodoxime
Generation				
First	First	Second	Third	Third
FDA indications				
CAP SSTI Cystitis	SSTI Cystitis	SSTI Cystitis	CAP SSTI	CAP SSTI Cystitis
Spectrum of Activity				
ALL: *S. aureus* (MSSA), *S. pneumoniae, E. Coli, K. pneumoniae, P.mirablis*				
Second and third generation: *Proteus multocida H. Influenzae*				

Other Staphylococcus and Streptococcus species are frequently susceptible to oral cephalosporins

KEFLEX (cephalexin) [package insert]. Locust Valley, N.Y: Pragma Pharmaceuticals, LLC; 2018.
DURICEF (cefadroxil monohydrate) [package insert]. Princeton, NJ: Bristol Myer Squibb Company; 2002.
CEFTIN (cefuroxime axetil) [package insert]. Research Triangle Park, NC. GlaxoSmithKline 2015.
OMNICEF (cefdinir) [package insert]. North Chicago, IL: AbbVie Inc.; 2015.
VANTIN (cefpodoxime)[package insert]. NY, NY; Pfizer Pharmaceuticals; 2013

Dosing and PK basics

	Cephalexin	Cefadroxil	Cefuroxime	Cefdinir	Cefpodoxime
Dosing	250-500 mg every 6 hours	500-1000 mg every 12 hours	250-500 mg every 12 hours	300-600 mg every 12 hours	100-400 mg every 12 hours
Cmax (mcg/mL)	9-32	17-35	4-7	1.6-2.8	1.4-3.9
Bio-availability	90%	Rapidly absorbed from GI tract	Fasting: 37%; Following food: 52%	16-25%	50%
Volume of distribution (L/kg)	0.23	0.31	0.25-0.3	0.35	0.7
Half life (h)	0.5 - 1.2	1-2	1.2	1.7	2.09-2.84
Urine excretion	>90%	>90%	50%	12-18%	29-33%

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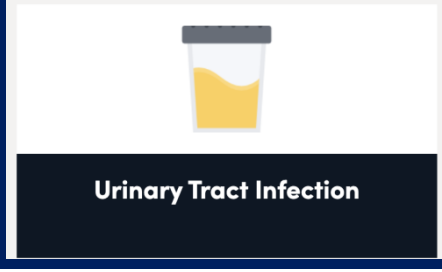
Case 1



- 28 YO female presents to clinic with 2 days of dysuria, increased urinary frequency, and urinary urgency. Urinalysis is performed and indicates presence of bacteria, leukocyte esterase, and nitrites.

- *Are oral cephalosporins an appropriate treatment option for cystitis?*

Oral Cephalosporins and Cystitis

Urinary Tract Infection

Oral beta-lactams are seen as inferior to FQ or TMP-SMX for treatment of cystitis

- Studies done in the 1970s and 1980s
- Heterogenous populations
- Lacked statical power, precise definitions, and consistent antimicrobial susceptibility testing
- Clinical failure vs microbiologic failure

Nguyen HM, et.al, *Int J Antimicrob Agents*. 2020;56(4):106085

Guidelines

Urinary Tract Infection

IDSA 2010 Guidelines for Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women

Oral cephalosporins are considered second line

Guidelines for the Prevention, Diagnosis, and Management of Urinary Tract Infections in Pediatrics and Adults: A WikiGuidelines Group Consensus Statement

Oral cephalosporins are considered second line

Gupta K, Hooton TM, Naber KG, et al. *Clin Infect Dis*. 2011;52(5):e103-e120.

Nelson Z, Aslan AT, Beahm NP, et al. *JAMA Netw Open*.2024;7(11):e2444495.

Cefpodoxime-Proxetil versus Trimethoprim-Sulfamethoxazole for Short-Term Therapy of Uncomplicated Acute Cystitis in Women

Prospective, open, randomized multicenter study

Enrolled 163 women 18-70 with acute cystitis

cefpodoxime 100 mg BID x 3 days compared to TMP-SMX 160/800 BID x 3 days

Primary outcome was clinical cure and bacterial eradication

Kavatha D, Giamarellou H, Alexiou Z, et al.*Antimicrob Agents Chemother*. 2003;47(3):897-900.

Results

Urinary Tract Infection

TABLE 3. Clinical and bacteriological results at the first and second follow-up visits for the two treatment groups

Visit and treatment	Clinical evaluation (total no. of patients treated/ no. cured [%])	Bacteriological evaluation (total no. of patients treated/no. with bacterial eradication [%])
First follow-up		
Cefpodoxime-proxetil	63/62 (98.4)	63/
TMP-SMX	70/70 (100)	70/
Second follow-up[a]		
Cefpodoxime-proxetil	55/48 (87.3)	55/ (86)
TMP-SMX	60/51 (85)	50[b]/42 (84)

[a] For the clinical evaluation, 8 patients in the cefpodoxime-proxetil arm and 10 patients in the TMP-SMX were lost to the second follow-up.

[b] The numbers do not coincide with those from the clinical evaluation for the second follow-up visit because urine cultures were not repeated for the relevant patients after they became permanently asymptomatic.

- History of prior UTI was independently associated with clinical failure

Kavatha D, Giamarellou H, Alexiou Z, et al.*Antimicrob Agents Chemother*. 2003;47(3):897-900.

PK/PD in Cystitis

Urinary Tract Infection

- PK/PD goal of cephalosporins: Time above the MIC for at least 40-50% of dosing interval

- Using cefpodoxime as an example:
  - 100 mg x 0.5 (bioavailability) x 0.33 (urine concentration) = 16.5 mg
  - 16.5 mg/ 1.5 L (urine amount) = 11 mg/L or 11 mcg/mL
  - Half life of ~3 hours
  - 11 mcg/mL->5.5 mcg/mL ->2.75 mcg/mL after 6 hours (50% of dosing interval)

- CLSI breakpoint for cefpodoxime susceptibility < 2 mcg/mL

- Similar for the other cephalosporins

Gilbert DN. Urinary tract infections in patients with chronic renal insufficiency. *Clin J Am Soc Nephrol*. 2006;1(2):327-331.

Summary of Cystitis

	Cephalexin	Cefadroxil	Cefuroxime	Cefdinir	Cefpodoxime
Option in guidelines	☑			☑	☑
PK/PD supports use	☑	☑	☑	☑	☑
Supportive clinical data	☑	☑	☑	☑	☑
My opinion	☑	☑	☑	☑	☑

Case 2

Pneumonia

- 60 YO male presenting to the ED with new SOB, productive cough with purulent sputum, fatigue, and fever. Chest Xray was done and shows left upper lobe infiltrates.

- *Are oral cephalosporins an appropriate treatment option for community acquired pneumonia?*

Guidelines

2019 IDSA Community Acquired Pneumonia Guidelines

- Oral cephalosporins are considered alternative agents
  - cefpodoxime 200 mg twice daily
  - cefuroxime 500 mg twice daily

Metlay JP, Waterer GW, Long AC, et al. *Am J Respir Crit Care Med*. 2019;200(7):e45-e67

Comparative Efficacy in CAP

Pneumonia

- Drehobl M et. al (1997) compared cefdinir to cefaclor in 690 patients
    - 89% vs 86% clinical success rate
- Blaser MJ et. al (1983) compared cefadroxil to cephalexin in 34 patients
    - All infections were deemed clinically cured

Drehobl M ,et. al. *Antimicrobial Agents and Chemotherapy*. 1997;41(7):1579-1583.

What If…

Pneumonia

- Same 60 YO male diagnosed with CAP but now presented with hypotension and was admitted to hospital medicine. Blood cultures are positive for S*treptococcus pneumoniae.* On day 3, patient is afebrile, normotensive, and on room air.

- *What is the role of oral cephalosporins as oral strep down for streptococcal bacteremia?*

Oral stepdown for Streptococcal Bacteremia

Pneumonia

Multicenter retrospective study of 238 patients with streptococcal bacteremia

12.6% respiratory source

14.3% *Streptococcus pneumoniae*

About half of patients received oral step-down therapy

Median of 3.9 days of IV therapy before transition to oral antibiotics

Lew, A et.al, Open Forum Infectious Diseases, Volume 11, Issue 7, July 2024

Oral Step-Down Regimens

Table 2. Oral Stepdown Regimens and Dosing

Antibiotic	Dose	Frequency, No. (%)
Amoxicillin	Total	15 (13.4)
	500 mg q12h	1 (0.9)
	500 mg q8h	3 (2.7)
	1000 mg q12h	1 (0.9)
	1000 mg q8h	10 (8.9)
Amoxicillin/clavulanate	875 mg q12h	30 (26.8)
Cephalexin	Total	14 (12.5)
	500 mg q12h	1 (0.9)
	500 mg q6h	5 (4.5)
	1000 mg q8h	8 (7.1)
Cefdinir	300 mg q12h	16 (14.3)
Cefpodoxime	400 mg q12h	2 (1.8)
Cefixime	400 mg q24h	1 (0.9)
Levofloxacin	Total	24 (21.4)
	500 mg q24h	3 (2.7)
	750 mg q24h	21 (18.8)

Lew, A et.al, Open Forum Infectious Diseases, Volume 11, Issue 7, July 2024

Results

Pneumonia

- Primary outcome of clinical success:
  - 94.4% vs 94.6% (P = .946)
- Length of stay shorter with PO step-down
  - 5.5 vs 9.2 days (P < .001)
- More complications with IV line (0% vs 7.9%)

- Conclusion: oral cephalosporins are safe an effective as oral step-down in uncomplicated streptococcal bacteremia

Lew, A et.al, Open Forum Infectious Diseases, Volume 11, Issue 7, July 2024

Summary of CAP/Stepdown for Streptococcal Bacteremia

	Cephalexin	Cefadroxil	Cefuroxime	Cefdinir	Cefpodoxime
Option in guidelines			☑		☑
PK/PD supports use	☑	☑	☑	☑	☑
Supportive clinical data	☑	☑	☑	☑	☑
My opinion	☑	☑	☑	☑	☑

Case 3

Cellulitis

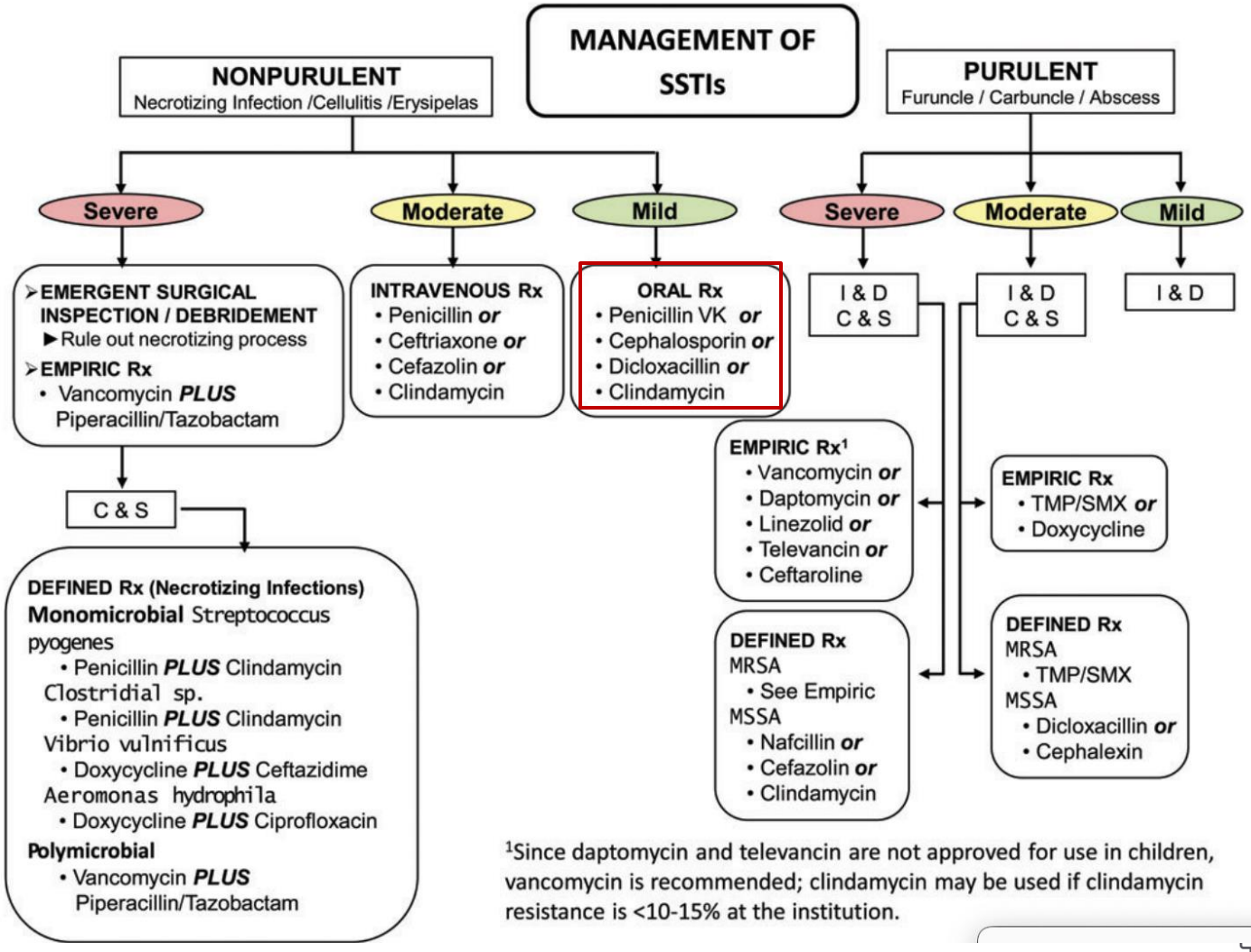
- 35 YO males presents to the ED with redness, swelling, and pain of his right leg after falling off his bike. On exam no purulence seen.

Are oral cephalosporins an appropriate treatment option for cellulitis?

Guidelines

Cellulitis

2014 IDSA SSTI Guidelines



Stevens DL, Bisno AL, Chambers HF, et al. *Clin Infect Dis*. 2014;59(2):e10-e52. doi:10.1093/cid/ciu444

UW Medicine Guidance

Cellulitis

Non-purulent skin/soft tissue infection

Common organism: (Streptococcus species)

- Cefazolin 2g IV q8h
- PO option for Strep/MSSA: Cephalexin 500mg QID or 1000mg BID
- MRSA coverage is not necessary for non-purulent SSTI

Typical Duration: 5 Days

SSTI Summary

	Cephalexin	Cefadroxil	Cefuroxime	Cefdinir	Cefpodoxime
Option in guidelines	☑	☑			
Clinical data supports use	☑	☑	☑	☑	☑
My opinion	☑	☑			

Conclusions

Clinical data and guidelines support the use of oral cephalosporins for treatment of common infections

Differences in spectrum and PK/PD may help you choose one oral cephalosporin over another

Take Aways

	Cephalexin	Cefadroxil	Cefuroxime	Cefdinir	Cefpodoxime
Cystitis *not as first line	☑	☑	☑	☑	☑
CAP *including bacteremia due to *S. pneumoniae*	☑	☑	☑	☑	☑
SSTI	☑	☑	☑	☑	☑

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