Online Only Lectures – Other Antibacterial Drugs

Speaker: David Gilbert, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Other Antibacterial Drugs (Macrolides, TMP, SMX, etc)

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Disclosures of Financial Relationships with Relevant Commercial Interests

- Consultant for Biomerieux
- Research Grant from Biofire

PLAN

- Review testable facets of activity of Polymyxins, Tetracyclines, TMP/SMX, Nitrofurantoin, and Fosfomycin vs gram-negative bacilli
- Dr. Boucher will touch on same drugs as their activity relates to clinical use vs Gram-Positive bacterial infections
- Embedded audience response questions (ARQs) for your interest without any polling

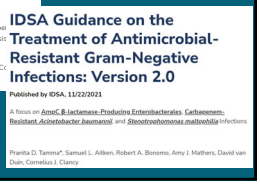
IDSA AMR Guidance – Sep 20, Nov 21


Infectious Diseases Society of America Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections

Published by IDSA, 9/8/2020

A Focus on Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance (DTR-*P. aeruginosa*)

Pranita D. Tamma*, Samuel L. Aitken, Robert A. Bonomo, Amy J. Mathers, David van Duin, Cornelius J. Clancy


IDSA Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections: Version 2.0

Published by IDSA, 11/22/2021

A focus on AmpC β-lactamase-Producing Enterobacterales, Carbapenem-Resistant *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia* Infections

Pranita D. Tamma*, Samuel L. Aitken, Robert A. Bonomo, Amy J. Mathers, David van Duin, Cornelius J. Clancy

https://www.idsociety.org/practice-guideline/amr-guidance/

IDSA Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections: Version 1.0 & 2.0

Focus on infections caused by

- Version 1.0
  - Extended-spectrum β-lactamase-producing Enterobacterales (ESBL-E)
  - Carbapenem-resistant Enterobacterales (CRE)
  - *Pseudomonas aeruginosa* with difficult-to-treat resistance (DTR-*P. aeruginosa*)
- Version 2.0
  - AmpC β-lactamase-producing Enterobacterales (AmpC-E)
  - Carbapenem-resistant *Acinetobacter baumannii* (CRAB,
  - *Stenotrophomonas maltophilia*

Nov, 2021, https://www.idsociety.org/practice-guideline/amr-guidance-2.0/

Polymyxin Family

- Polymyxin B
- Polymyxin E (Colistin)
- Clinical indication:
  - Alternative salvage therapy for susceptible MDR aerobic GNB

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Polymyxins: Mechanisms of action and Resistance

- Mechanism:
  - Binds to LPS (lipid A) & Phospholipids of cell walls of susceptible GNB
  - Displaces divalent cations; resulting membrane disruption, and bactericidal activity
- Acquired Cross Resistance is increasing, esp. among Carbapenemase producing GNBs
  - "R" Due to LPS target change and efflux pumps
  - Plasmid spread of mcr-1 gene
- Guideline reference: Pharmacotherapy 2019;39: 10

Activity vs Aerobic GNB

- Susceptible: *Enterobacterales, ESBLs, KPCs, non-fermenters (Acinetobacter, Stenotrophas, Ps. aeruginosa)*
- Intrinsic Resistance: M—*Morganella sp.*
  - *A---Anaerobes*
  - *P---Proteus sp.*
  - *P---Providencia sp.*
  - *S---Serratia sp.*
- All gram + bacteria are "Resistant"

Polymyxin Pharmacology

- Polymyxin B
  - Uncomplicated dosing
  - Non-renal clearance
  - Drug of choice except for UTI (low/absent urine concentrations)
- Colistin (pro-drug): Colistimethate
  - Complicated dosing
  - Renal excretion
    - Use for UTIs(high urine concentrations)
    - Adjust dose for renal insufficiency
- Often used as part of combination therapy(combination with meropenem failed)

Polymyxins: Reversible Adverse Effects

- Nephrotoxicity (20-60%). Lower risk with polymyxin B
- Neurotoxicity (7-68%). Wide range of problems:
  - Dizziness
  - Paresthesias (circumoral)
  - Vertigo
  - Confusion
  - Ataxia
  - Neuromuscular blockade

The Bottom Line

- Potential salvage therapy for infections due to susceptible aerobic GNB "R" to all beta-lactams, FQs, and AGs
  - Prefer Polymyxin B, over Colistin, except for UTIs
- Mixed results with combination therapy
- Mixed results when used as adjuvant therapy: e.g.
  - Airway nebulization of colistin in patients with pneumonia
  - Intrathecal polymyxin B in patients with meningitis
- Reversible renal and neurotoxicity

Tetracyclines: The Family

- Doxycycline (Many indications)
- Minocycline(Many indications)
- Tigecycline (Don't use)
- Omadacycline(SSTIs, CABP)
- Eravacycline (cIAIs)

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Tetracyclines: Mechanisms

- Mechanism of Action:
  - Bacteriostatic: Inhibits protein synthesis
  - Don't combine with bacteriocidal drug
- Major mechanisms of Resistance:
  - Efflux pumps
  - Target protective proteins

Tetracycline Spectrum of Activity

- Aerobic Gram-positive bacteria
- Aerobic Gram-negative bacteria
- Atypical bacteria
- Spirochetes
- New tetracyclines (Eravacycline-a fluorocycline- & Omadacycline- an aminomethylcycline) expand the spectrum of antibacterial activity

In vitro Activity of Eravacycline and Omadacycline vs. Mostly Enteric GNB

- Aerobic Gram-negative bacilli to include:
  - *Enterobacterales*
    - To include ESBL and CPE producers
    - Not active vs *Morganella, Proteus, and Providencia sp.*
- Non-Fermenters
  - Active vs *Acinetobacter baumannii and Stenotrophomonas*
  - *No activity vs Ps. aeruginosa*
- Activity vs ANAEROBIC GNB: e.g. *Bacteroides sp*

New Tetracyclines: In Vitro Activity versus MDR GNB

Bacteria	Minocycline	Omadacycline* (FDA: SSTI;CABP)	Eravacycline* (FDA:IAIs; UTI-NO!)
ESBL producers	0	+	+
KPCs	0	+	+
Metallo-Carbapen.	0	+	+
Acinetobacter	Variable	+	+
Stenotropho.	+	+	+
Pseudomonas	-	-	-
Bacteroides	-	+	+

*Resistant to expulsion by efflux pumps

Tetracycline Pharmacology

- Oral absorption impaired by multivalent cations
- Distribution largest with minocycline (greatest lipid solubility)
- Distribution and Tigecycline:
  - High intracellular levels; very low extracellular concentrations
  - FDA review found increased mortality(CAP, IAI, SSTI)
  - "Only use when no other option"

Women and Children

- Avoid tetracyclines during pregnancy for fear of :
  - Hepatoxicity
  - In utero damage to dentition and bones due to calcium chelation
  - Breast feeding OK as calcium in the milk chelates the tetracycline
- Children and tetracyclines:
  - Try to avoid in children </= 8 y.o. to avoid dental staining and bone damage
  - If needed for critical illness, Amer. Acad. Peds considers DOXYCYCLINE safe for up to 21 days of therapy

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Tetracycline Adverse Effects

- *Clostridioides difficile* colitis
- Photosensitivity
- Hepatotoxicity: minocycline; pregnancy
- Treatment of Spirochetal* infections can precipitate Jarisch-Herxheimer reaction
- Vertigo: Minocycline most often

*Pertinent spirochets: *Treponema pallidum* (80%), Tick-borne & Louse-borne Relapsing fever (54%),

ARQ 1

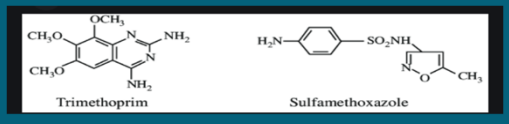
- A 25 y.o pregnant female (2nd trimester) is admitted with fever, hypotension, nausea, vomiting, and diarrhea.
- She just returned from a week camping with family and pet dog in a heavily forested area of northern California. While camping she dutifully picked ticks off the dog !
- After blood cultures , empiric therapy was started with piperacillin-tazobactam and vancomycin.
- After one week , she is clinically still "septic".
- Now, the lab reports the presence of *Francisella tularensis* in her admitting blood cultures.
- There is a family history of drug-induced deafness

- Which one of the following treatments do you recommend ?

A. Gentamicin
B. Doxycycline
C.Ceftriaxone
D. Chloramphenicol

Typhoidal Tularemia

- Doxycycline is now deemed non-teratogenic and is the best option of those offered.
  - Systematic reviews demonstrate no correlation between the use of doxycycline during pregnancy and teratogenic effects or dental staining.
  - This conclusion applies only to doxycycline and not the other tetracylines.
- None of the beta-lactam antibiotics are active vs *F. tularensis*
- *Even though active, Need to avoid the p*otential toxicities of the aminoglycosides and chloramphenicol



TMP-SMX: Mechanism

- TMP and SMX act in sequence to inhibit bacterial synthesis of tetrahydrofolic acid (THF)
- THF needed for thymidine synthesis
- Thymidine synthesis needed for DNA synthesis

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TMP-SMX Spectrum of Activity vs. Gram Negative Bacilli

Clinical Syndrome	Susceptible Pathogens	Resistant Pathogens
UTIs	*Enterobacterales*	*ESBL producers*
RTIs	*COPD Big 3*; Pneumocystis*	*Mycoplasma*
Diarrhea	*Shigella, Salmonella, ETEC*	*Campylobacter*
Misc.	*Listeria, Nocardia*	
Non-fermenters	*Stenotrophomonas, Burkholderia*	*Pseudomonas aeruginosa, Acineto.*
Anaerobic bacteria	*None*	*Bacteroides fragilis*

**Big 3= S.pneumoniae, Haemophilous influenza, Moraxella catarrhalis*

Multiple Mechanisms of Resistance; Varies with organism

- Mutation of target enzymes
- Decrease in cell wall permeability
- Efflux pumps
- Excess thymidine in the environment

TMP-SMX for *S.pyogenes* Infections

- Failures in treatment of Streptococcal pharyngitis in clinical trials: both IV and PO (JID 1973(supplement) 1973;S693.
- Theorized mechanism: ability of streptococci to utilize exogenous thymidine for DNA synthesis and thereby bypass the inhibitory activities of the sulfamethoxazole and trimethoprim

TMP/SMX: Pharmacology

- Widely distributed to include CSF and Prostate
- Renal excretion by both tubular secretion and glomerular filtration
- Lots of Drug-Drug interactions: e.g.
  - Oral anticoagulants (warfarin)
  - Rifampin
  - Phenytoin
  - ACE inhibitors and ARBs

TMP/SMX: Adverse Effects

- Hemolysis if G6PD deficient
- Promotes folate deficiency;
  - Dangerous in early pregnancy----neural tube defects
  - Low folate associated with pancytopenia
- Derm.: Stevens Johnson syndrome; toxic epidermal necrolysis (TEN), erythema multiforme, photosensitivity
  - More common in elderly and HIV patients
- Aseptic meningitis

TMP-SMX & Proximal Convoluted Tubules

- TMP and creatinine compete for tubular secretion of creatinine by proximal convoluted tubules
  - Creatinine used as surrogate marker of GFR
  - Hence, the calculated Creatinine Clearance falls with TMP therapy due to competition for secretion but no effect on directly measured GFR

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More TMP and Distal Renal Tubules

- TMP blocks reabsorption of Na+ in distal convoluted tubules, less exchange for K+ , and serum K+ increases.
- Elevated K+ exaggerated by concomitant ACE Inhibitors or ARB due to reduced serum aldosterone

IV TMP-SMX: Association with Lactic Acidosis

- Possible association of lactic acidosis.
- Hypothesis: caused by propylene glycol in IV formulation Of TMP-SMX

TMP-SMX: Pregnancy and Breastfeeding

- Pregnancy:
  - Avoid in first trimester: risk of neural tube defects
  - Avoid in last trimester: SMX displaces bilirubin bound to albumin; increases unconjugated bilirubin levels with risk of neonatal kernicterus
- Breastfeeding:
  - TMP-SMX is in breast milk; avoid use in G6PD deficient infants
  - "Mothers taking TMP-SMX can breast feed healthy, full-term infants who are at least one month old". AAPs

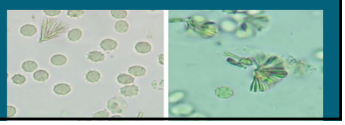
Many Adverse Drug-drug interactions

- Examples:
  - Warfarin
  - Cyclosporin
  - Rifampin
  - ACE inhibitors
  - ARB drugs
  - Many others
- Where available: Therapeutic Drug Monitoring (serum levels)

ARQ 2: Recurrent *E.coli* Cystitis

- 55 y.o. female complains of dysuria and suprapubic tenderness
  - She has a known neurogenic bladder secondary to multiple sclerosis
  - In addition, she is taking an ACE inhibitor and low dose furosemide for hypertension
- Baseline renal function is normal
- Started on TMP-SMX via telemedicine
  - Two days later she presents with fatigue and nausea

Vital signs normal.
U/A: WBCs, RBCs, and Crystals
WBC: 11,000
Serum creatinine: 1.6 mg/dl
Serum Potassium: 5.8 meq/ml
Renal ultrasound: No hydronephrosis



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What explains the elevated K+ and Creatinine concentrations ?

- A. Drug induced decrease in the Glomerular Filtration Rate (GFR)
- B. Crystalluria with obstructive uropathy
- C. Impaired distal tubular absorption of sodium
- D. TMP Decreased tubular secretion of creatinine plus impaired distal tubular sodium absorption

ARQ 2 answer

- The correct answer is D:
  - A. Serum creatinine and TMP compete for the proximal tubular secretion of creatinine.
  - B. In addition, the ACE inhibitor impairs the aldosterone-mediated distal tubular absorption of sodium in exchange for the tubular secretion of potassium.
  - C. The result is elevation of the serum levels of both creatinine and potassium.
  - D. The elevated creatinine does not reflect a decrease in the GFR
- Sulfamethoxazole crystals are in the urine but they are soluble enough to not cause obstruction of flow.

ARQ 3

- Which one of the following drugs does not achieve therapeutic concentrations in urine ?
  - A. Colistin (Polymyxin E)
  - B. Nitrofurantoin (Macrobid)
  - C. Moxifloxacin
  - D. Fosfomycin

ARQ 3 Answer

- C is the correct answer.
  - The renal excretion of moxifloxacin is low and hence, moxifloxacin is not recommended for the treatment of UTIs.
- Colistin (Polymyxin E) is a prodrug. Both the prodrug (colistimethate)and active constituent, colistin, reach therapeutic urine concentrations.
  - In distinction, polymyxin B is excreted by the GI tract and does not achieve therapeutic urine concentrations.
- Nitrofurantoin has high urine concentrations but low concentrations in the renal parenchyma.
- Fosfomycin reaches therapeutic concentraions in urine with FDA approved oral regimen. Higher parenteral doses, not available in the US, are needed to achieve adequate renal tissue concentrations.

Nitrofurantoin (Macrobid): Spectrum of Activity

	Susceptible	*Resistant*
Gram-Positive	*Staph. saprophyticus*	*Other Coag neg staph*
	E.faecalis; E.faecium	
		S. aureus (MRSA/MSSA)
	Strep. agalactiae, GpB	
Gram-Negative	*E.coli*	*Proteus species*
	Klebsiella sp	*Serratia species*
		Pseudomonas species

Nitrofurantoin: Mechanisms

- Bactericidal via multiple antibacterial inhibitory mechanisms:
  - Inhibits protein synthesis
  - Blocks aerobic metabolism of susceptible bacteria
  - Inhibits both RNA and DNA synthesis
  - Blocks cell wall synthesis
- FDA licensed in 1953; Resistance remains minimal, perhaps due to multiple antibacterial mechanisms

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Warnings

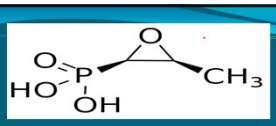
- Avoid in late stage pregnancy and neonates due to risk of hemolytic anemia
- With months of therapy, insidious pulmonary fibrosis
- Risk of hepatic toxicity (often cholestatic)
- Associated with:
  - Peripheral neuropathy
  - Hemolytic anemia in those with G6PD deficiency
- DRESS syndrome: drug rash, eosinophilia, & systemic symptoms

Can you name 4 antibacterials that cause hepatoxiciy ?

- N: for Nitrofurantoin (cholestatic)
- A: for Amoxicillin-clavulanate (cholestatic)
- F: for Fluoroquinolones
- T: for Tetracyclines (in pregnancy)
- A: needed an "A" for NAFTA

Nitrofurantoin dose

- For uncomplicated cystitis:
  - One 100 mg capsule PO with meals BID x 7 days
  - Due to low serum and tissue concentrations, Package Insert recommends pre- and post-treatment urine cultures (rarely done) if worried about associated pyelonephritis
- Nitrofurantoin is Not recommended if CrCl is < 30 ml /min



• Fosfomycin

- Originally Phosphonomycin
- Alternative oral therapy for uncomplicated cystitis
- Not yet approved for parenteral therapy in the US
- Distribution includes prostate tissue

Spectrum of activity of oral fosfomycin vs GNBs

- Activity vs Enterobacterales:
  - *E. coli*, to include ESBL + strains
  - *Klebsiella sp.* To include ESBL + strains
  - *Citrobacter sp.*
  - *Proteus sp.*
  - Carbapenemase producers: NO ACTIVITY
- Activity vs Non-fermenters:
  - NO ACTIVITY

Fosfomycin tromethamine (Monurol)

- Uncomplicated cystitis in females
  - Dose: 3.0 gms po X one dose with or without food
- Complicated UTI, but no pyelonephritis
  - Dose: 3 gm po q3d x 3 doses
  - Lower dose in patients with renal insufficiency
- No serious AEs; Diarrhea in 10% of patients
- Bactericidal mechanism:
  - Inhibition of cell wall synthesis
  - Decreased adherence of bacteria to uroepithelial cells

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Susceptibility of non-fermentative Gram-Negative Bacilli Producing ESBLs, Carbapenemases, & "R" to all FQs and AGs

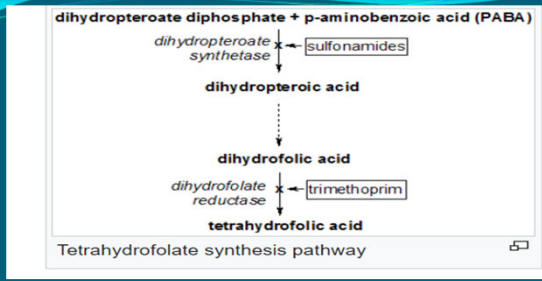
Drug	*Ps.aeruginosa*	*Burkholderia*	*Stenotropho-monas*	*Acinetobacter baumannii com.*
Cefiderocol	+	+	+	+
Eravacycline	---	---	+	+
Polymyxins	+	---	+	+
TMP-SMX	---	+	+	---
Other				See footnote*
Adjunctive Phage Rx	+	?	?	+

*Polymyxin plus minocycline &/or amp-sulbactam (AAC2021; 65:2021.02.17; Aztreonam + Ceftaz-avi (Infection 2020;48:835); Sulbactam+Durlobactam(I): Current Opinion in Infect. Diseases 2020;33: 214;

Tetracycline Activity Spectrum

Bacteria	Doxycycline	Minocycline	Omadacycline	Eravacycline
Aerobic GPCs	+	+	+	+
MRSA	+	+	+	+
Aerobic GNB	+	+	+	+
Rickettsial	+	+	+	+
Spirochetal*	+	+	+	+
Plasmodia	+	?	?	?
Ps.aeruginosa	0	0	0	0
Acineto/Steno.	0	Variable	+	+

*Borrelia, Treponema, Leptospira



TMP-SMX: Beyond CA-MRSA

Clinical uses

- UTI
- AECB
- *Pneumocystis jiroveci*
- Traveler's diarrhea
- Shigella
- *Coxiella burnetii*
- *Mycobacteria marinum*
- *Tropheryma whipplei*

More Clinical uses

- Nocardia
- Cholera
- Listeria
- Stenotrophomonas
- Cyclospora
- Isospora
- Toxoplasmosis

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Trimethoprim-Sulfamethoxazole

- Mechanism of action:
  - Sequential blockade of two enzymes needed to synthesize folate
- Broad spectrum---Activity vs. GNB:
  - Enterobacterales
  - Non-Fermentative GNBs: ***Burkholderia and Stenotrophomonas.***
    - *No activity vs Ps.aeruginosa*
    - Also , no activity vs:*Mycoplasma, Francisella tularensis, and Bacteroides fragilis*

Nitrofurantoin for uncomplicated *E.coli* UTI*

- Pulmonary toxicity with chronic therapy: desquamative interstitial pneumonia with fibrosis
- Intrahepatic cholestasis and hepatitis
- DRESS syndrome: drug rash, eosinophilia, & systemic symptoms

*Cystitis only