CRACKING THE CODE ON ID CONUNDRUMS

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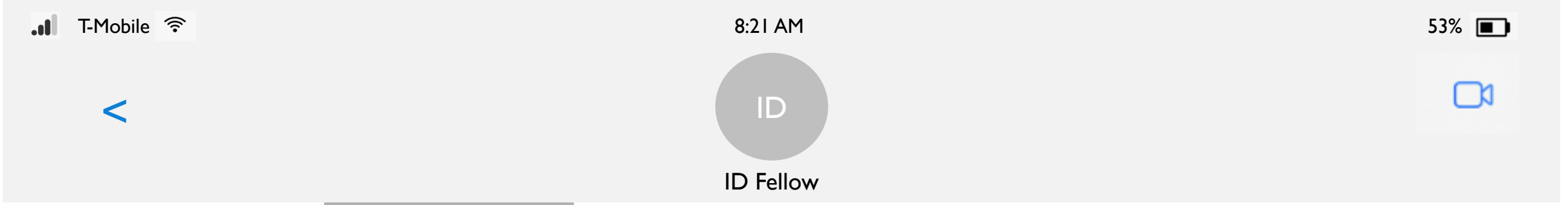
DISCLOSURES

- Nicole Bradley and Yumi Lee have nothing to disclose

OBJECTIVES

- Identify the role of bacteriostatic antibiotics in management of bloodstream infections
- Discuss oral antibiotics as treatment options for osteomyelitis (OM) and bloodstream infections (BSI)
- Describe the role of doxycycline use in the pediatric population

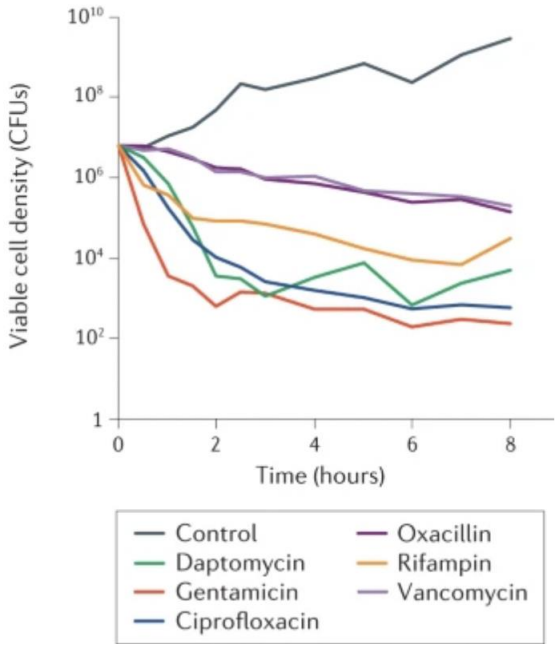


CONUNDRUM #1:
CAN BACTERIOSTATIC ANTIBIOTICS BE USED TO TREAT BLOODSTREAM INFECTIONS?

DEFINITIONS

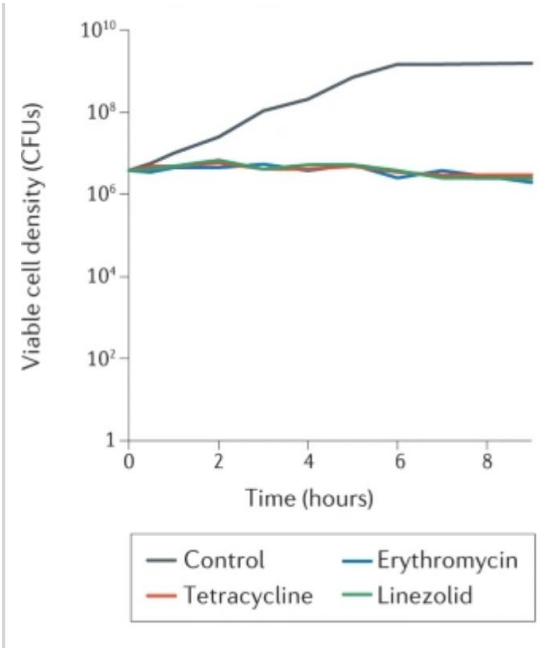
Bactericidal

- MBC/MIC ratio ≤ 4
- 99.9% reduction in the bacterial load



Bacteriostatic

- MBC/MIC ratio > 4
- *Less than 99.9% reduction in the bacterial load*



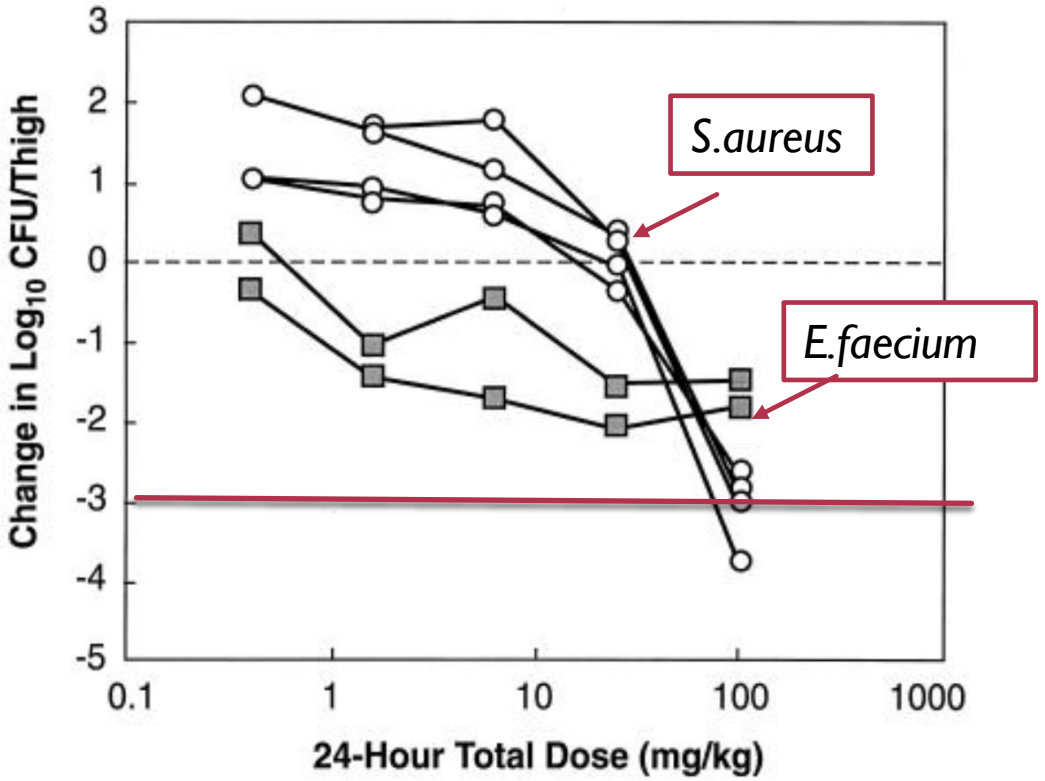
PACKAGE INSERT CLASSIFICATION OF ANTIBIOTICS

Bactericidal
Beta-lactams
Aminoglycosides
Fluoroquinolones
Daptomycin
Glycopeptides
Colistin

Bacteriostatic
Clindamycin
Tetracyclines*
Oxazolidinones*
*exceptions within class

BUT…A DRUG CAN BE BOTH CIDAL AND STATIC

- Cidal vs static activity is not an intrinsic property of antibiotics
- Some antibiotics are cidal OR static depending on organism:
  - **Linezolid:** static against enterococci and staphylococci; cidal against streptococci
  - **Vancomycin:** static against enterococci; cidal against staphylococci
  - **Daptomycin:** concentration dependent cidal activity against staphylococci



Safdar N. In vivo PD activity of daptomycin. Antimicrob Agents Chemother. 2004 Jan;48(1):63-8.

HISTORICAL APPROACH TO USING CIDAL VS STATIC

- **Cidal:**
  - Severe infections, difficult to treat infections, high organism burden
  - Immunocompromised patients

Bloodstream Infections
Endocarditis
Febrile Neutropenia

- **Static:**
  - Mild-moderate infections, uncomplicated, low organism burden
  - Immunocompetent patients

Uncomplicated UTI
Mild-mod SSTI

Bacteriostatic versus bactericidal antibiotics for patients with serious bacterial infections: systematic review and meta-analysis

Johannes Nemeth[1]*†, Gabriela Oesch[2]† and Stefan P. Kuster[1]†

- 33 studies, including over 9500 patients
  - ~50% of participants received bacteriostatic monotherapy
- Infection type:
  - PNA (13)
  - SSTI (8)
  - IAI (4)
  - Other (8)

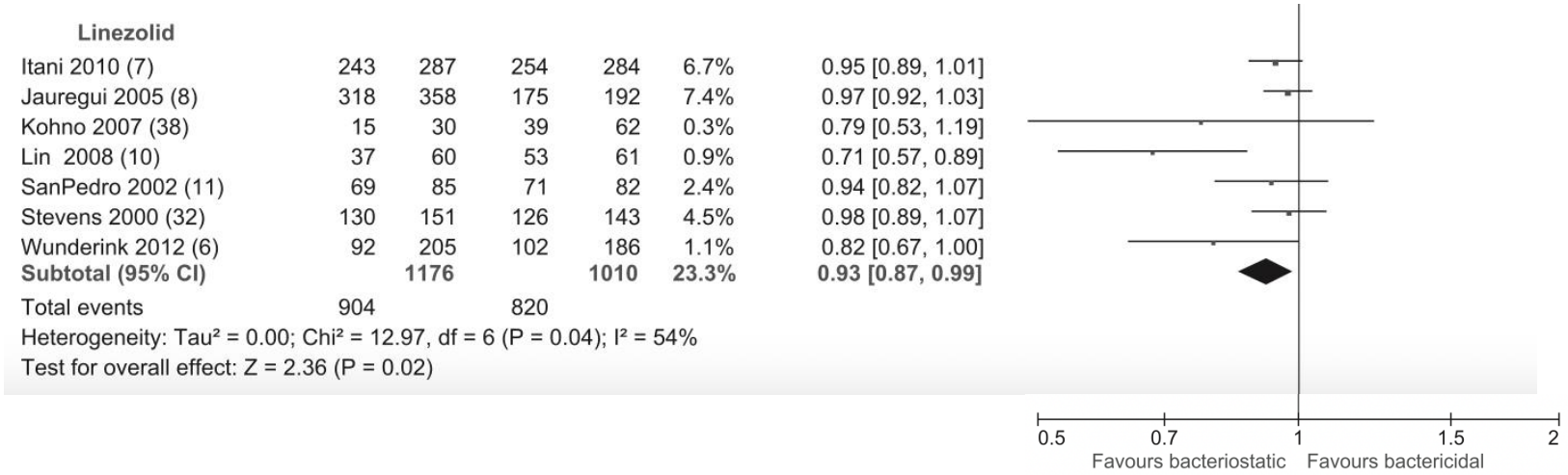
- No difference in clinical cure rates
  - RR, 0.99; 95% CI, 0.97-1.01; P = 0.11
- No difference in mortality rates
  - RR, 0.91; 95% CI, 0.76-1.08; P = 0.28

J Antimicrob Chemother. 2015 Feb;70(2):382-95.

Bacteriostatic versus bactericidal antibiotics for patients with serious bacterial infections: systematic review and meta-analysis

Johannes Nemeth[1]*†, Gabriela Oesch[2]† and Stefan P. Kuster[1]†

- Subgroup analysis
  - Treatment with linezolid (STATIC) appeared to be with better clinical cure rates compared to comparator



Linezolid						
Itani 2010 (7)	243	287	254	284	6.7%	0.95 [0.89, 1.01]
Jauregui 2005 (8)	318	358	175	192	7.4%	0.97 [0.92, 1.03]
Kohno 2007 (38)	15	30	39	62	0.3%	0.79 [0.53, 1.19]
Lin 2008 (10)	37	60	53	61	0.9%	0.71 [0.57, 0.89]
SanPedro 2002 (11)	69	85	71	82	2.4%	0.94 [0.82, 1.07]
Stevens 2000 (32)	130	151	126	143	4.5%	0.98 [0.89, 1.07]
Wunderink 2012 (6)	92	205	102	186	1.1%	0.82 [0.67, 1.00]
Subtotal (95% CI)		**1176**		**1010**	**23.3%**	**0.93 [0.87, 0.99]**
Total events	904		820			

Heterogeneity: Tau² = 0.00; Chi² = 12.97, df = 6 (P = 0.04); I² = 54%

Test for overall effect: Z = 2.36 (P = 0.02)

J Antimicrob Chemother. 2015 Feb;70(2):382-95.

Clinical Infectious Diseases
INVITED ARTICLE

Busting the Myth of "Static vs Cidal": A Systemic Literature Review

Noah Wald-Dickler,[1,2] Paul Holtom,[1,2] and Brad Spellberg[1,2]

[1]Los Angeles County + University of Southern California Medical Center and [2]Division of Infectious Diseases, Keck School of Medicine at the University of Southern California, Los Angeles

- 56 Randomized control trials
- Patients with serious, or life-threatening bacterial infections
  - **No difference in efficacy between static vs cidal: 49**
    - Included bacteremia, typhoid fever, plague, and pneumonia
  - **Bacteriostatic MORE effective: 6**
  - **Bactericidal MORE effective: 1**
    - Tigecycline vs imipenem for VAP
    - Tigecycline dose used was too low --> subsequent trial with optimized tigecycline dosing showed similar efficacy

Clin Infect Dis. 2018 Apr 17;66(9):1470-1474.

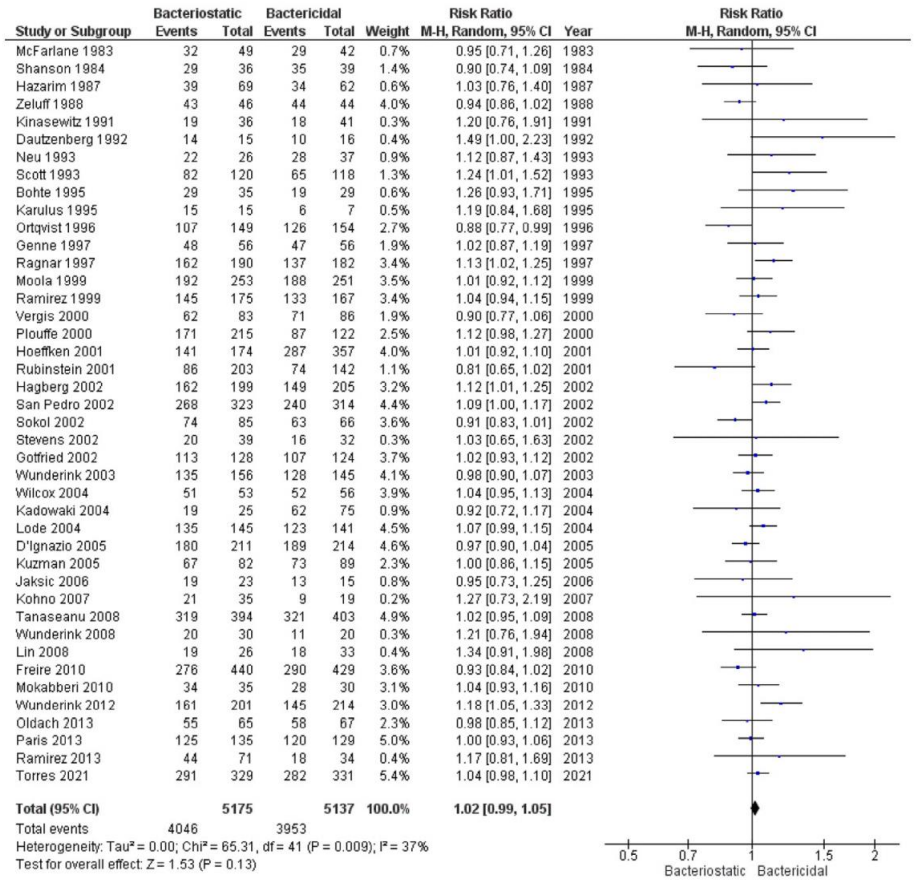
Systematic review

Mortality and clinical cure rates for pneumonia: a systematic review, meta-analysis, and trial sequential analysis of randomized control trials comparing bactericidal and bacteriostatic antibiotic treatments

CMI CLINICAL MICROBIOLOGY AND INFECTION
ESCMID

- Systematic review and meta-analysis of RCTs comparing bactericidal to bacteriostatic antibiotics in adults with bacterial pneumonia to determine clinical superiority
  - Primary outcome: clinical cure rates
  - Secondary outcomes: all-cause mortality, microbiologic cure, treatment failure, relapse rates
- 43 RTCs including 10,752 patients
- **Primary and secondary outcomes similar between bactericidal and bacteriostatic antibiotics**

(a) Effect of bactericidal and bacteriostatic antibiotics on clinical cure rate in included trials



Study or Subgroup	Bacteriostatic Events	Total	Bactericidal Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
McFarlane 1983	32	49	29	42	0.7%	0.95 [0.71, 1.26]	1983
Shanson 1984	29	36	35	39	1.4%	0.90 [0.74, 1.09]	1984
Hazarim 1987	39	69	34	62	0.6%	1.03 [0.76, 1.40]	1987
Zeluff 1988	43	46	44	44	4.0%	0.94 [0.86, 1.02]	1988
Kinasewitz 1991	19	36	18	41	0.3%	1.20 [0.76, 1.91]	1991
Dautzenberg 1992	14	15	10	16	0.4%	1.49 [1.00, 2.23]	1992
Neu 1993	22	26	28	37	0.9%	1.12 [0.87, 1.43]	1993
Scott 1993	82	120	65	118	1.3%	1.24 [1.01, 1.52]	1993
Bohte 1995	29	35	19	29	0.6%	1.26 [0.93, 1.71]	1995
Karulus 1995	15	15	6	7	0.5%	1.19 [0.84, 1.68]	1995
Ortqvist 1996	107	149	126	154	2.7%	0.88 [0.77, 0.99]	1996
Genne 1997	48	56	47	56	1.9%	1.02 [0.87, 1.19]	1997
Ragnar 1997	162	190	137	182	3.4%	1.13 [1.02, 1.25]	1997
Moola 1999	192	253	188	251	3.5%	1.01 [0.92, 1.12]	1999
Ramirez 1999	145	175	133	167	3.4%	1.04 [0.94, 1.15]	1999
Vergis 2000	62	83	71	86	1.9%	0.90 [0.77, 1.06]	2000
Plouffe 2000	171	215	87	122	2.5%	1.12 [0.98, 1.27]	2000
Hoeffken 2001	141	174	287	357	4.0%	1.01 [0.92, 1.10]	2001
Rubinstein 2001	86	203	74	142	1.1%	0.81 [0.65, 1.02]	2001
Hagberg 2002	162	199	149	205	3.2%	1.12 [1.01, 1.25]	2002
San Pedro 2002	268	323	240	314	4.4%	1.09 [1.00, 1.17]	2002
Sokol 2002	74	85	63	66	3.6%	0.91 [0.83, 1.01]	2002
Stevens 2002	20	39	16	32	0.3%	1.03 [0.65, 1.63]	2002
Gotfried 2002	113	128	107	124	3.7%	1.02 [0.93, 1.12]	2002
Wunderink 2003	135	156	128	145	4.1%	0.98 [0.90, 1.07]	2003
Wilcox 2004	51	53	52	56	3.9%	1.04 [0.95, 1.13]	2004
Kadowaki 2004	19	25	62	75	0.9%	0.92 [0.72, 1.17]	2004
Lode 2004	135	145	123	141	4.5%	1.07 [0.99, 1.15]	2004
D'Ignazio 2005	180	211	189	214	4.6%	0.97 [0.90, 1.04]	2005
Kuzman 2005	67	82	73	89	2.3%	1.00 [0.86, 1.15]	2005
Jaksic 2006	19	23	13	15	0.8%	0.95 [0.73, 1.25]	2006
Kohno 2007	21	35	9	19	0.2%	1.27 [0.73, 2.19]	2007
Tanaseanu 2008	319	394	321	403	4.9%	1.02 [0.95, 1.09]	2008
Wunderink 2008	20	30	11	20	0.3%	1.21 [0.76, 1.94]	2008
Lin 2008	19	26	18	33	0.4%	1.34 [0.91, 1.98]	2008
Freire 2010	276	440	290	429	3.6%	0.93 [0.84, 1.02]	2010
Mokabberi 2010	34	35	28	30	3.1%	1.04 [0.93, 1.16]	2010
Wunderink 2012	161	201	145	214	3.0%	1.18 [1.05, 1.33]	2012
Oldach 2013	55	65	58	67	2.3%	0.98 [0.85, 1.12]	2013
Paris 2013	125	135	120	129	5.0%	1.00 [0.93, 1.06]	2013
Ramirez 2013	44	71	18	34	0.4%	1.17 [0.81, 1.69]	2013
Torres 2021	291	329	282	331	5.4%	1.04 [0.98, 1.10]	2021
Total (95% CI)		**5175**		**5137**	**100.0%**	**1.02 [0.99, 1.05]**	
Total events	4046		3953				

Heterogeneity: Tau² = 0.00; Chi² = 65.31, df = 41 (P = 0.009); I² = 37%
Test for overall effect: Z = 1.53 (P = 0.13)

Risk Ratio M-H, Random, 95% CI
0.5 0.7 1 1.5 2
Bacteriostatic Bactericidal

Clin Microbiol Infect. 2022 Jul; 28 (7):936-945.

KEY CONSIDERATIONS IN TREATING BSI

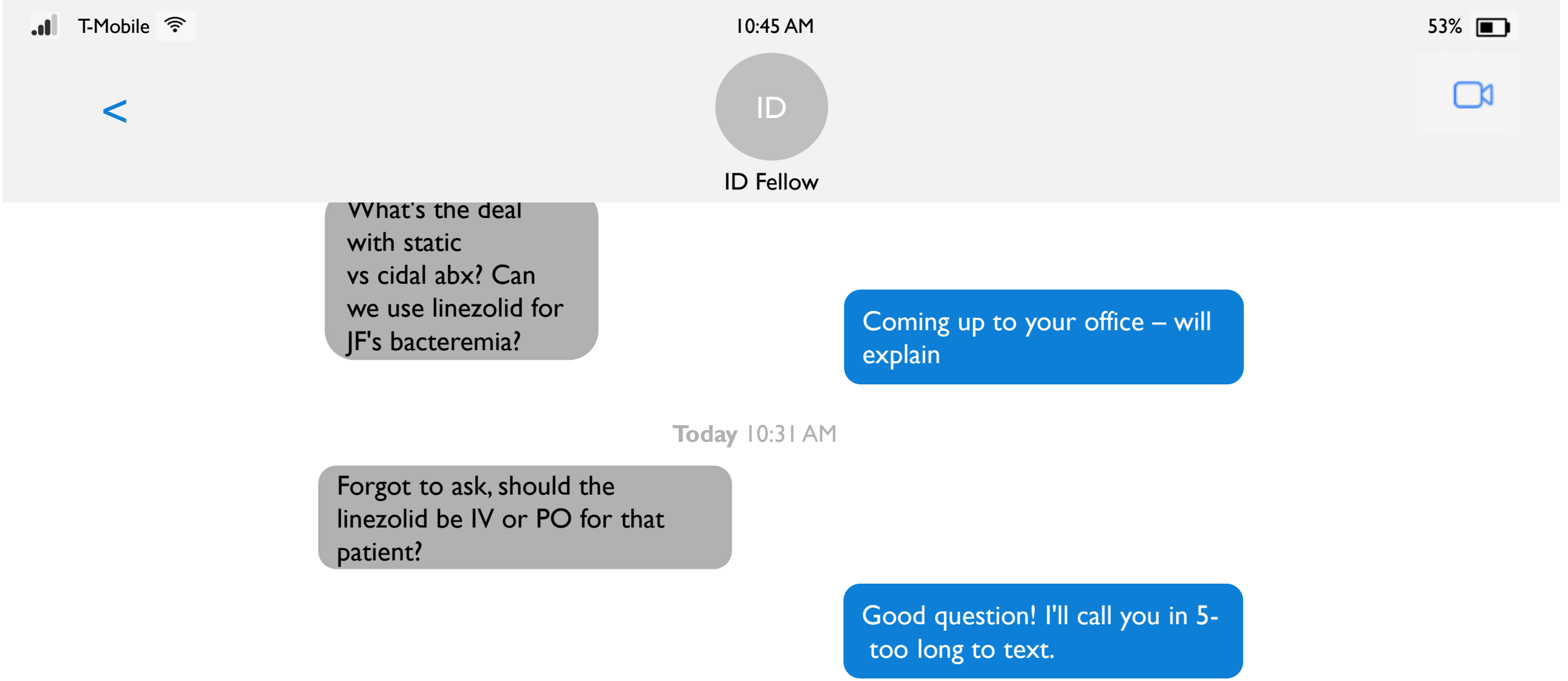
Microbiologic definitions of cidal & static alone (in-vitro activities) don't necessarily translate to clinical activity!

- Microbiologic Factors:
  - Specific pathogen
  - In-vitro activity
  - MICs
  - Antibiotic breakpoints
  - Resistance mechanisms
- Drug Factors:
  - PK
  - PD
  - Therapeutic drug monitoring
  - Dose/frequency optimization
  - Drug-drug interactions
- Patient Factors:
  - Clinical outcomes data
  - Source of infection
  - Severity of infection
  - Immune function
  - Co-morbid conditions

WHERE DOES THAT LEAVE US?

*Bactericidal antibiotics **are NOT essential** to the treatment of bloodstream and other difficult to treat infections;*

clinically effective agents are.



CONUNDRUM #2:
CAN ORAL ANTIBIOTICS BE USED FOR OM OR BSI?

HISTORICAL APPROACH TO TREATMENT

- Intravenous antibiotic therapy assumed to be needed to treat difficult to manage infections like OM and BSI
  - IV therapy is 100% bioavailable --> better antibiotic concentrations at the site of infection --> better treatment outcomes?

- Assumption is based on early studies from the 1940s-1950s in OM where the authors concluded successful treatment was rare without prolonged course IV therapy
  - Uncontrolled, patient case series
  - Used antibiotics with poor PO bioavailability (sulfanilamide, erythromycin)

Spellberg B. Systemic antibiotic therapy for chronic osteomyelitis in adults. Clin Infect Dis. 2012 Feb 1;54(3):393-407.

THE AMERICAN JOURNAL of MEDICINE.
Official Journal of the Alliance for Academic Internal Medicine

Oral Is the New IV. Challenging Decades of Blood and Bone Infection Dogma: A Systematic Review

- Systematic review of published, prospective controlled trials that compared IV-only therapy to oral step-down regimens in the treatment of:
  - Bone infections (n=8)
  - Blood infections (n=10)
  - Infective endocarditis (n=3)

Am J Med. 2022 Mar; 135 (3): 369-379.

ORAL STEP-DOWN FOR OM

- 8 randomized controlled trials including 1,321 patients comparing IV-only therapy to oral step-down:
  - Only adults included
  - Majority of trials excluded axial OM
    - ~39 patients with vertebral OM
  - 4 of the trials included patients with infected hardware
  - No trials included OM underlying a decubitus ulcer

- <u>Microbiology:</u>
  - *Staphylococcus* most common, followed by *Pseudomonas*

- <u>Antibiotic regimens:</u>
  - PO fluoroquinolone +/- rifampin vs various IV regimens (n=6)
  - PO TMP/SMX + rifampin vs IV cloxacillin (n=1)
  - Various PO regimens (fluoroquinolones, combinations, macrolides, lincosamides, penicillins) vs standard IV regimens (n=1)

Am J Med. 2022 Mar; 135 (3): 369-379.

ORAL STEP-DOWN FOR OM

- Outcomes:
  - **Similar success rates between IV and PO groups: 6**
  - **Superiority of PO over IV: 1**
    - 69% vs 50% for oral ofloxacin over IV imipenem/cilastatin
  - Severe drug reactions were either similar in among both groups, or more frequent in the IV group
    - In the largest trial included, IV arm had significantly more severe adverse effects (line complications, decreased patient satisfaction, longer hospital stays)

Am J Med. 2022 Mar; 135 (3): 369-379.

ORAL STEP DOWN FOR OM

Study or Subgroup	Oral Events	Oral Total	IV Events	IV Total	Weight	Risk Difference M-H, Random, 95% CI	Year
Greenberg 1987	7	14	11	16	1.2%	-0.19 [-0.53, 0.16]	1987
Mader 1990	11	14	10	12	1.7%	-0.05 [-0.35, 0.25]	1990
Gentry 1990	24	31	22	28	3.3%	-0.01 [-0.22, 0.20]	1990
Gentry 1991	14	19	12	14	2.1%	-0.12 [-0.39, 0.15]	1991
Gomis 1999	11	16	8	16	1.3%	0.19 [-0.15, 0.52]	1999
Schrenzel 2004	18	22	11	17	1.9%	0.17 [-0.11, 0.45]	2004
Euba 2009	17	21	21	27	2.8%	0.03 [-0.20, 0.26]	2009
Li 2019	457	527	450	527	85.6%	0.01 [-0.03, 0.06]	2019
Total (95% CI)		**664**		**657**	**100.0%**	**0.01 [-0.03, 0.05]**	
Total events	559		545				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.74$, df = 7 (P = 0.69); $I^2 = 0\%$

Test for overall effect: Z = 0.61 (P = 0.54)

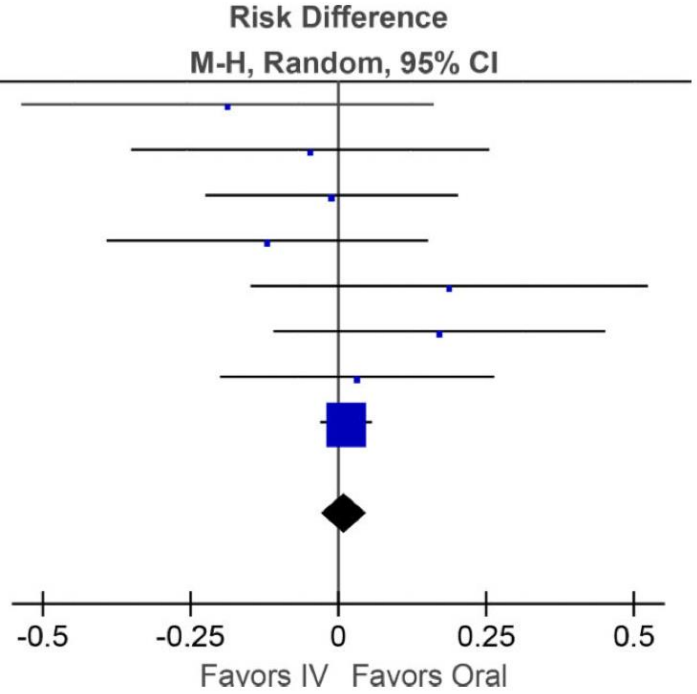


Figure 2. Meta-Analysis Forest Plot of Osteomyelitis Treatment Success.
Overall treatment success was not significantly different.

THE AMERICAN JOURNAL of MEDICINE
Official Journal of the Alliance for Academic Internal Medicine

Oral Is the New IV. Challenging Decades of Blood and Bone Infection Dogma: A Systematic Review

- Systematic review of published, prospective controlled trials that compared IV-only therapy to oral step-down regimens in the treatment of:
  - Bone infections (n=8)
  - Blood infections (n=10)
  - Infective endocarditis (n=3)

Am J Med. 2022 Mar; 135 (3): 369-379.

ORAL THERAPY FOR BSI

- 10 RCTs including 705 patients randomized to PO or IV therapy for non-endocarditis bacteremia:
  - 7 included only adults
  - 2 included only children
  - 1 included only neonates

- <u>Source of infection:</u>
  - Urinary, respiratory, skin and soft tissue, biliary, catheter-related and primary/unknown

- <u>Microbiology:</u>
  - Gram positive
    - Equal distribution of MRSA, MSSA, enterococci, CoNS, and streptococci
  - Gram negative
    - *E.coli* most common, followed by *K.pneumoniae*

Am J Med. 2022 Mar; 135 (3): 369-379.

ORAL THERAPY FOR BSI

- Outcomes:
  - **No difference** between oral and IV arms: **6**
  - **Higher rates of success** with oral versus IV (non-significant): **2**
  - **Higher rates of success** with oral versus IV (significant): **2**

  - **Shorter length of hospital stay** with oral vs IV (1.5-11 days shorter): **3**
  - **Similar rates of adverse drug events** with oral and IV: **5**

Am J Med. 2022 Mar; 135 (3): 369-379.

ORAL THERAPY FOR BSI

Study or Subgroup	Oral Events	Oral Total	IV Events	IV Total	Weight	Risk Difference M-H, Random, 95% CI	Year
Greenberg 1987	7	14	11	16	1.2%	-0.19 [-0.53, 0.16]	1987
Mader 1990	11	14	10	12	1.7%	-0.05 [-0.35, 0.25]	1990
Gentry 1990	24	31	22	28	3.3%	-0.01 [-0.22, 0.20]	1990
Gentry 1991	14	19	12	14	2.1%	-0.12 [-0.39, 0.15]	1991
Gomis 1999	11	16	8	16	1.3%	0.19 [-0.15, 0.52]	1999
Schrenzel 2004	18	22	11	17	1.9%	0.17 [-0.11, 0.45]	2004
Euba 2009	17	21	21	27	2.8%	0.03 [-0.20, 0.26]	2009
Li 2019	457	527	450	527	85.6%	0.01 [-0.03, 0.06]	2019
Total (95% CI)		**664**		**657**	**100.0%**	**0.01 [-0.03, 0.05]**	
Total events	559		545				

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Test for overall effect: Z = 0.61 (P = 0.54)

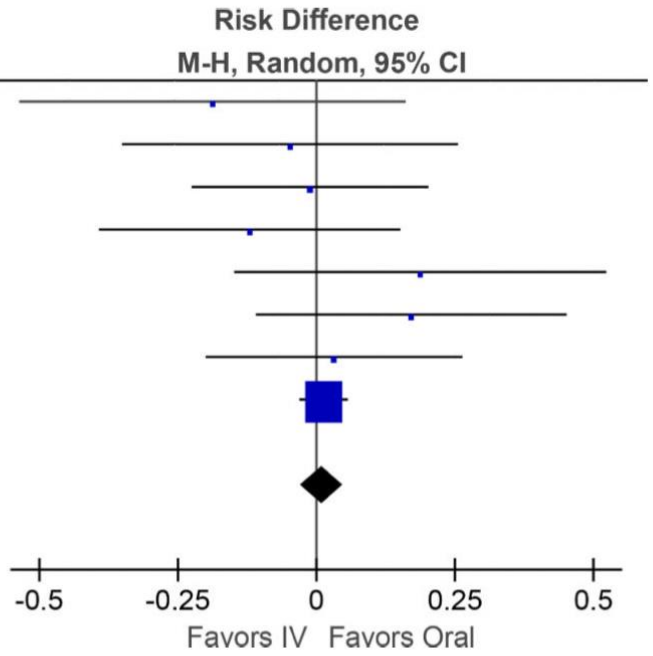


Figure 3. Meta-Analysis Forest Plot of Bacteremia Treatment Success.
Overall treatment success was not significantly different, although the confidence interval favored oral therapy.

Early Oral Switch to Linezolid for Low-risk Patients With *Staphylococcus aureus* Bloodstream Infections: A Propensity-matched Cohort Study

Clinical Infectious Diseases

MAJOR ARTICLE

- Cohort study comparing efficacy, safety, and length of hospitalization for SAB in patients receiving standard IV therapy (n=90) versus those switched to PO linezolid (n=45) on days 3-9 of treatment until completion

- Low risk defined as:
  - Clinically stable, appropriate source control, negative follow-up blood cultures

- Source of bacteremia:
  - Catheter related (~55%), SSTI (~16%), PNA (~10%)

Clin Infect Dis. 2019 Jul 18;69(3):381-387.

Early Oral Switch to Linezolid for Low-risk Patients With *Staphylococcus aureus* Bloodstream Infections: A Propensity-matched Cohort Study

Clinical Infectious Diseases

MAJOR ARTICLE

- Outcomes:
  - No difference in relapse rates between standard IV and linezolid PO (4.4% vs 2.2%)
  - 30 day all-cause mortality lower in linezolid PO vs standard IV (2.2% vs 13.3%; *P* = .08 - not significant)
  - Median length of stay shorter in linezolid PO group bs standard IV (8 days vs 19 days, P <.01)

Table 2. Outcomes in Adult Patients With *Staphylococcus aureus* Bacteremia Comparing Treatment With Early Oral Switch to Linezolid and Standard Parenteral Treatment

	Whole Cohort			Propensity Score–matched Cohort		
Outcome	Oral Linezolid (n = 45)	Standard Treatment (n = 107)	*P* Value	Oral Linezolid (n = 45)	Standard Treatment (n = 90)	*P* Value
90-d relapse in survivors	1 (2.2)	4 (3.7)	1.00	1 (2.2)	4 (4.4)	.87
14-d mortality	0 (0.0)	10 (9.3)	.08	0 (0.0)	6 (6.7)	.18
30-d mortality	1 (2.2)	17 (15.9)	.04	1 (2.2)	12 (13.3)	.08
Length of hospital stay after index culture, d, median (IQR)[a]	8 (7–10)	19 (15–32)	<.01	8 (7–10)	19 (15–30)	<.01

Clin Infect Dis. 2019 Jul 18;69(3):381-387.

JAMA Internal Medicine | Original Investigation | LESS IS MORE

Association of 30-Day Mortality With Oral Step-Down vs Continued Intravenous Therapy in Patients Hospitalized With Enterobacteriaceae Bacteremia

- Retrospective cohort study of 2,161 patients with Enterobacterales bacteremia who received IV only tx vs oral-step down

- PO step-down patients were:
  - Less likely to be neutropenic
  - Less severely ill at onset of bacteremia
  - Less likely to need ICU level care
  - Propensity score matching used to account for differences in baseline demographics

- Source of bacteremia:
  - UTI (40.2%)
  - GI (20.1%)
  - Catheter-associated (18.4%)
  - Biliary (14.2%)
  - Pulmonary (3.9%)

- Microbiology:
  - *E.coli* (43.6%)
  - *Klebsiella* spp. (35.7%)
  - *Enterobacter* spp. (11.7%)

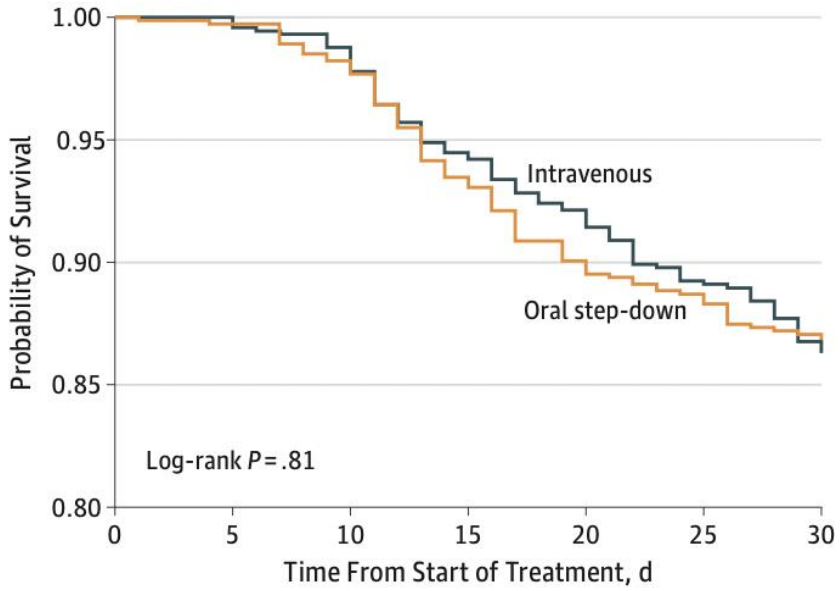
JAMA Intern Med. 2019;179(3):316-323.

JAMA Internal Medicine | Original Investigation | LESS IS MORE

Association of 30-Day Mortality With Oral Step-Down vs Continued Intravenous Therapy in Patients Hospitalized With Enterobacteriaceae Bacteremia

- 97 deaths in PO step down within 30 days vs 99 in IV
- No difference in rates of recurrent bacteremia
- Shorter time from bacteremia to hospital discharge in PO step down group than IV (5 days vs 7 days)

Figure 3. Probability of 30-Day Survival in the Propensity Score–Matched Cohort



No. at risk							
Intravenous	739	739	730	699	682	661	640
Oral step-down	739	739	726	691	666	656	642

JAMA Intern Med. 2019;179(3):316-323.

KEY CONSIDERATIONS IN PO FOR OM OR BSI

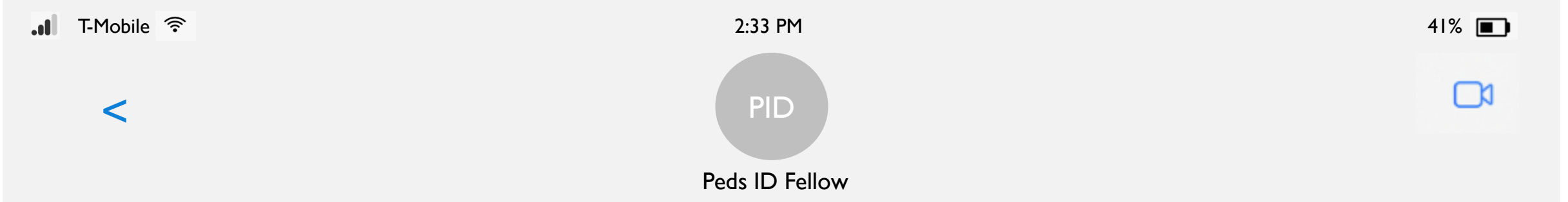
IV versus PO is not the only factor in determining success of antibiotic treatment!

- Microbiologic Factors:
  - Specific pathogen
  - In-vitro activity
  - MICs
  - Antibiotic breakpoints
  - Resistance mechanisms
- Drug Factors:
  - PK
  - PD
  - Therapeutic drug monitoring
  - Dose/frequency optimization
  - Drug-drug interactions
- Patient Factors:
  - Clinical outcomes data
  - Source of infection
  - Severity of infection
  - Immune function
  - Co-morbid conditions

WHERE DOES THAT LEAVE US?

*IV only therapy **is NOT essential** to the treatment of OM or BSI;*

oral therapy is at least as effective as IV only



CONUNDRUM #3:
CAN DOXYCYCLINE BE USED IN PEDIATRICS LESS THAN 8 YEARS OLD?

TETRACYCLINE TIMELINE

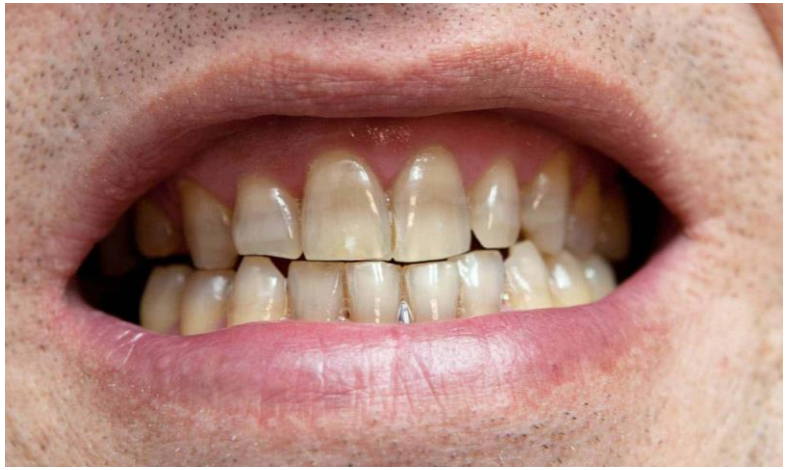
- Discovered as natural products from actinomycetes soil bacteria in late 1940s
- MOA: inhibit protein synthesis by preventing the attachment of aminoacyl-tRNA to the ribosomal acceptor (A) site

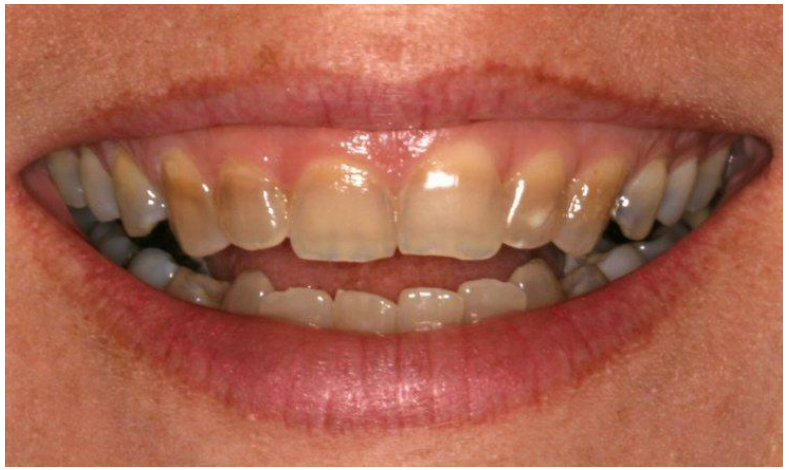
Generation	Tetracycline	FDA Approval
First	tetracycline	1954
Second	doxycycline, minocycline	1967, 1971
Third	tigecycline omadacycline, sarecycline, eravacycline	2005 2018

NELSON ET AL. ANN N Y ACAD SCI. 2011;1241:17-32
RUSU ET AL. PHARMACEUTICS 2021:13(12);2085

TOOTH DISCOLORATION WITH TETRACYCLINE

- Gray or brown, deep, dark stains covers entire tooth or appear as horizontal stripes
- Permanent, embedded in tooth's enamel and inner layers
- May depend on degree of exposure, # of courses, total dosage, timing of tooth development
- Children susceptible from time they are in utero to 8 years old
- Avoid in pregnant women





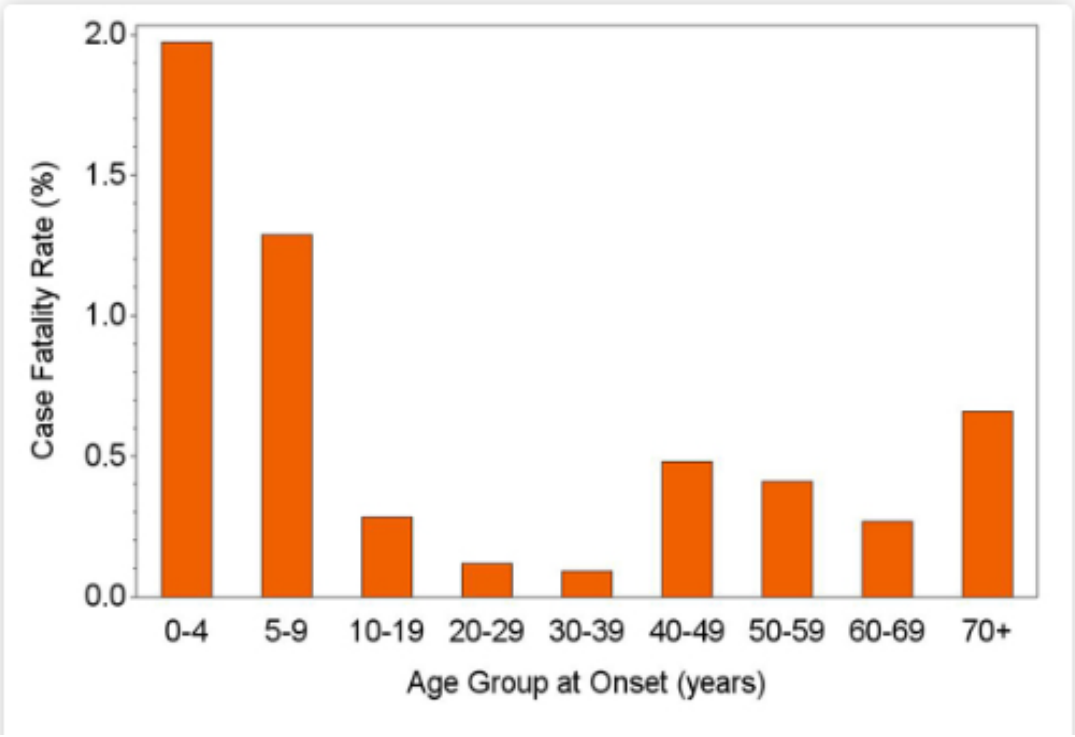
GROSSMAN ET AL. PEDIATRICS. 1971;47:567-570

THE USE OF DRUGS OF THE TETRACYCLINE CLASS DURING TOOTH DEVELOPMENT (LAST HALF OF PREGNANCY, INFANCY AND CHILDHOOD TO THE AGE OF 8 YEARS) MAY CAUSE PERMANENT DISCOLORATION OF THE TEETH (YELLOW -GRAY -BROWN). This adverse reaction is more common during long-term use of the drugs but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. TETRACYCLINE DRUGS, THEREFORE, SHOULD NOT BE USED IN THIS AGE GROUP UNLESS OTHER DRUGS ARE NOT LIKELY TO BE EFFECTIVE OR ARE CONTRAINDICATED.

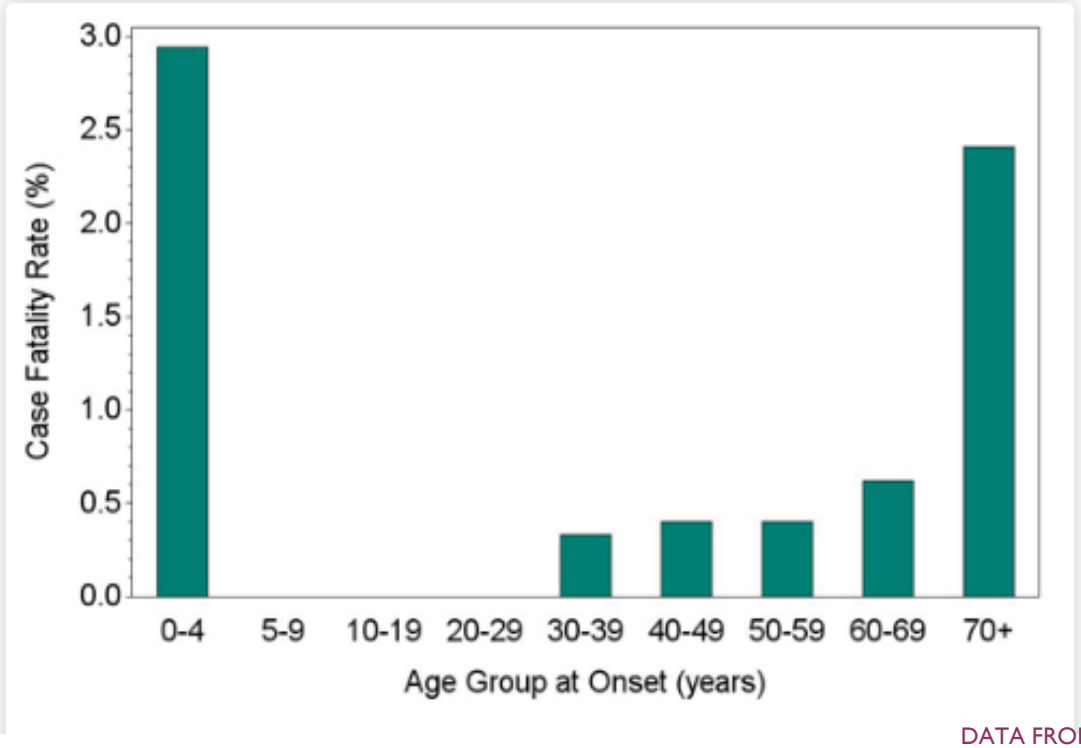
FDA WARNING FOR ALL TETRACYCLINES (1970)

HIGHER FATALITY IN CHILDREN WITH RICKETTSIAL DISEASES

Case Fatality Rate of Spotted Fever Rickettsiosis by Age Group, 2008-2013



Case Fatality Rate of *Ehrlichia chaffeensis* by Age Group, 2008-2013



DATA FROM CDC

PRESCRIBING PATTERNS IN RICKETTSIAL DISEASES

Self-Reported Treatment Practices by Healthcare Providers Could Lead to Death from Rocky Mountain Spotted Fever

Jillian Zientek, DVM[1], **F. Scott Dahlgren, MSPH**[2], **Jennifer H. McQuiston, DVM**[2], and **Joanna Regan, MD**[2]

[1]The Ohio State University, College of Veterinary Medicine, Columbus, OH

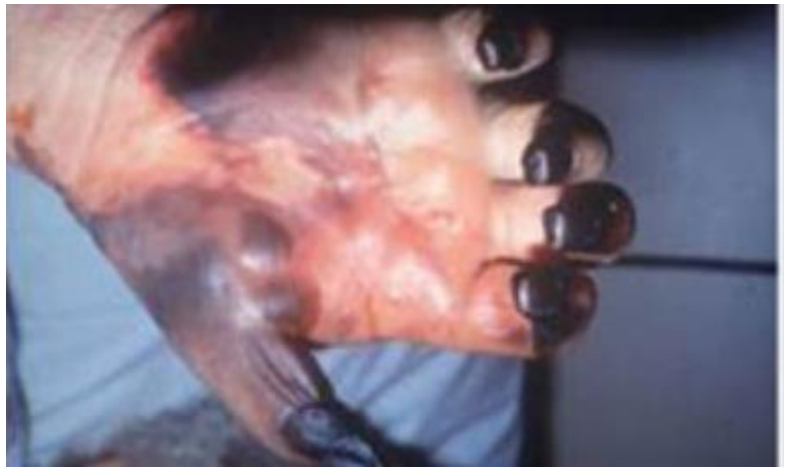
[2]Rickettsial Zoonoses Branch, Division of Vectorborne Diseases, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA

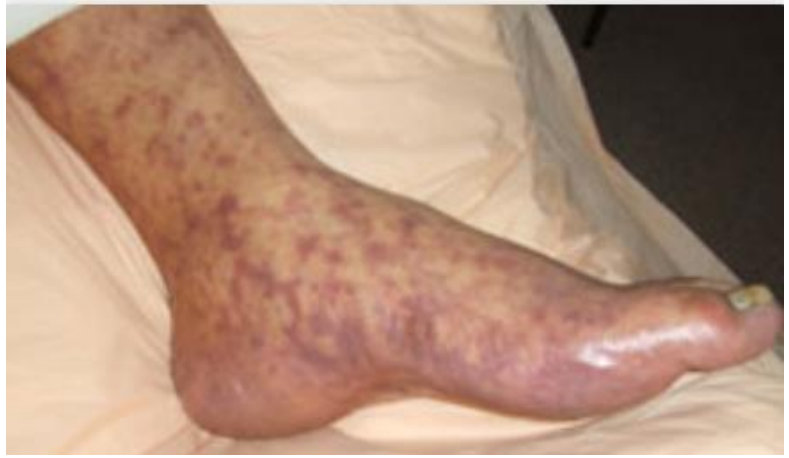
J Pediatr. 2014 February ; 164(2): 416–418. doi:10.1016/j.jpeds.2013.10.008.

- National survey conducted in 2012 on general practitioners and internists
- Majority (80%) correctly selected doxycycline as treatment of choice for Rocky Mountain Spotted Fever in >8 years old
- Only 35% correctly chose doxycycline as treatment of choice for <8 years old
- May contribute to increased fatality rate among children

RICKETTSIAL DISEASES

- Spread through ticks, mites, fleas, or lice
- Begins with non-specific symptoms (fever, headache, and GI illness)
- Rash develops 2-5 days after start of symptoms
- Progresses rapidly into severe illness requiring hospitalization (damage to blood vessels, organ failure, amputation of extremities, and neurological deficits)
- >20% of untreated cases of Rocky Mountain Spotted Fever (RMSF) are fatal
- No rapid diagnosis test, clinicians must treat based on clinical suspicion alone
- Doxycycline is most effective when given within 5 days of illness!





IMAGES FROM CDC

ORIGINAL ARTICLES

www.jpeds.com • THE JOURNAL OF PEDIATRICS

No Visible Dental Staining in Children Treated with Doxycycline for Suspected Rocky Mountain Spotted Fever

Suzanne R. Todd, DVM[1], F. Scott Dahlgren, MSPH[1], Marc S. Traeger, MD[2], Eugenio D. Beltrán-Aguilar, DMD, DrPH[3], Donald W. Marianos, DDS[1], Charlene Hamilton, MPH[4], Jennifer H. McQuiston, DVM[1], and Joanna J. Regan, MD[1]

- Conducted by CDC and Indian Health Services
- Evaluated whether dental staining occurred in children <8 years who lived on an American Indian reservations with high incidence of RMSF who were treated with doxycycline
- Compared 58 children who received an average of 1.8 courses of doxycycline before 8 years old and who had exposed permanent teeth to 213 children who never received doxycycline

ORIGINAL ARTICLES

www.jpeds.com • THE JOURNAL OF PEDIATRICS

No Visible Dental Staining in Children Treated with Doxycycline for

Suzanne R. To… MD, DrPH[3], Donald W. M… gan, MD[1]

- Conducted b…
- Evaluated wh… an reservations …
- Compared 58 … d and who had exposed …

- No tetracycline-like staining observed in any of the exposed children's teeth (0/58, 95% CI 0%-5%)
- No significant difference in tooth shade (P = .20) or hypoplasia (P = 1.0) found between the 2 groups

INCIDENCE OF TOOTH DISCOLORATION IN CHILDREN <8 YEARS WHO RECEIVED TETRACYCLINE

Reference	Antibiotic (duration)	Study population	Proportion (%) exposed with stained teeth
Shwachman et al. Antibiot Annu 1958;6:692-9.	Chlortetracycline and oxytetracycline (long-term)	Cystic fibrosis	40/50 (80%)
Wallman and Hilton. Lancet 1962;1: 827-9.	Tetracycline (short-term)	Neonates	46/50 (92%)
Swallow et al. Arch Dis Child 1967;42:311-8.	Chlortetracycline, tetracycline, and oxytetracycline (long-term)	Cystic fibrosis	24/63 (38%)
Conchi et al. Can Med Assoc J 1970; 103:351-6.	Mixed tetracyclines (unknown duration)	Children who received drug <6 years and who are now 8-11 years	55/238 (23%)
Rebich et al. J Am Dental Assoc 1983;106:630-3.	Mixed tetracyclines (unknown duration)	American Indian children 4-19 years	55/137 (40%)
Volovitz et al. Clin Pediatr 2007;46:121-6.	Doxycycline (short-term)	Asthma	0/31 (0%)

TODD ET AL. J PEDIATR 2015;166:1246-51

Commentary

Doxycycline and Tooth Discoloration in Children: Changing of Recommendations Based on Evidence of Safety

Annals of Pharmacotherapy
2019, Vol. 53(11) 1162–1166

DOI: 10.1177/1060028019863796
journals.sagepub.com/home/aop
SAGE

Jeremy S. Stultz, PharmD, BCPPS[1,2], and Lea S. Eiland, PharmD, BCPS, BCPPS, FASHP, FPPAG[3]

- PubMed Database using search terms "doxycycline" or "tetracycline" and "children" or "pediatric"
- Identified 6 studies from 1969 to 2017, included 338 patients with doxycycline exposure between the ages of 4 days and 8 years

INCIDENCE OF TOOTH DISCOLORATION IN CHILDREN <8 YEARS WHO RECEIVED DOXYCYCLINE

Out of 388 patients.....

- 1 patient born premature and exposed to doxycycline before 60 days of age — "slight spotted discoloration of upper incisors" noted at age 1
- 5 other patients had potential discoloration noted 1 year after treatment — authors considered as likely related to doxycycline

Impact of age and dosage.....

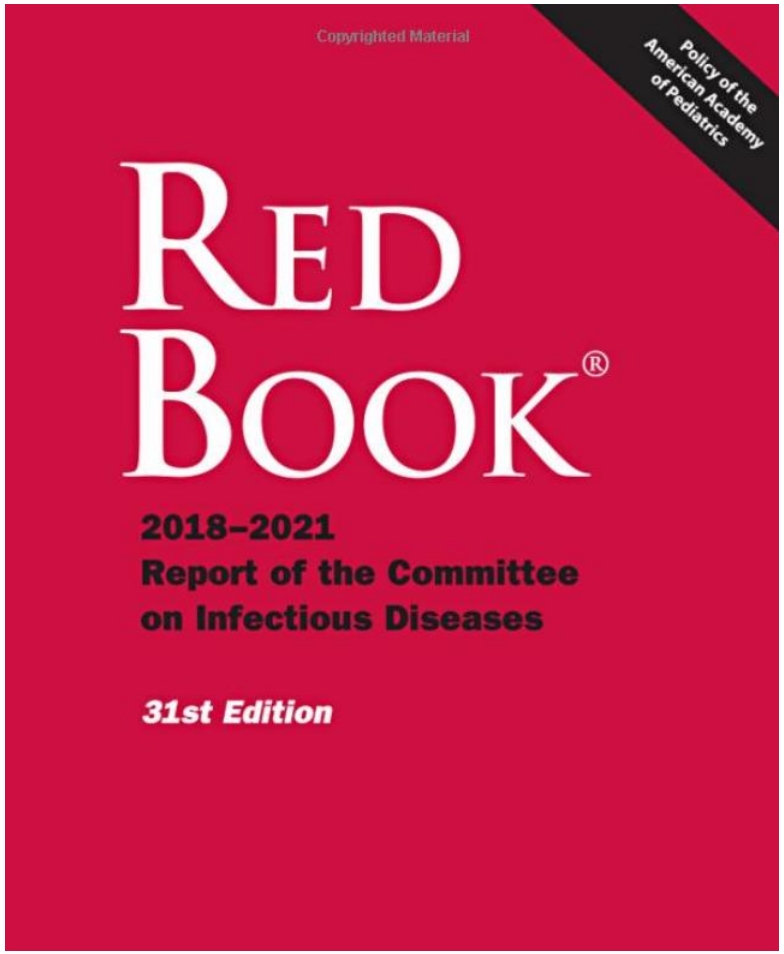
- 4 of the 6 possible tooth discolorations occurred in <2 years old
- However, based on more recent studies, age does not appear to increase risk of tooth discoloration

TETRACYCLINES & CALCIUM BINDING

- Tetracyclines stain teeth through their ability to form a complex with calcium ions via chelation
  - Greatest risk when drug exposure occurs during odontogenesis before complete formation of permanent teeth enamel with calcification (8 years old)
  - Tetracycline has higher calcium binding capacity compared with doxycycline (39.5% vs. 19%)
- Minocycline affects discoloration of teeth via different mechanism and occur at any age
  - Preferential binding to higher collagen containing tissue (ie, teeth and bone)
  - High concentration of minocycline excreted in gingival fluid that stains by etching onto the enamel and get oxidized
  - Chelation with iron forming insoluble complex with teeth

VON WITTENAU. CHEMOTHERAPIA (BASEL). 1968;13(SUPPL):41-50.
SANCHEZ ET AL. *INT J DERMATOL*. 2004;4:709-715
RAYMOND AND COOK. AUSTRALAS MED J. 2015; 8(4): 139–142.

RED BOOK UPDATED RECOMMENDATIONS



- "Doxycycline can be administered for short durations (ie, 21 days or less) without regard to the patient's age."
- Comments related to potential for tooth discoloration removed from doxycycline, remain for tetracycline

AMERICAN ACADEMY OF PEDIATRICS. TETRACYCLINES. IN: KIMBERLIN DW, BRADY MT, JACKSON MA, LONG SS, EDS. RED BOOK: 2018 REPORT OF THE COMMITTEE ON INFECTIOUS DISEASES. ELK GROVE VILLAGE, IL: AMERICAN ACADEMY OF PEDIATRICS; 2018: 905-906.

FDA INDICATIONS FOR DOXYCYCLINE

ADULTS

- Sexually transmitted, respiratory tract, ophthalmic, and rickettsial disease
- Anthrax
- Acute intestinal amebiasis
- Malaria prophylaxis
- Severe acne
- Plague, tularemia, cholera, bartonellosis, and brucellosis

PEDIATRICS

- Rickettsial diseases
- Q fever

What about.....

- SSTIs (impetigo, cellulitis, CA-MRSA, alternative to TMP/SMX)?
- CAP (atypicals, mycobacteria, macrolide-resistance, QT prolongation)?

WHERE DOES THIS LEAVE US?

CRACKING THE CODE ON ID CONUNDRUMS

QUESTIONS?

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