Antimicrobial Stewardship
- safest antibiotic at the right dose for the shortest duration

Grand Rounds April 17th, 2024

Edith Blondel-Hill

Objectives

Review:

- current situation with AROs
- safety of antibiotics
- optimal dosing of most commonly used antibiotics
- latest data on duration of antibiotics

Multi-resistant Organisms

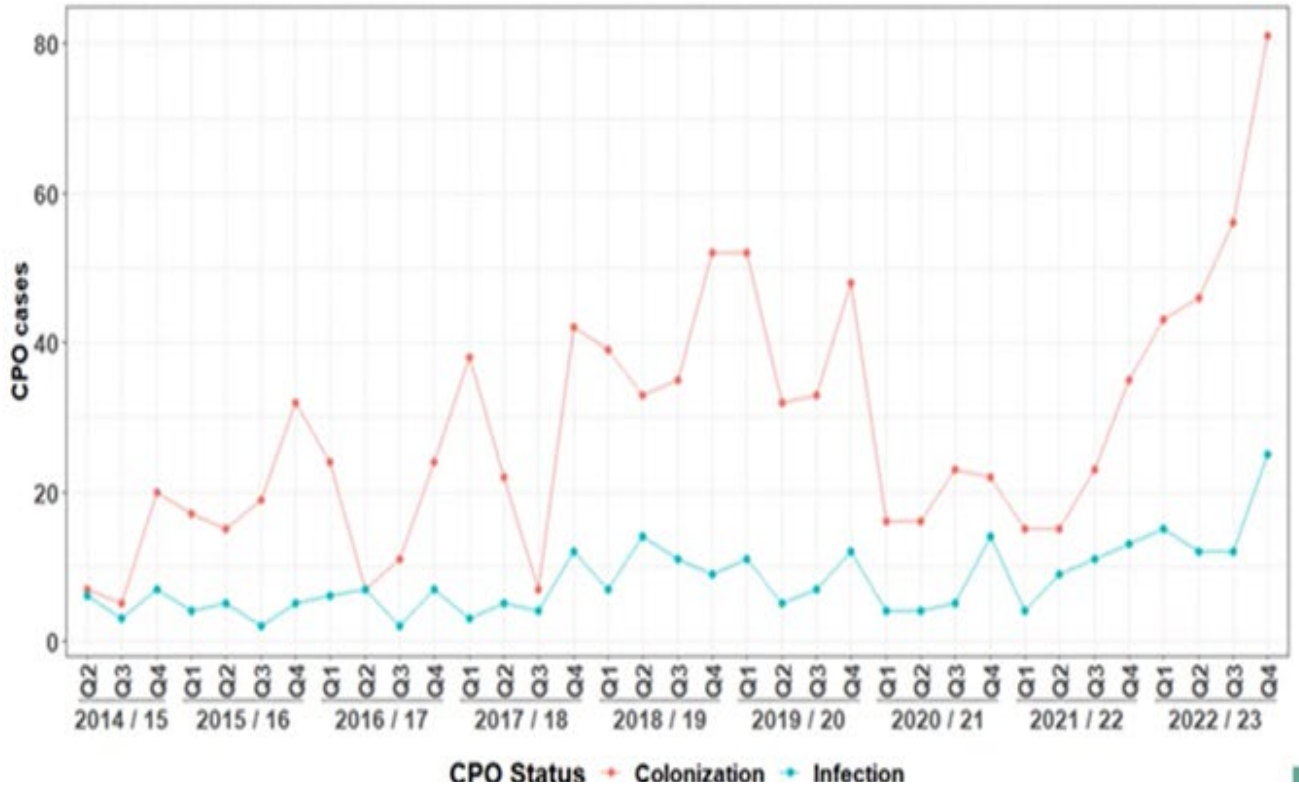
CURRENT STATE

BC Centre for Disease Control
Provincial Health Services Authority

PICNet
PROVINCIAL INFECTION CONTROL NETWORK OF BRITISH COLUMBIA
A program of the Provincial Health Services Authority

Provincial Health Services Authority

CPO cases by colonization/infection



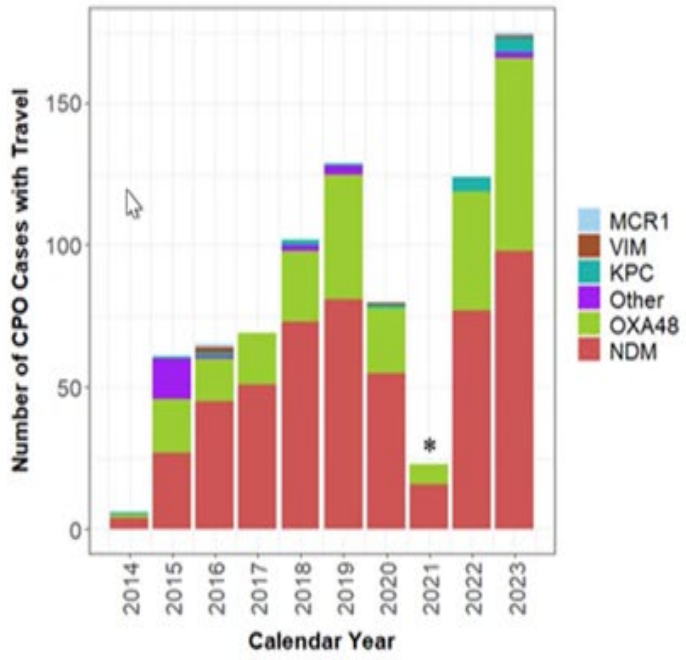
BC Centre for Disease Control
Provincial Health Services Authority

PICNet
PROVINCIAL INFECTION CONTROL NETWORK OF BRITISH COLUMBIA
A program of the Provincial Health Services Authority

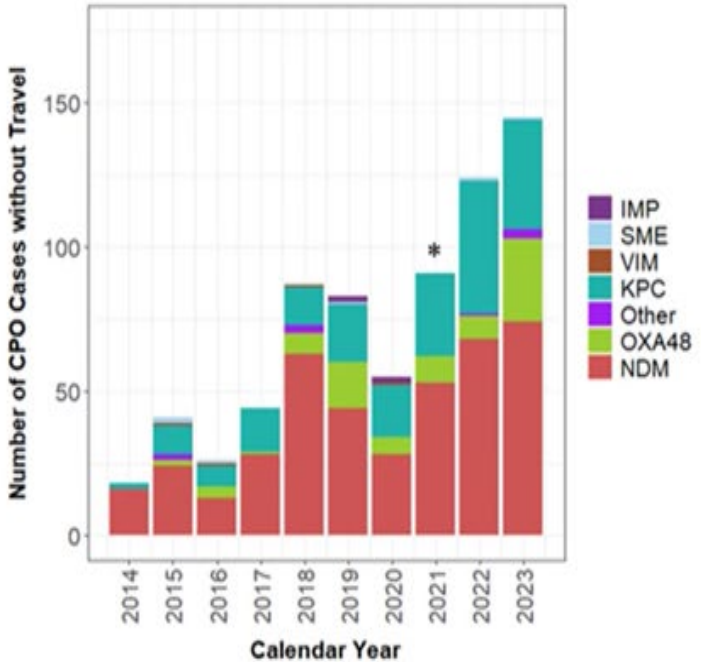
Provincial Health Services Authority

CPO Genes identified among cases in BC with or without travel

CPO cases in BC with travel history



CPO cases in BC without travel history



AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

Antimicrobial Chemotherapy | Full-Length Text

A multi-species outbreak of VIM-producing carbapenem-resistant bacteria in a burn unit and subsequent investigation of rapid development of cefiderocol resistance

Jeffrey A. Freiberg,[1,2] Lili Tao,[3] Carmila Manuel,[3] Laura A. Mike,[4] George E. Nelson,[1] Bryan D. Harris,[1] Amy J. Mathers,[5] Thomas R. Talbot,[1] Eric P. Skaar,[2,3] Romney M. Humphries[2,3]

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

Antimicrobial Chemotherapy | Short Form

Effect of modification of penicillin-binding protein 3 on susceptibility to ceftazidime-avibactam, imipenem-relebactam, meropenem-vaborbactam, aztreonam-avibactam, cefepime-taniborbactam, and cefiderocol of *Escherichia coli* strains producing broad-spectrum β-lactamases

Christophe Le Terrier,[1,2] Patrice Nordmann,[1,3] Chloé Buchs,[1] Laurent Poirel[1,2]

Candida auris

Multi-resistant *Candida species:*

CDC- urgent threat / highest level of concern

WHO - critical priority fungus

Global: reported in 50 countries / 6 continents

USA : ~8,000 cases in 2022 (clinical /screening cases)

- endemic in some areas
- healthcare transmission is responsible for majority of cases

Canada:

- 43 cases (up to 2022)

Interior Health:

- *C. auris* and enhanced CPO screening starting this spring

Worsening Spread of Candida auris in the United States, 2019 to 2021 | Annals of Internal Medicine (acpjournals.org)
Public Health Ontario. Candida auris; 2023 Candida auris (publichealthontario.ca)
Candida auris | Fungal Diseases | CDC

Safety of Antibiotics

NOT AS SAFE AS ADVERTISED

Review › Clin Microbiol Infect. 2022 Apr;28(4):479-490. doi: 10.1016/j.cmi.2021.10.022.
Epub 2021 Nov 12.

Estimating daily antibiotic harms: an umbrella review with individual study meta-analysis

Jennifer Curran [1], Jennifer Lo [2], Valerie Leung [3], Kevin Brown [4], Kevin L Schwartz [4], Nick Daneman [5], Gary Garber [6], Julie H C Wu [7], Bradley J Langford [8]

35 systemic reviews / 71 RCTs

> 23,000 patients

- 36.5% RTIs / 29.4% UTIs

Each day of antibiotic associated : 4% risk

Update on the adverse effects of antimicrobial therapies in community practice

Samiha Mohsen James A. Dickinson MB BS PhD CCFP FRACGP
Ranjani Somayaji MD MPH FRCPC

Canadian Family Physician
Vol 66: SEPTEMBER 2020

AVOID FLUOROQUINOLONES AS FIRST-LINE TREATMENT

Rationale

- FQs have a significant association with *Clostridioides difficile* infection (CDI).
- FQs are associated with the development of antibiotic resistance and subsequent failure of therapy:
    - In most of BC over 20% of *Escherichia coli* are resistant to FQs: however, the rate of resistance is much higher in the elderly (>50%).[2]
- Health Canada, the US Food and Drug Administration (FDA) and the European Medicines Agency have issued several warnings for FQs as a cause of disabling and persistent serious adverse events that affect multiple systems, including:
    - Musculoskeletal (tendon rupture most common);
    - Neurologic (seizures, delirium, neuropsychiatric disturbances, peripheral neuropathy);
    - Cardiovascular (QTc prolongation, aortic dissection, aortic regurgitation, arrhythmias); and,
    - Metabolic (hypoglycemia, hyperglycemia).[3,4]

Clinical Infectious Diseases
MAJOR ARTICLE

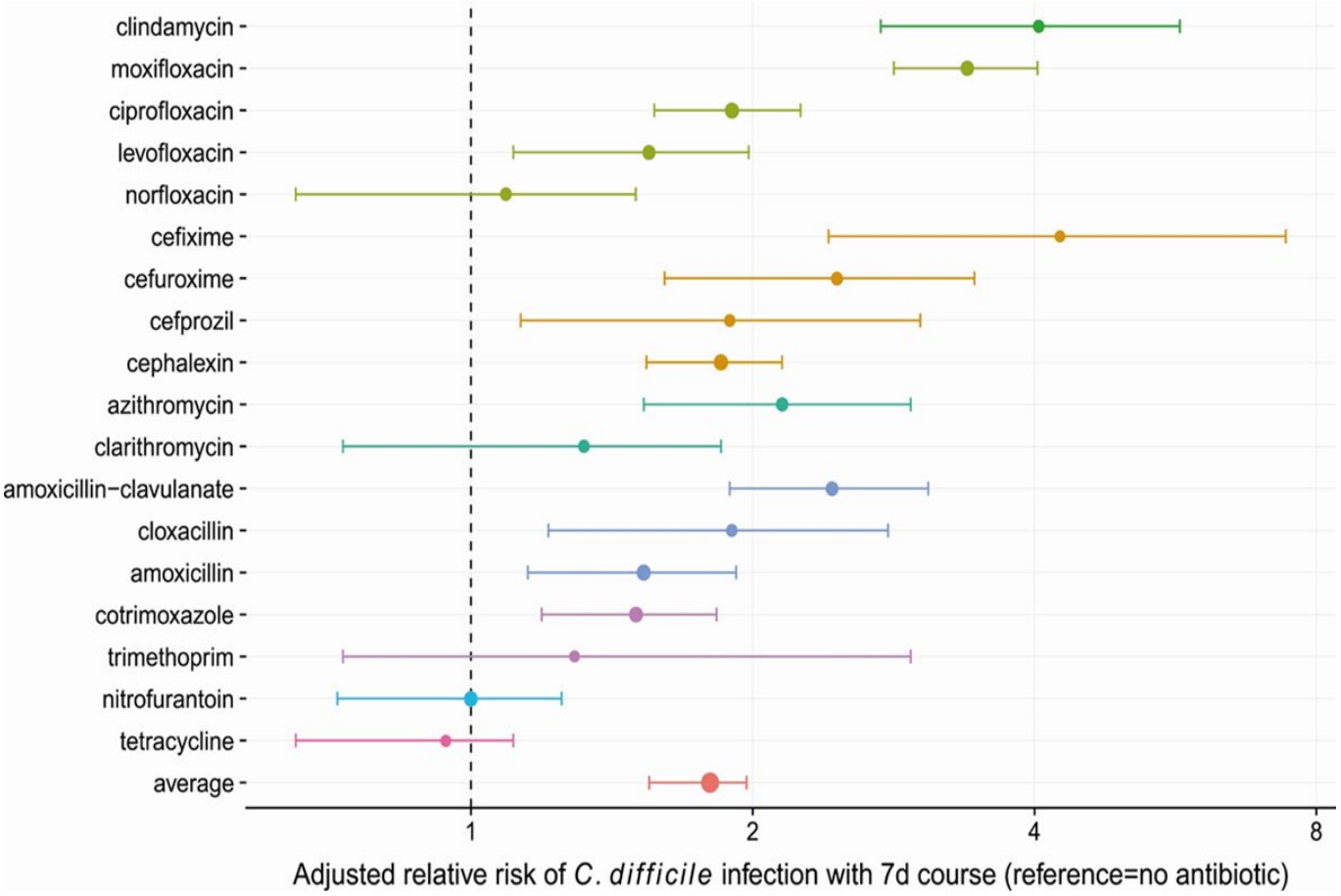
Antibiotic Prescribing Choices and Their Comparative *C. Difficile* Infection Risks: A Longitudinal Case-Cohort Study

Kevin Antoine Brown,[1,2,3] Bradley Langford,[1] Kevin L. Schwartz,[1,2,3,4] Christina Diong,[2] Gary Garber,[1,5] and Nick Daneman[1,2,6,7]

Clin Infect Dis. 2021 Mar 1;72(5):836-844

Compared to 7days of therapy:

- 5days: ↓9% risk
- 10days:↑12% risk
- 14days:↑27% risk



Schwartz et al. Genome Medicine (2020) 12:82
https://doi.org/10.1186/s13073-020-00782-x

Genome Medicine

REVIEW Open Access

Understanding the impact of antibiotic perturbation on the human microbiome

Drew J. Schwartz[1,2*†], Amy E. Langdon[2,3†] and Gautam Dantas[2,3,4,5*]

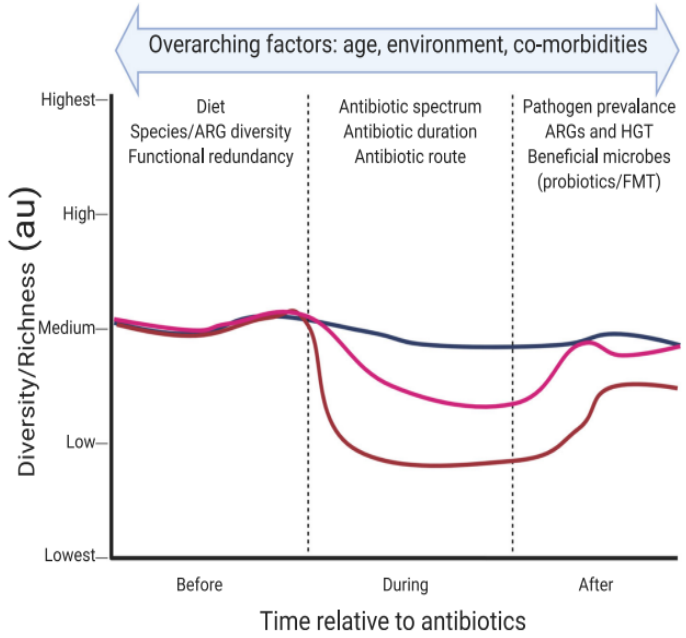


Fig. 1 Antibiotic perturbation to the microbiome needs to be considered in context. Certain factors are important to consider throughout life (overarching factors). Other factors such as diet and the functional and species diversity and redundancy are important to consider when the antibiotic perturbation is applied. The duration, spectrum, and route of antibiotics are vitally important in the context of how the microbiome responds during an intervention. The post-antibiotic environment including availability and colonization of pathogens, frequency of horizontal gene transfer (HGT), MDROs, and beneficial microbes is important to consider the resilience and response after antibiotic cessation. These factors influence the structure and function of the microbiome before, during, and after antibiotics throughout life. Created with BioRender

Autologous FMT:

- accelerated microbiome recovery

Probiotics:

- prevented microbiome recovery

CME

ACG Clinical Guidelines: Prevention, Diagnosis, and Treatment of *Clostridioides difficile* Infections

Colleen R. Kelly, MD, AGAF, FACG[1], Monika Fischer, MD, MSc, AGAF, FACG[2], Jessica R. Allegretti, MD, MPH, FACG[3], Kerry LaPlante, PharmD, FCCP, FIDSA[4], David B. Stewart, MD, FACS, FASCRS[5], Berkeley N. Limketkai, MD, PhD, FACG (GRADE Methodologist)[6] and Neil H. Stollman, MD, FACG[7]

Role of probiotics for *C. difficile* infection

American College Gastroenterology Clinical Guidelines - May 2021

recommend **against** probiotics for prevention of :

- CDI in patients being treated with antibiotics
- CDI recurrence

American College of Chest Physicians (CHEST) 2022 -Annual Meeting:

Probiotics in ICU:

- measurable increase in bacteremia and related mortality

Note: 2019- probiotics removed from Provincial/Interior Health Formularies

biomedicines

Review

Effects of Antibiotics upon the Gut Microbiome: A Review of the Literature

Theocharis Konstantinidis [1], Christina Tsigalou [1], Alexandros Karvelas [1], Elisavet Stavropoulou [2], Chrissoula Voidarou [3] and Eugenia Bezirtzoglou [4,*]

Biomedicines 2020, 8(11), 502; https://doi.org/10.3390/biomedicines8110502

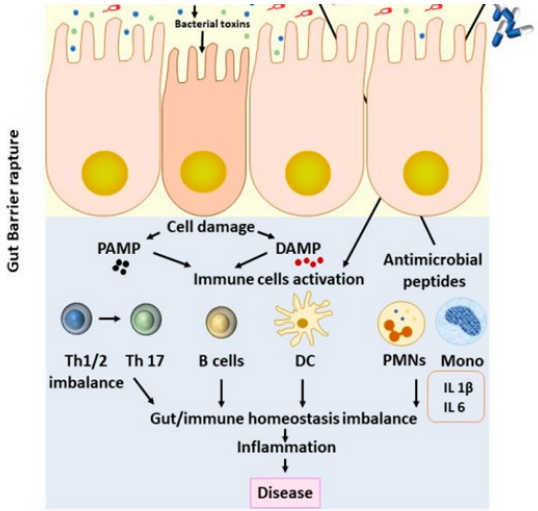


Figure 1. Effects of antibiotics upon the gut microbiome. Antibiotic treatment is crucial for combating infections. On the other hand, antibiotic exposure can alter many basic equilibria in terms of intestinal microbiota and host immunity, promoting long-term disease. DC: dendritic cells; DAMP: damage-associated molecular patterns; PMNs: polymorphonuclear leukocytes; PAMP:

J Antimicrob Chemother
https://doi.org/10.1093/jac/dkac254

Journal of Antimicrobial Chemotherapy

TLR2 and TLR4 activity in monocytes and macrophages after exposure to amoxicillin, ciprofloxacin, doxycycline and erythromycin

Luis Silva Lagos [1]*, Thy Viet Luu[1], Bart De Haan[1], Marijke Faas[1] and Paul De Vos[1]

[1]*Immunoendocrinology, Pathology and Medical Biology, University Medical Center Groningen (UMCG), University of Groningen, Groningen, The Netherlands*

*Corresponding author. E-mail: l.a.silva.lagos@umcg.nl

Received 28 March 2022; accepted 7 July 2022

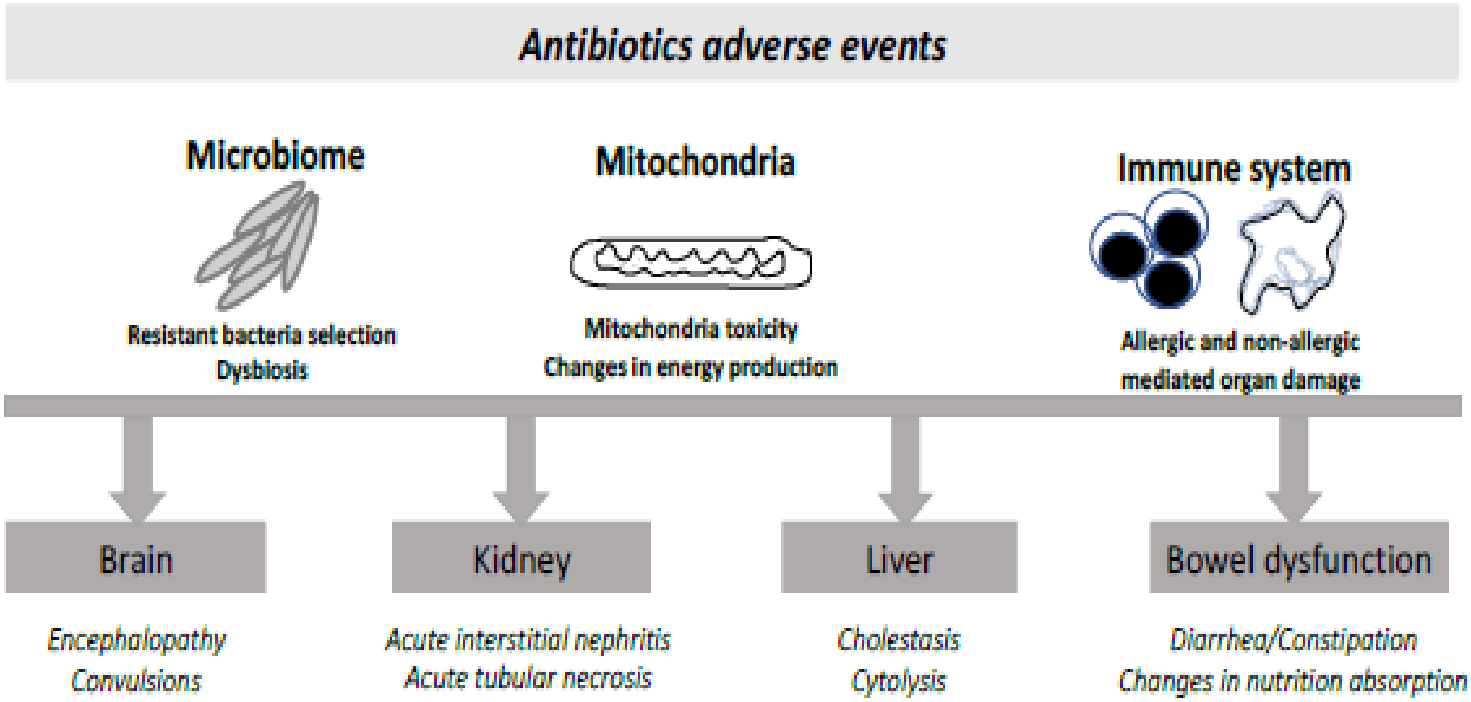


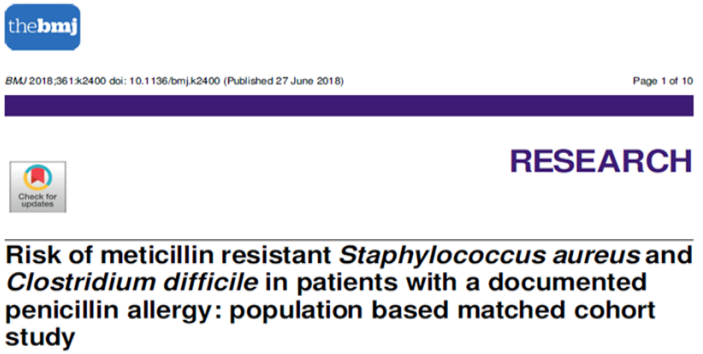
Figure 4. Antibiotic-related adverse events in patients.

Konstantinidis,Antibiotics ;2020

Harm of a Penicillin Allergy Label

Alternatives to β-lactams:

- less effective
- more adverse effects
  - 21% β-lactams vs 66.8% alternative
  - *C. difficile* infection
- more broad spectrum:
  - increased risk ARO colonization/infection
  - VRE, MRSA, ESBLs, *Amp*C, CPOs, yeast
- effect on microbiome


thebmj

BMJ 2018;361:k2400 doi: 10.1136/bmj.k2400 (Published 27 June 2018)

Page 1 of 10

RESEARCH

Check for updates

Risk of meticillin resistant *Staphylococcus aureus* and *Clostridium difficile* in patients with a documented penicillin allergy: population based matched cohort study

UK- cohort study

- 64,141-documented penicillin allergy
- 237,258 matched comparators

Penicillin allergy label:

- 69% increased risk of MRSA
- 26% increased risk of *C. difficile*

Beta-lactam Antibiotic Cross-Allergy Chart

Beta-lactams	AMOXICILLIN*	AMPICILLIN	CLOXACILLIN	PENICILLIN	PIPERACILLIN*	CEFADROXIL	CEFAZOLIN	CEPHALEXIN	CEFOXITIN	CEFPROZIL	CEFUROXIME	CEFIXIME	CEFOTAXIME	CEFTAZIDIME	CEFTRIAXONE	CEFEPIME	ERTAPENEM	IMIPENEM	MEROPENEM
AMOXICILLIN*		X[1]	X[5]	X[4]	X[3]	X[1]	✓	X[1]	✓	X[2]	✓	✓	✓	✓	✓	✓	✓	✓	✓
AMPICILLIN	X[1]		X[5]	X[4]	X[3]	X[2]	✓	X[2]	✓	X[2]	✓	✓	✓	✓	✓	✓	✓	✓	✓
CLOXACILLIN	X[5]	X[5]		X[5]	X[5]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
PENICILLIN	X[4]	X[4]	X[5]		X[5]	✓	✓	✓	X[3]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
PIPERACILLIN*	X[3]	X[3]	X[5]	X[5]		X[3]	✓	X[3]	✓	X[3]	✓	✓	✓	✓	✓	✓	✓	✓	✓
CEFADROXIL	X[1]	X[2]	✓	✓	X[3]		✓	X[1]	✓	X[2]	✓	✓	✓	✓	✓	✓	✓	✓	✓
CEFAZOLIN	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
CEPHALEXIN	X[1]	X[2]	✓	✓	X[3]	X[1]	✓		✓	X[2]	✓	✓	✓	✓	✓	✓	✓	✓	✓
CEFOXITIN	✓	✓	✓	X[3]	✓	✓	✓	✓		✓	X[2]	✓	✓	✓	✓	✓	✓	✓	✓
CEFPROZIL	X[2]	X[2]	✓	✓	X[3]	X[2]	✓	X[2]	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓
CEFUROXIME	✓	✓	✓	✓	✓	✓	✓	✓	X[2]	✓		X[3]	X[1]	X[3]	X[1]	X[2]	✓	✓	✓
CEFIXIME	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	X[3]		X[3]	X[3]	X[3]	X[3]	✓	✓	✓
CEFOTAXIME	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	X[1]	X[3]		X[3]	X[1]	X[1]	✓	✓	✓
CEFTAZIDIME	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	X[3]	X[3]	X[3]		X[3]	X[3]	✓	✓	✓
CEFTRIAXONE	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	X[1]	X[3]	X[1]	X[3]		X[1]	✓	✓	✓
CEFEPIME	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	X[2]	X[3]	X[1]	X[3]	X[1]		✓	✓	✓
ERTAPENEM	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		X[5]	X[5]
IMIPENEM	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	X[5]		X[5]
MEROPENEM	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	X[5]	X[5]	

* Also applies to beta-lactamase inhibitor combinations (amoxicillin-clavulanate and piperacillin-tazobactam)

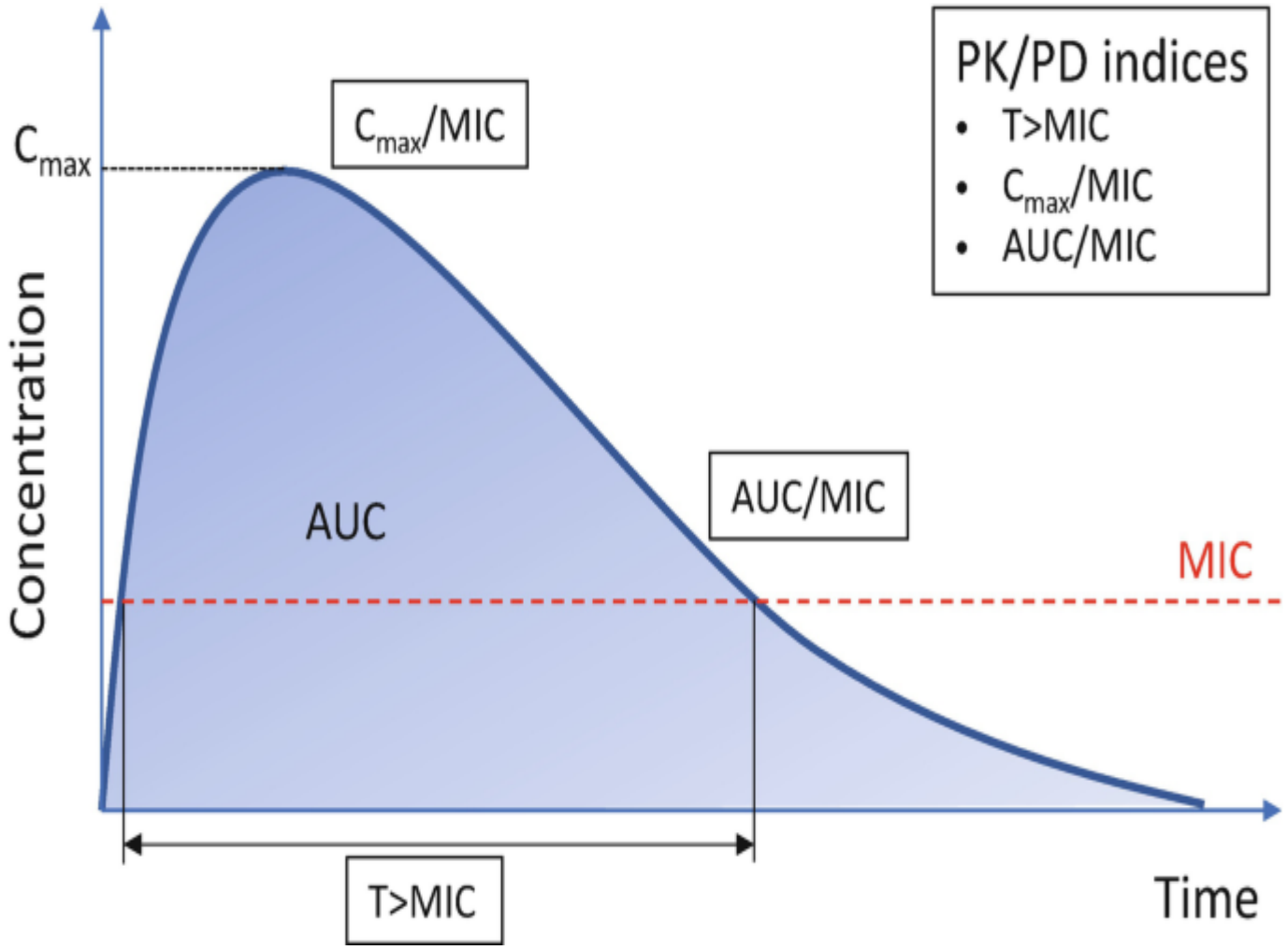
AVOID ALL beta-lactam antibiotics if:

- ICU admission related to allergy
- Delayed beta-lactam antibiotic allergy causing:
  - interstitial nephritis
  - hepatitis
  - hemolytic anemia
- Delayed severe skin allergic reactions:
  - Stevens-Johnson syndrome
  - toxic epidermal necrolysis
  - exfoliative dermatitis
  - acute generalized exanthematous pustulosis (AGEP)
  - drug reaction with eosinophilia and systemic symptoms (DRESS)

LEGEND:	
Penicillins	
1st Generation Cephalosporins	
2nd Generation Cephalosporins	
3rd Generation Cephalosporins	
4th Generation Cephalosporins	
Carbapenems	
✓	Different structure. CONSIDERED SAFE TO PRESCRIBE
Reaction likely based on side chain:	
X[1]	Same side chain - clinical evidence of cross reaction. DO NOT PRESCRIBE
X[2]	Same side chain - Theoretical risk of cross reaction, no clinical studies. DO NOT PRESCRIBE
X[3]	Similar side chain - Potential for cross reaction. DO NOT PRESCRIBE
Reaction likely based on Beta-lactam ring	
X[4]	Clinical evidence of cross reaction. DO NOT PRESCRIBE
X[5]	Theoretical risk of cross reaction, no clinical studies. DO NOT PRESCRIBE

Optimal Dosing of Antibiotics

NO LONGER ONE DOSE FOR ALL



https://images.app.goo.gl/2x55SfcRxRuoJCuXA

PK/PD of beta-lactams

Beta-lactams optimal T/MIC:

- penicillins - 40%
- cephalosporins- 60%
- carbapenems – 40%
  - added advantage of post antibiotic effect
- severe infections - 100%

Not achieving optimal PK/PD:

- clinical failure
- microbiologic selective pressure and resistance

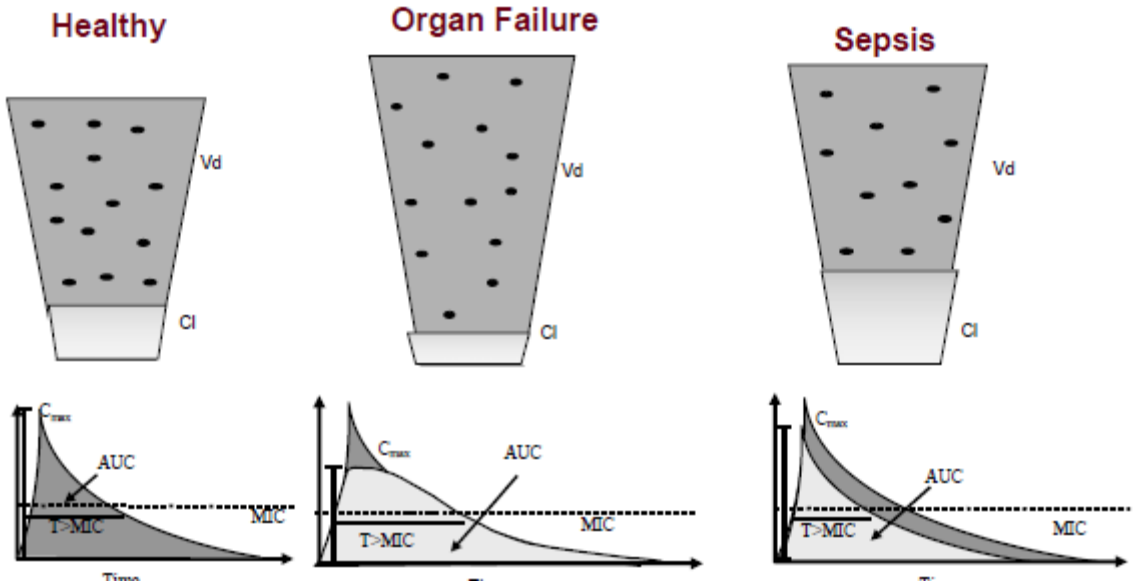
antibiotics

MDPI

Review

β-Lactam Dosing in Critical Patients: A Narrative Review of Optimal Efficacy and the Prevention of Resistance and Toxicity

João Gonçalves Pereira [1,2,*], Joana Fernandes [3], Ana Rita Duarte [4] and Susana Mendes Fernandes [2,5]

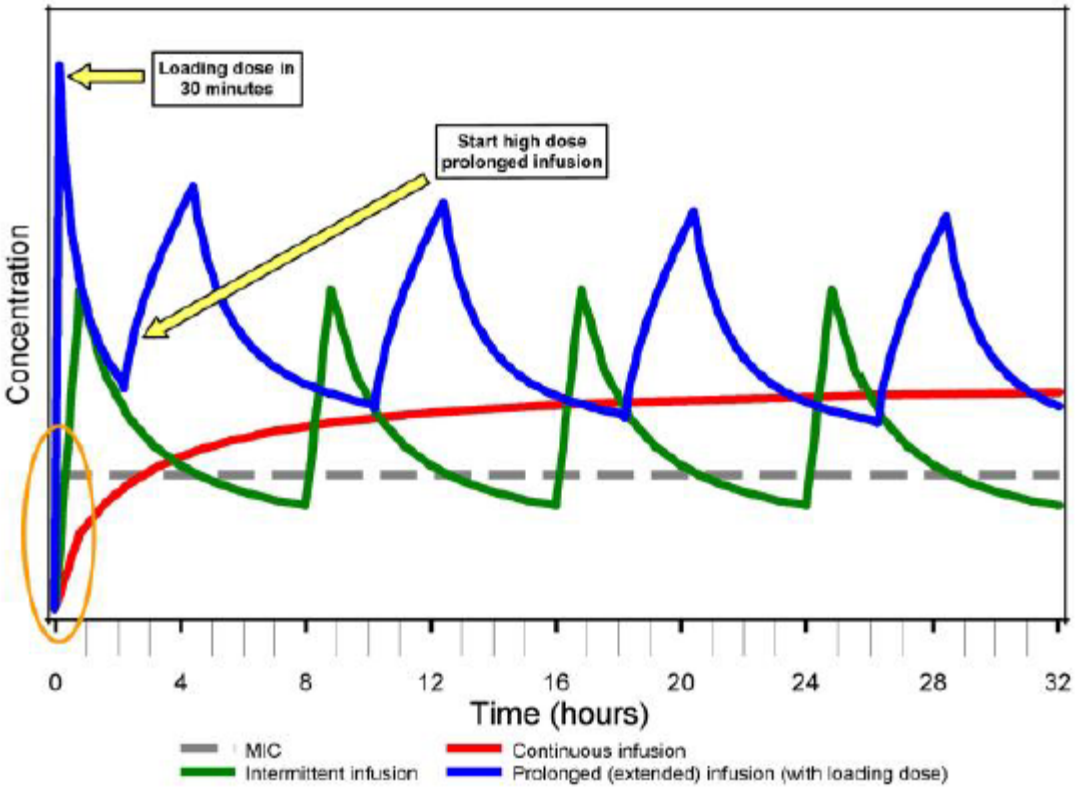


Open Forum Infectious Diseases
MAJOR ARTICLE

Optimizing the Use of Beta-Lactam Antibiotics in Clinical Practice: A Test of Time

Alwin Tilanus[1] **and George Drusano**[2]
[1]Department of Infectious Diseases, Clinica Los Nogales, Bogotá, Colombia, and [2]Institute for Therapeutic Innovation at University of Florida, Orlando, Florida, USA

2023



MacVane et al 2014:

- 50% increase in T/MIC if prolonged infusion

Other studies:

- better clinical outcome
- less mortality

› Int J Antimicrob Agents. 2020 Oct;56(4):106113. doi: 10.1016/j.ijantimicag.2020.106113. Epub 2020 Jul 25.

What is the optimal loading dose of broad-spectrum β-lactam antibiotics in septic patients? Results from pharmacokinetic simulation modelling

Isabelle K Delattre [1], Maya Hites [2], Pierre-Francois Laterre [3], Thierry Dugernier [4], Herbert Spapen [5], Pierre E Wallemacq [6], Frédérique Jacobs [2], Fabio Silvio Taccone [7]

Affiliations + expand

PMID: 32721604 DOI: 10.1016/j.ijantimicag.2020.106113

Oral beta-lactams:
Enterobacterales: optimal dose for optimal T/MIC?

Table 3. Percentage of free time above the minimum inhibitory concentration for various oral beta-lactam antibiotics.

		%fT>MIC						
Antibiotic	Dose (mg)/dosing interval (h)	16 mg/L	8 mg/L	4 mg/L	2 mg/L	1 mg/L	0.5 mg/L	0.25 mg/L
Amoxicillin	500/8	–	13.0	23.0	33.0	43.0	53.0	63.0
Amoxicillin	1000/8	–	23.0	33.0	43.0	53.0	63.0	73.0
Amoxicillin-clavulanate	875/12	–	11.0	17.6	24.3	31.0	37.6	44.3
Amoxicillin-clavulanate	875/8	–	16.4	26.4	36.4	46.4	56.4	66.4
Cephalexin	500/6	3.30	22.7	42.1	61.5	80.9	100	100
Cephalexin	1000/6	22.7	42.1	61.5	80.9	100	100	100
Cefaclor	500/6	–	11.0	23.5	36.0	48.5	61.0	73.5
Cefprozil	500/12	–	12.6	20.1	27.5	35.0	42.5	50.0
Cefuroxime	500/12	–	–	0.43	10.2	20.5	29.7	39.5
Cefdinir	300/12	–	–	–	–	7.41	12.4	17.3
Cefpodoxime	400/12	–	–	–	22.8	39.7	56.6	73.5

Expert Opinion Pharmacother. 2019 Jun;20(8):903-907
https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Consultation/2021/Aminopenicillins_and_Enterobacterales_General_consultation_November_2021.pdf

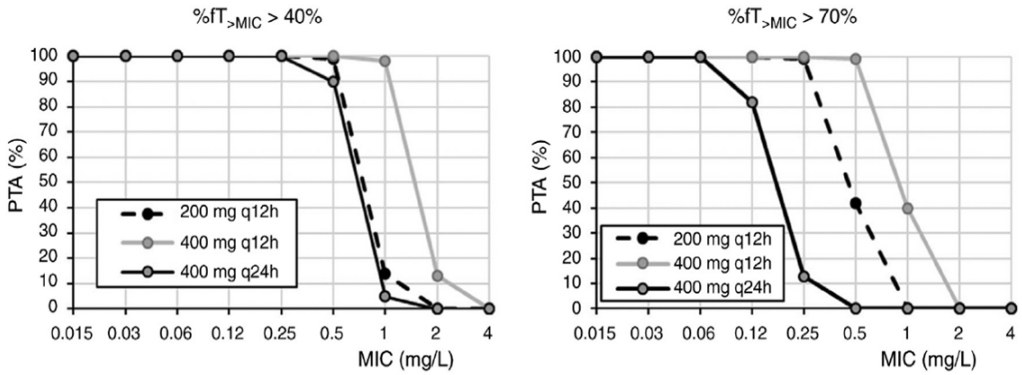
Amox-clav		
MIC	Count	Average
<=2	5949	49%
4	3517	29%
8	1536	13%
16	772	6%
>=32	488	4%
Total:	12262	

Original article

Are oral cefuroxime axetil, cefixime and cefditoren pivoxil adequate to treat uncomplicated acute pyelonephritis after switching from intravenous therapy? A pharmacokinetic/pharmacodynamic perspective

Alicia Rodríguez-Gascón [a], Amaia Aguirre-Quiñonero [b,*], Andrés Canut-Blasco [b]

Enferm Infecc Microbiol Clin (Engl Ed). 2020 Aug-Sep;38(7):306-311



CFR (%)	%fT>MIC > 40%	%fT>MIC > 70%
200 mg q12 h	88	76
400 mg q12 h	91	89
400 mg q24 h	86	9

Fig. 2. The probability of target attainment (PTA) and the cumulative fraction of response (CFR) of three cefixime regimens. Numbers in bold when ≥90%. Numbers in italics when ≥80% and <90%.

Caution if MIC 1µg/mL – considered susceptible

Cefixime		
MIC	Count	Average
<=0.25	8411	70%
0.5	2394	20%
1	206	2%
2	75	1%
>=4	873	7%
Total:	11959	

Take home message for oral beta-lactams as step down therapy

Oral cephalosporins:

- do not bind as well as penicillins to PBPs
  - likely need higher T/MIC than penicillins (60% vs 40%)
  - higher doses for UTIs if step down from bacteremia/pyelonephritis

Cephalexin:

- 1000 g QID optimal for lower UTI only
  - 5-7 days (based on clinical studies)
  - most narrow spectrum
  - best PK/PD but rapid elimination (hence QID dosing)

Cefixime:

- lower bioavailability
  - absorption is diminished at higher doses lower urinary excretion
  - 200 mg BID is actually more desirable than 400 mg once daily
    - lowers toxicity and adverse events
- PK/PD not optimal if cefixime MIC of 1 ug/mL (still considered S)

Haeseker *et al. BMC Pharmacology and Toxicology* 2014, **15**:38
http://www.biomedcentral.com/2050-6511/15/38

BMC Pharmacology & Toxicology

RESEARCH ARTICLE Open Access

Is the standard dose of amoxicillin-clavulanic acid sufficient?

Michiel Haeseker[1,3,5*], Thomas Havenith[2], Leo Stolk[2], Cees Neef[2], Cathrien Bruggeman[1,3] and Annelies Verbon[4]

Measured amoxicillin-clavulanate concentrations:

- 57 hospitalized patients - intra-abdominal infections
- 1000/200 mg IV Q6H

Results:

- only 65% achieved 40% T/MIC if MIC 8µg/mL

Prediction:

- if increase to Q4H 95% achieve T/MIC 40%

Conclusion:

- Q4H dosing for severe Enterobacterales infections

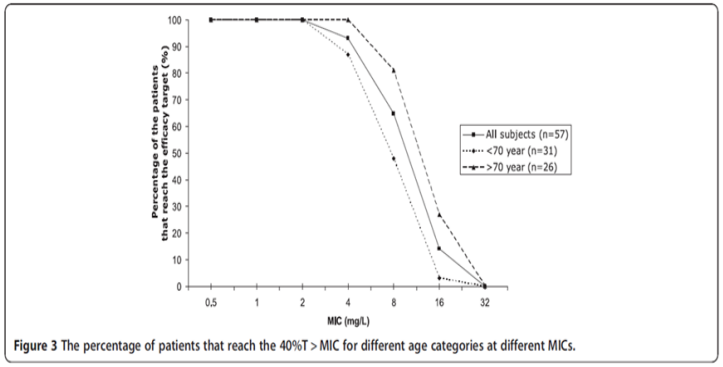


Figure 3 The percentage of patients that reach the 40%T > MIC for different age categories at different MICs.

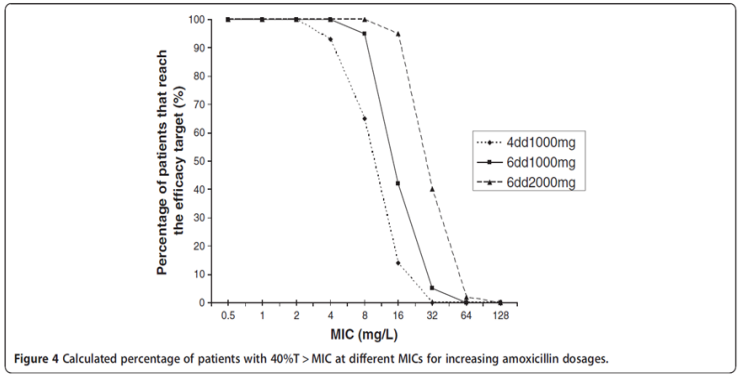


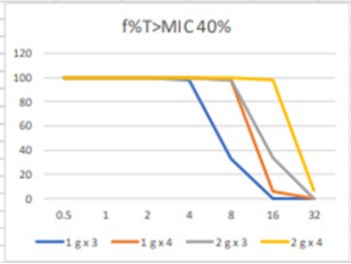
Figure 4 Calculated percentage of patients with 40%T > MIC at different MICs for increasing amoxicillin dosages.

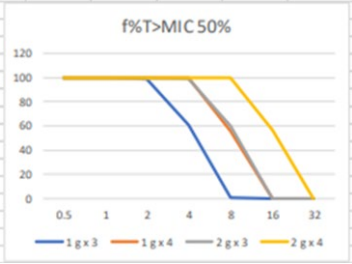
f%T>MIC 40%

	1 g x 3	1 g x 4	2 g x 3	2 g x 4
0.5	100	100	100	100
1	100	100	100	100
2	100	100	100	100
4	98	100	100	100
8	33	98	98	100
16	0	6	34	98
32	0	0	0	7

f%T>MIC 50%

	1 g x 3	1 g x 4	2 g x 3	2 g x 4
0.5	100	100	100	100
1	100	100	100	100
2	99	100	100	100
4	61	100	99	100
8	1	56	60	100
16	0	0	0	57
32	0	0	0	0





IV Amoxicillin-Clavulanate — Now Available on the BC Health Authority Drug Formulary

Key Messages: IV Amoxicillin-Clavulanate

- Added to the BC Health Authority Drug Formulary with no restrictions
- Not to be used when ceftriaxone ± azithromycin OR ceftriaxone ± metronidazole is standard of care
- Usual dose: amoxicillin-clavulanate 1.2 g IV Q8H to treat respiratory tract infections
- Higher dose: amoxicillin-clavulanate 2.2 g IV Q8H to treat intra-abdominal infections, complicated urinary tract infections, moderate-severe diabetic foot infections, and invasive Enterobacterales infections with an MIC of 8 mcg/L

Beta-lactamase inhibitor combination drugs

Amoxicillin-clavulanate:

- not effective against ESBL or *Amp*C producing organisms
- anaerobic resistance higher than piperacillin-tazobactam
- 2.2 grams Q8H minimum to treat Enterobacterales (Q6H for severe infections)
- 1.2 grams Q8H - OK for respiratory pathogens

Piperacillin-tazobactam:

- not effective against ESBL or *Amp*C producing organisms(except *M. morganii*)
- NOT better than penicillin for *S.pneumoniae*
  - ceftriaxone better coverage
- severe infection:
  - loading dose and prolonged infusions
  - minimum 4.5 grams Q6H

Covering Enterococcus

Empiric coverage of *Enterococcus spp* if:

- post-operative infection
- recent cephalosporin use
- immunocompromised
- valvular heart disease
- prosthetic intravascular material

Ampicillin resistance:

- predicts resistance to piperacillin-tazobactam and imipenem

Ampicillin susceptibility:

- endocarditis 2 g Q4H + ceftriaxone 2 gQ12H
- does not predict susceptibility to piperacillin-tazobactam and imipenem

Amoxicillin-clavulanate:

- poor PK/PD for Enterobacterales
- need 875mg Q8H unless MIC ≤2µg/mL-

  Note: 4-8µg/mL still considered S

Carbapenem sparing - is cefepime the answer ?

RCT- > 2500 hospitalized adults:

- piperacillin-tazobactam:
  - did not increase the incidence of acute kidney injury or death

  Note: reported nephrotoxicity +/- vancomycin- likely pseudotoxicity

- cefepime:
  - more neurological dysfunction
    - not effective against ESBLs
    - not effective against up regulated *Amp*C
    - not routinely tested

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Cefepime vs Piperacillin-Tazobactam in Adults Hospitalized With Acute Infection
The ACORN Randomized Clinical Trial

JAMA. 2023;330(16):1557-1567. doi:10.1001/jama.2023.20583

CEFAZOLIN

Cefazolin for Gram negative infections

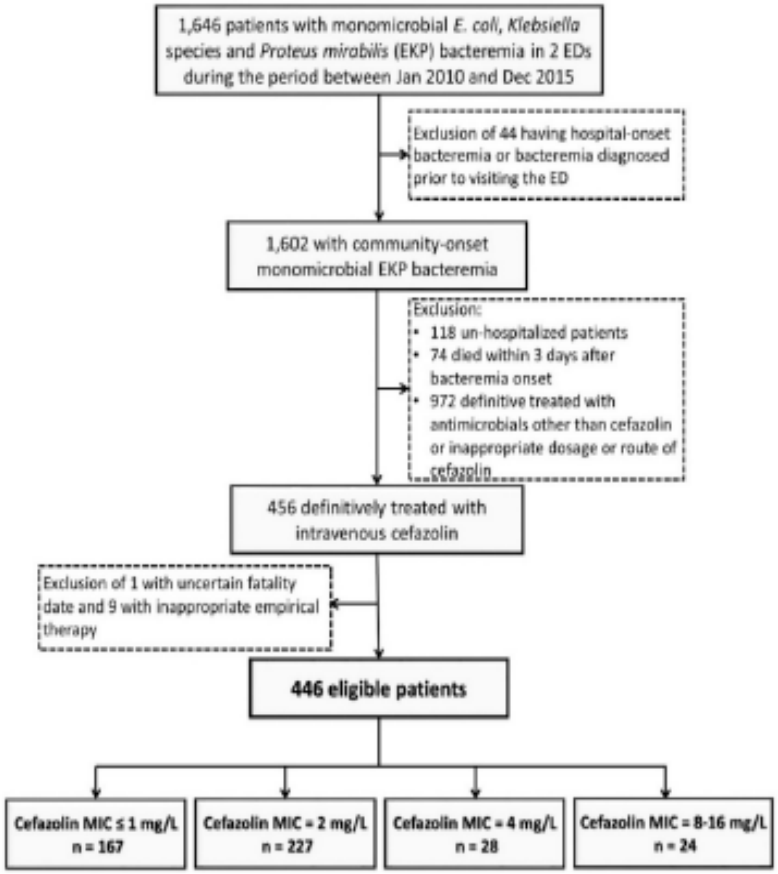


Figure 1. Flowchart of patient selection. ED = emergency department; MIC = minimum inhibitory concentration.

Journal of *Clinical Medicine*

MDPI

Article

Definitive Cefazolin Therapy for Stabilized Adults with Community-Onset *Escherichia coli*, *Klebsiella* Species, and *Proteus mirabilis* Bacteremia: MIC Matters

Chih-Chia Hsieh [1], Po-Lin Chen [2], Chung-Hsun Lee [1], Chao-Yung Yang [1], Ching-Chi Lee [1,2,3,4,*] and Wen-Chien Ko [2,5,*]

Journal of Clinical Medicine

MDPI

Article

Definitive Cefazolin Therapy for Stabilized Adults with Community-Onset *Escherichia coli*, *Klebsiella* Species, and *Proteus mirabilis* Bacteremia: MIC Matters

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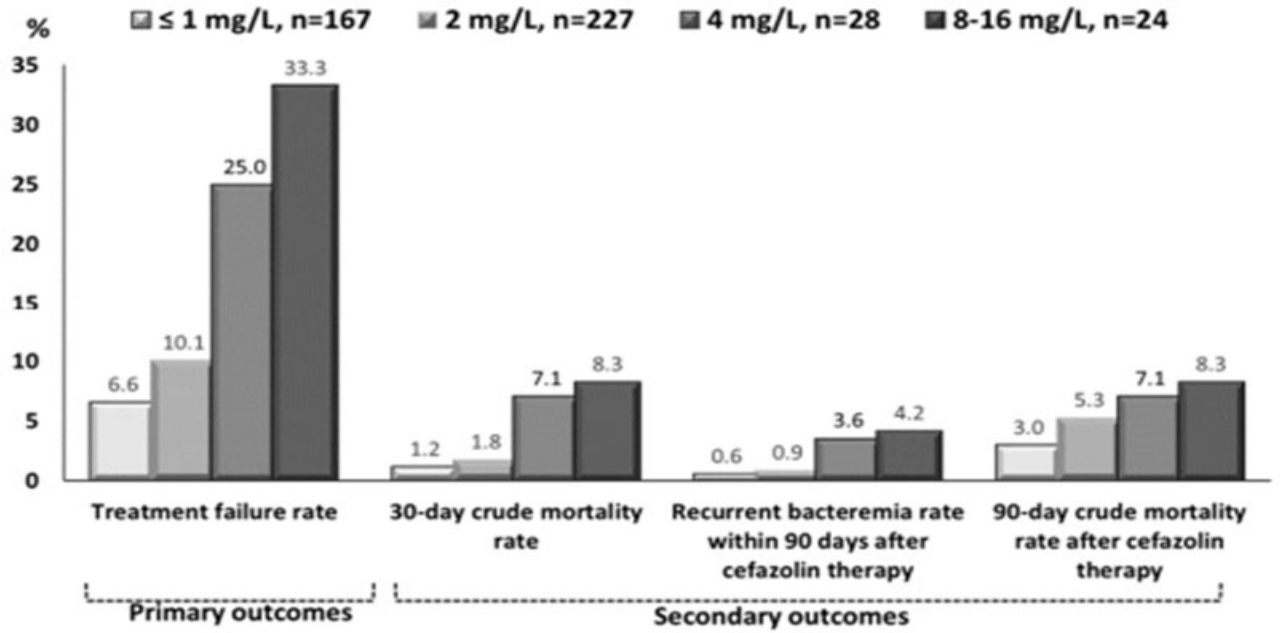


Figure 2. The cefazolin-MIC-related trend (all $\gamma = 1.00$, $p = 0.01$) in primary and secondary outcomes of adults with community-onset monomicrobial *Escherichia coli*, *Klebsiella* species, or *Proteus mirabilis* bacteremia definitively treated by cefazolin. Early treatment failure, i.e., primary outcome, was the composite of antimicrobial escalation to broad-spectrum agents, the development of breakthrough bacteremia, the need for intensive care during definitive cefazolin therapy, and crude mortality within 15 days after bacteremia onset.

Cefazolin Dosing in Obesity

Obesity Surgery (2022) 32:3130–3149
https://doi.org/10.1007/s11695-022-06196-5

REVIEW

Prophylactic Cefazolin Dosing in Obesity—a Systematic Review

Matthew Coates[1] · Alison Shield[1] · Gregory M. Peterson[1,2] · Zahid Hussain[1]

Received: 10 April 2022 / Revised: 29 June 2022 / Accepted: 30 June 2022 / Published online: 9 July 2022

International Journal of Antimicrobial Agents 61 (2023) 106751

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Population pharmacokinetics and pharmacodynamics of cefazolin using total and unbound serum concentrations in patients with high body weight

Eun Kyoung Chung[a,b,c,d,*], S. Christian Cheatham[e], Daniel P. Healy[f], Andrea H. Stock[e], Sara Utley[e], Maureen Campion[g], Timothy Murrey[e], Alicia M. Gesenhues[f], Julia Jeffery[f], Michael B. Kays[g,†]

able 1. Cefazolin dosing *f*T>MIC

Cefazolin dose	MIC (mcg/mL)	*f*T>MIC - 40%- Obese	*f*T>MIC - 40% Non-obese	*f*T>MIC - 60% Obese	*f*T>MIC - 60% Non-obese	*f*T>MIC -100% Obese	*f*T>MIC -100% Non-Obese
1 g IV Q8H	1	✓	✓	✓	✓	X	X
1 g IV Q8H	2	✓	✓	X	✓	X	X
1 g IV Q8H	4	X	✓	X	X	X	X
1 g IV Q8H	8	X	X	X	X	X	X
2 g IV Q8H	1	✓	✓	✓	✓	✓	✓
2 g IV Q8H	2	✓	✓	✓	✓	X	X
2 g IV Q8H	4	✓	✓	X	✓	X	X
2 g IV Q8H	8	X	✓	X	X	X	X
3 g IV Q8H	1	✓	✓	✓	✓	✓	✓
3 g IV Q8H	2	✓	✓	✓	✓	✓	✓
3 g IV Q8H	4	✓	✓	X	✓	X	X
3 g IV Q8H	8	✓	✓	X	X	X	X

Recommendation:

cefazolin 2 g IV x 1 dose pre-op for all patients

cefazolin 2 g IV Q8H for Gram-positive infections

- may need higher dose for Gram negative infections

› Clin Infect Dis. 2023 Oct 13;77(8):1120-1125. doi: 10.1093/cid/ciad357.

Antibiotic Myths for the Infectious Diseases Clinician

Erin K McCreary [1], Melissa D Johnson [2], Travis M Jones [2], S Shaefer Spires [2], Angelina E Davis [2], April P Dyer [2], Elizabeth Dodds Ashley [2], Jason C Gallagher [3]

Affiliations + expand

PMID: 37310038 DOI: 10.1093/cid/ciad357

Cefazolin for CNS Infections

may actually have better pharmacokinetics than cloxacillin for CNS infections

- especially epidural abscess
  - 11 reports of success in epidural abscess in 104 patients with MSSA

Dose?

- 2 grams q6h (instead of q8h) or
- 8 -10 grams / day by continuous infusion

CEFTRIAXONE

Ceftriaxone for pneumonia

1 gram equivalent to 2 grams Q24H

Meta-Analysis › Expert Rev Anti Infect Ther. 2019 Jul;17(7):501-510.
doi: 10.1080/14787210.2019.1627872. Epub 2019 Jun 10.

Efficacy of Ceftriaxone 1 g daily Versus 2 g daily for The Treatment of Community-Acquired Pneumonia: A Systematic Review with Meta-Analysis

1g versus 2 g daily intravenous ceftriaxone in the treatment of community onset pneumonia - a propensity score analysis of data from a Japanese multicenter registry.

BMC Infectious Diseases, 26 Dec 2019, 19(1):1079
DOI: 10.1186/s12879-019-4552-8 PMID: 31878894 PMCID: PMC6933656

Ceftriaxone for *S. aureus*

DO NOT BELIEVE EVERYTHING YOU READ

Open Forum Infectious Diseases
MAJOR ARTICLE

Outcomes of Outpatient Parenteral Antimicrobial Therapy With Ceftriaxone for Methicillin-Susceptible *Staphylococcus aureus* Bloodstream Infections—A Single-Center Observational Study

Yasir Hamad, Lee Connor, Thomas C. Bailey, and Ige A. George
Division of Infectious Diseases, Washington University School of Medicine, St. Louis, Missouri, USA

Problem with this study:

- single centre retrospective study
- 243 patients: insufficient to prove non-inferiority of ceftriaxone
  - 74 patients – medical device removal

Ceftriaxone group:

- lower rates of ICU patients
- shorter duration of bacteremia / shorter IV antibiotic duration
- lower rates of valvular heart disease /TEEs /endocarditis/valve replacement
- 16% received > 48 hours of cefazolin /cloxacillin therapy
- 7% received 2 grams q12h
- ceftriaxone treated endocarditis patients:
  - higher 90 day mortality (14.3% vs 2.4%) / composite outcome (25.6% vs 10%)

Oxacillin/cefazolin group:

- more patients (26% vs 13%) had oral suppression antibiotics post IV antibiotics

Other issues:

- ceftriaxone - not best antimicrobial stewardship option
- authors concluded- probably only outpatient option for Medicare patients

Open Forum Infectious Diseases
MAJOR ARTICLE

Outcomes of Ceftriaxone Compared With Cefazolin or Nafcillin/Oxacillin for Outpatient Therapy for Methicillin-Sensitive *Staphylococcus aureus* Bloodstream Infections: Results From a Large United States Claims Database

Yasir Hamad,[1] Katelin B. Nickel,[2] Margaret A. Olsen,[2,3] and Ige A. George[2]

Problem with this study:

- retrospective cohort/insurance claims 2010-2018
- 1895 adults - MSSA bacteremia
  - excluded Medicare/Medicaid, uninsured, patients > 65 years
  - looked only at readmission rate/ not reason for readmission rate

No review of:

- medical records
- adequacy of source control /time to blood culture clearance
- duration and type of antibiotic received during initial admission
- no confirmation of primary diagnosis (*ICD*9/10 codes)
- did not assess mortality

Patients with endocarditis and epidural abscess:

- more likely to be given cefazolin/oxacillin/nafcillin

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases

Cefazolin **[ECOFF = 2]**

Healthy volunteers. PB(%): 91.6 ± 6.7; Vd (L): 6.94 ± 2.2; $t_{½\beta}$ (h): 1.45 ± 0.15 [3,9]

f%T>MIC 25%

Regimen	1 g x 3	1 g x 4	2 g x 3	2 g x 4
0.125	100	100	100	100
0.25	100	100	100	100
0.5	100	100	100	100
1	99	99	100	100
2	99	99	99	99
4	94	97	99	99
8	68	82	94	97

f%T>MIC 30%

Regimen	1 g x 3	1 g x 4	2 g x 3	2 g x 4
0.125	100	100	100	100
0.25	100	100	100	100
0.5	100	100	100	100
1	99	99	100	100
2	98	99	99	99
4	90	95	98	99
8	53	74	90	95

f%T>MIC 35%

Regimen	1 g x 3	1 g x 4	2 g x 3	2 g x 4
0.125	100	100	100	100
0.25	100	100	100	100
0.5	99	100	100	100
1	99	99	99	100
2	97	99	99	99
4	83	93	97	99
8	37	64	84	93

Red text and shading represent the ECOFF and the wild type respectively of ***Staphylococcus aureus***
Purple dosages are those already listed as either Standard or High on the Dosages tab

Cefazolin **[ECOFF = 2]**

Patients. PB(%): 91.6 ± 6.7; Vd (L): 13.01 ± 4.4; $t_{½\beta}$ (h): 1.8 ± 0.38 [3,10]

f%T>MIC 25%

Regimen	1 g x 3	1 g x 4	2 g x 3	2 g x 4
0.125	100	100	100	100
0.25	100	100	100	100
0.5	99	99	100	100
1	99	99	99	99
2	95	97	99	99
4	79	87	96	97
8	34	47	79	87

f%T>MIC 30%

Regimen	1 g x 3	1 g x 4	2 g x 3	2 g x 4
0.125	100	100	100	100
0.25	100	100	100	100
0.5	99	99	100	100
1	99	99	99	99
2	93	96	98	99
4	71	82	93	97
8	24	38	71	83

f%T>MIC 35%

Regimen	1 g x 3	1 g x 4	2 g x 3	2 g x 4
0.125	100	100	100	100
0.25	100	100	100	100
0.5	99	99	100	100
1	98	99	99	99
2	89	95	97	99
4	61	77	90	95
8	17	31	60	77

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases

Ceftriaxone **(Craig targets [1])** **[ECOFF = 8]**

Patients. PB(%): 92.7 ± 3.2; Vd (L): 7.8 ± 6.4; $t_{½\beta}$ (h): 8.1 ± 3.9 [3,14]

f%T>MIC 25%

	Regimen			
	1 g x 1	1 g x 2	2 g x 1	2 g x 2
0.5	95	97	96	98
1	92	95	95	97
2	83	90	92	95
4	58	71	82	90
8	27	38	58	72
14	11	15	25	38
32	5	6	10	15

f%T>MIC 30%

	Regimen			
	1 g x 1	1 g x 2	2 g x 1	2 g x 2
0.5	94	97	96	97
1	90	95	94	97
2	79	88	90	95
4	53	69	79	88
8	24	35	53	69
14	9	14	23	35
32	4	6	9	14

f%T>MIC 35%

	Regimen			
	1 g x 1	1 g x 2	2 g x 1	2 g x 2
0.5	93	96	95	97
1	88	94	93	96
2	75	87	88	94
4	48	66	75	86
8	21	33	48	56
14	8	13	20	33
32	4	5	8	13

Ceftriaxone **(Craig targets [1])** **[ECOFF = 8]**

Healthy volunteers. PB(%): 92.7 ± 3.2; Vd (L): 14.0 ± 2.1; $t_{½\beta}$ (h): 5.8 ± 1.2 [3,15]

f%T>MIC 25%

	Regimen			
	1 g x 1	1 g x 2	2 g x 1	2 g x 2
0.5	96	98	98	98
1	91	95	96	98
2	65	83	90	95
4	13	40	65	83
8	0	1	13	41
14	0	0	0	2
32	0	0	0	0

f%T>MIC 30%

	Regimen			
	1 g x 1	1 g x 2	2 g x 1	2 g x 2
0.5	96	97	98	98
1	87	94	95	97
2	54	80	86	94
4	7	33	55	80
8	0	1	7	34
14	0	0	0	1
32	0	0	0	0

f%T>MIC 35%

	Regimen			
	1 g x 1	1 g x 2	2 g x 1	2 g x 2
0.5	94	97	97	98
1	83	93	94	97
2	43	77	82	93
4	3	27	43	78
8	0	0	3	28
14	0	0	0	0
32	0	0	0	0

International Journal of Antimicrobial Agents
Volume 59, Issue 3, March 2022, 106537

Short Communication

Pharmacodynamics of ceftriaxone for the treatment of methicillin-susceptible *Staphylococcus aureus*: is it a viable treatment option?

Open Forum Infectious Diseases
MAJOR ARTICLE

A Comparison of Cefazolin Versus Ceftriaxone for the Treatment of Methicillin-Susceptible *Staphylococcus aureus* Bacteremia in a Tertiary Care VA Medical Center

Ceftriaxone:

limited bacterial killing

- even 2 g q12h if normal renal function
  - some activity if CrCl ≤50 mL/min
- inferior to cefazolin: bacteremia/cellulitis in children
- high protein binding (95%)

clinical data and PK/PD supports:

- only cefazolin and cefepime
- cefuroxime iv:
  - only at 1.5 grams IV Q8H (not oral)

  Danish study:
    - higher 30 day mortality with bacteremia

Table 3. Clinical Outcomes of 71 Patients With MSSA Bacteremia

	Cefazolin (n = 38), n (%)	Ceftriaxone (n = 33), n (%)	*P* Value[a]
Treatment failure	11 (29)	18 (55)	.029
Extension of parenteral therapy	0 (0)	7 (21)	.003
Incomplete course	5 (13)	0 (0)	.031
Relapse after treatment	2 (5)	4 (12)	NS
Readmission	5 (13)	6 (18)	NS
Unplanned surgical intervention	1 (3)	5 (15)	NS
Unplanned oral antimicrobials	2 (5)	4 (12)	NS
Lost to follow-up	2 (5)	4 (12)	NS
Mortality	4 (11)	1 (3)	NS
Clostridium difficile infection	2 (5)	1 (3)	NS
Adverse events	2 (5)	1 (3)	NS
Change of therapy due to adverse event	2 (5)	0 (0)	NS

Abbreviations: MSSA, methicillin-susceptible *Staphylococcus aureus*; NS, nonsignificant.
[a]Not significant ($P \geq .05$).

CLSI: recently changed dose to 2 grams Q12-24 H

EUCAST: 2 grams Q12H / for non- serious infections only

Cephalosporins:

Cefazolin:

- best cephalosporin for *S. aureus*
- 2 grams Q8H – fine in obesity for surgical prophylaxis
- not optimal for Enterobacterales if MIC is 4 µg/mL (still considered S)
  - lab can only determines ≤ 4 µg/mL
- may be better than cloxacillin for epidural abscess
  - dose still in question- Q6H or continuous infusion?

Ceftriaxone:

- 1 g Q24H- sufficient for pneumonia
- 1-2 g Q24H for Enterobacterales
- 2 g Q12H for *S. aureus* (MSSA) non severe - controversial
  - not recommended for severe infections
    - epidural abscess, endocarditis, high burden infections (osteomyelitis)

Research Article

Antistaphylococcal Efficacy of Cefepime, Meropenem, and Piperacillin-Tazobactam in Patients with Polymicrobial Infection with MSSA Bacteremia or Pneumonia

Laila M. Najia,[1] Eric Pyles,[1] Arnaldo Lopez-Ruiz,[2] and Bibidh Subedi[1]

Does this study tell us anything?

- polymicrobial infections including *S. aureus*
  - vastly different than mono-microbial infections with MSSA
- cefepime, meropenem and piperacillin–tazobactam:
  - excellent *S. aureus* coverage / expected to cover MSSA

Vancomycin Dosing

TABLE 1. INITIAL DOSE PER INTERVAL

TOTAL BODY WEIGHT	LOADING DOSE (suggested maximum 3000 mg/dose)	MAINTENANCE DOSE*
kg	(25 mg/kg)	(15 mg/kg)
40-50	1250 mg	750 mg
51-60	1500 mg	1000 mg
61-70	1750 mg	1000 mg
71-80	2000 mg	1250 mg
81-90	2250 mg	1250 mg
91-100	2500 mg	1500 mg*
101-110	2750 mg	1500 mg*
111-120	3000 mg	1500 mg*

*1500 mg Q8H-maximum maintenance dose

TABLE 2. INITIAL VANCOMYCIN DOSING INTERVAL

Pre-vancomycin Level 10-15 mg/L
Usual target

TABLE 3 USUAL TARGET 10-15 mg/L
INITIAL DOSING INTERVAL (hours)

SCr (mcmol/L)	Age Group (years)					
	20-29	30-39	40-49	50-59	60-69^	70-79^
40-60	8	8	12	12	12	18
61-80	8	12	12	12	18	18
81-100	12	12	12	18	18	18
101-120	12	12	18	18	18	24
121-140	12	18	18	18	24	
141-160	18	24	24	24		
161-180	24	24				
181-200	24					
Above 200						

Daptomycin:

- suboptimal for *E. faecalis* (even at high dose)
- not recommended for *E. faecium* / VRE

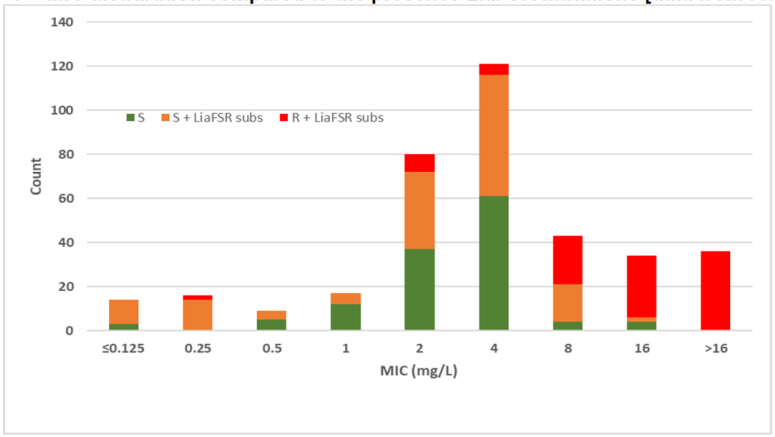
Table 1

Probability of survival threshold (*f*AUC/MIC >27.43) attainment using Monte Carlo simulation [8]

Daptomycin MIC (mg/L)	Daptomycin dose			
	6 mg/kg/day	8 mg/kg/day	10 mg/kg/day	12 mg/kg/day
0.25	100	100	100	100
0.5	100	100	100	100
1	91.0, 97.9[a]	98.7, 99.9[a]	99.9, 100[a]	100
2	32.4, 54.4[a]	60.7, 80.4[a]	80.4, 92.9[a]	91.0, 97.9[a]
4	1.5, 5.5[a]	7.3, 18.1[a]	18.1, 36.2[a]	32.4, 54.4[a]
8	0	0.0, 0.2[a]	0.2, 2.0[a]	1.5, 5.5[a]
16	0	0	0	0

[a] Males and females were simulated separately. Values are presented as 'male, female' for MICs at which the probability differs.

Figure 1 MIC distribution compared to the presence LiaFSR mutations [data from ref 11



Forty strains, reference BMD, three labs, three lots of medium, replicate testing

Clinical Microbiology and Infection 26 (2020) 1039–1043

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Position paper

Daptomycin in the treatment of enterococcal bloodstream infections and endocarditis: a EUCAST position paper

J. Turnidge [1,*], G. Kahlmeter [2], R. Cantón [3], A. MacGowan [4], C.G. Giske [5], on behalf of the European Committee on Antimicrobial Susceptibility Testing

Dalbavancin

Long acting antibiotic - adults with acute bacterial skin /skin structure infections

- caused by susceptible isolates of Gram-positive microorganisms
- $2000/dose

Restricted to treatment of adults with:

- confirmed MRSA skin and soft tissue infections; AND
- oral anti-MRSA agents are not an option; AND
- outpatient use OR inpatient use if dalbavancin allows earlier hospital discharge;AND
- intended treatment duration is 1 week or more; AND
- patient unable to receive IV vancomycin or daptomycin due to logistical barriers

Dalbavancin- Caution

Prolonged half life - risk for resistance

- including cross resistance to vancomycin and daptomycin
  - Werth et al; 2018, Janabi et al; 2023

Relapse rate significant from several reports of prosthetic joint infections

- Gatti et al; 2021, De Vito et al; 2023

Decreased efficacy in high inoculum infections

- in vitro studies indicating lack of bactericidal activity
- adjunctive therapy with daptomycin or only as sequential therapy
  - Kebriaei et al; 2023

Antimicrobial Agents and Chemotherapy

Antimicrobial Chemotherapy | Short Form

Proactive therapeutic monitoring of dalbavancin concentrations in the long-term management of chronic osteoarticular/ periprosthetic joint infections

Dario Cattaneo,[1] Marta Fusi,[2] Lucia Galli,[1] Camilla Genovese,[1] Riccardo Giorgi,[1] Maddalena Matone,[1] Stefania Merli,[1] Marta Colaneri,[1] Andrea Gori[1,2]

Study of 16 patients (58% periprosthetic joint infections/ 42% osteoarticular)

- 42% MRSA/42% MSSA /16% *E. faecalis*, 9% *S. anginosus*
- TDM: recommended for osteoarticular infections
  - need to maintain concentration > 8 µg/mL

Dose: 1500 mg every 39-47 days (6 - 12 injections) over 15 months

- > 90% could achieve dalbavancin concentration > 8 µg/mL

Caveat:

- hypoalbulinemia, overweight, renal insufficiency:
  - can result in suboptimal drug exposure for staphylococcal infections

Reality for BC:

- no current TDM
- $12,000-24,000 - drug costs alone
- risk for resistance??

Optimal Duration of Antibiotics

LESS IS MORE

Open Forum Infectious Diseases
PERSPECTIVES

Can the Future of ID Escape the Inertial Dogma of Its Past? The Exemplars of Shorter Is Better and Oral Is the New IV

Kusha Davar,[1,©] Devin Clark,[1] Robert M. Centor,[2] Fernando Dominguez,[1] Bassam Ghanem,[3] Rachael Lee,[4] Todd C. Lee,[5,©] Emily G. McDonald,[6,©] Matthew C. Phillips,[7,8] Parham Sendi,[9] and Brad Spellberg[1]

Table 1. Summary of Shorter Is Better Randomized Controlled Trials

Diagnosis	Short (d)	Long (d)	Result	No. of RCTs	Refs.
Community-acquired pneumonia	3–5	5–14	Equal	14	[32–45]
Atypical community-acquired pneumonia	1	3	Equal	1	[46]
Possible pneumonia in ICU	3	14–21	Equal	1	[47]
Ventilator-associated pneumonia	8	15	Equal	2	[48, 49]
Complicated UTI/pyelonephritis	5 or 7	10 or 14	Equal	9	[50–58]
Complicated intra-abdominal infection	4–8	10–15	Equal	2	[59, 60]
Gram-negative bacillus bacteremia	7	14	Equal	3	[61–63]
Cellulitis/wound/abscess	5–6	10	Equal	4	[64–67]
Osteomyelitis	42	84	Equal	2	[68, 69]
Osteomyelitis s/*P* implant removal	28	42	Equal	1	[70]
Diabetic osteomyelitis s/*P* Debridement	10–21	42–90	Equal	2	[71, 72]
Septic arthritis	14	28	Equal	1	[73]
Acute exacerbations of bronchitis and sinusitis	≤5	≥7	Equal	>25	[74–81]
Neutropenic fever	AFx72 h/3d	ANC > 500/9d	Equal	2	[82, 83]
Perioperative prophylaxis	0–1	1–5	Equal	56	[84–88]
Plasmodium vivax malaria	7	14	Equal	1	[89]
Erythema migrans (Lyme disease)	7	14	Equal	1	[90]

Abbreviations: ANC, absolute neutrophil count; d, day; h, hour; ICU, intensive care unit; RCT, randomized controlled trial; Refs., references; UTI, urinary tract infection.

Discontinuing β-lactam treatment after 3 days for patients with community-acquired pneumonia in non-critical care wards (PTC): a double-blind, randomised, placebo-controlled, non-inferiority trial

Aurélien Dinh, Jacques Ropers, Clara Duran, Benjamin Davido, Laurène Deconinck, Morgan Matt, Olivia Senard, Aurore Lagrange, Sabrina Makhloufi, Guillaume Mellon, Victoire de Lastours, Frédérique Bouchand, Emmanuel Mathieu, Jean-Emmanuel Kahn, Elisabeth Rouveix, Julie Grenet, Jennifer Durmoulin, Thierry Chinet, Marion Pépin, Véronique Delcey, Sylvain Diamantis, Daniel Benhamou, Virginie Vitrat, Marie-Christine Dombret, Bertrand Renaud, Christian Perronne, Yann-Erick Claessens, José Labarère, Jean-Pierre Bedos, Philippe Aegerter, Anne-Claude Crémieux, for the Pneumonia Short Treatment (PTC) Study Group

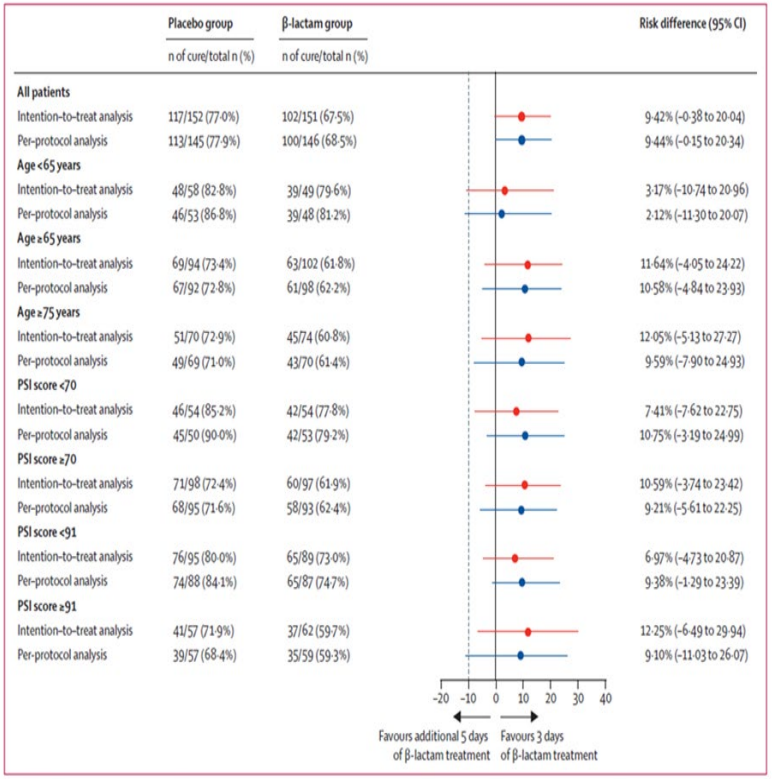


Figure 2: Primary outcome of cure at day 15, in the intention-to-treat and per-protocol population, and post-hoc subgroup analyses
Data are n/N (%) and risk difference with 95% CI in parentheses. Vertical dotted line indicates non-inferiority margin. PSI=Pneumonia Severity Index.

Duration of therapy: 3-5 days

Minimum 3 days if clinically stable:

- temperature ≤ 37.80C
- heart Rate < 100/min
- respiratory rate < 24/min
- O_2 on room air
- blood pressure ≥90mm HG
- normal/baseline mental status

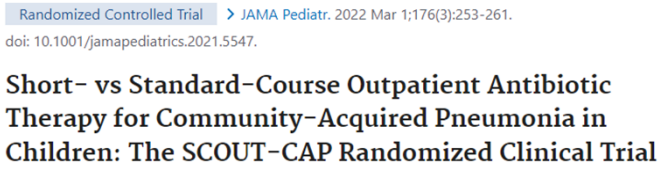
Exceptions:

P. aeruginosa
Stenotrophomonas maltophilia
Legionella spp

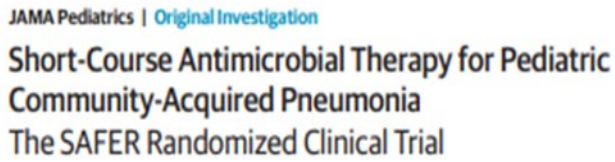
Paediatric Pneumonia

- 2008 Cochrane review non severe CAP: 3 days as effective as 5 days
- WHO 2009:3-5 days for pneumonia
- UK NICE guidelines: 5days

Note: CPS (2015) / AAP(2011) : still recommend 7-10 days


Randomized Controlled Trial > JAMA Pediatr. 2022 Mar 1;176(3):253-261.
doi: 10.1001/jamapediatrics.2021.5547.

Short- vs Standard-Course Outpatient Antibiotic Therapy for Community-Acquired Pneumonia in Children: The SCOUT-CAP Randomized Clinical Trial


JAMA Pediatrics | Original Investigation

Short-Course Antimicrobial Therapy for Pediatric Community-Acquired Pneumonia
The SAFER Randomized Clinical Trial

5 days superior to 10 days

- risk of antimicrobial resistance assessed in 171 children
- significantly lower in 5 vs 10 day course

Cellulitis

MINIMUM CLINICAL CRITERIA (ALL):

- redness
- warmth
- swelling
- pain
- unilateral

Refer to DIFFERENTIAL DIAGNOSIS if bilateral or not all minimum clinical criteria met

GENERAL MANAGEMENT:

- **ELEVATION OF LIMB ESSENTIAL**
- if systemic symptoms: CBC ± CRP
- if fever / chills or lymphangitis: blood cultures

Management:

- outpatient for majority
  - *Streptococci spp* 90%/ *S.aureus* 10%
    - cefazolin vs ceftriaxone
    - cephalexin
  - duration of therapy: 5 days

Randomized Controlled Trial > Clin Microbiol Infect. 2022 May;28(5):739-740.
doi: 10.1016/j.cmi.2021.12.008. Epub 2021 Dec 21.

Seven-versus 14-day course of antibiotics for the treatment of bloodstream infections by enterobacterales: a randomized, controlled trial: authors' response

Randomized Controlled Trial > Clin Infect Dis. 2019 Sep 13;69(7):1091-1098.
doi: 10.1093/cid/ciy1054.

Seven Versus 14 Days of Antibiotic Therapy for Uncomplicated Gram-negative Bacteremia: A Noninferiority Randomized Controlled Trial

Clin Infect Dis. 2018 Jan 15; 66(2): 172–177. Published online 2017 Oct 8. doi: 10.1093/cid/cix767

PMCID: PMC5849997 | PMID: 29190320

Comparing the Outcomes of Adults With Enterobacteriaceae Bacteremia Receiving Short-Course Versus Prolonged-Course Antibiotic Therapy in a Multicenter, Propensity Score–Matched Cohort

Gram negative bacteremia:

Support for 7day course if clinical response within 7 days

- may protect against development of resistance
- oral step down therapy with bioavailable agent
  - pyelonephritis – initial 1-2 doses ceftriaxone

JAMA Netw Open. 2020 Oct; 3(10): e2020166.
Published online 2020 Oct 8. doi: 10.1001/jamanetworkopen.2020.20166: 10.1001/jamanetworkopen.2020.20166

PMCID: PMC7545306
PMID: 33030555

Oral β-Lactam Antibiotics vs Fluoroquinolones or Trimethoprim-Sulfamethoxazole for Definitive Treatment of Enterobacterales Bacteremia From a Urine Source

Where Are We Now?

MAKING PROGRESS

Open Forum Infectious Diseases
PERSPECTIVES

Can the Future of ID Escape the Inertial Dogma of Its Past? The Exemplars of Shorter Is Better and Oral Is the New IV

Kusha Davar,[1,*] Devin Clark,[1] Robert M. Centor,[2] Fernando Dominguez,[1] Bassam Ghanem,[3] Rachael Lee,[4] Todd C. Lee,[5,*] Emily G. McDonald,[6,*] Matthew C. Phillips,[7,8] Parham Sendi,[9] and Brad Spellberg[1]

Table 2. Summary of Randomized Controlled Trials of Oral vs IV-Only Therapy

Diagnosis	No. of RCTs Demonstrating IV > Oral	No. of RCTs Demonstrating Oral ≥ IV	References
Osteomyelitis	0	9 (all equal)	[103–111]
Bacteremia	0	10 (8 equal, 2 superior cure for oral)	[109, 112–120]
Endocarditis	0	3 (2 equal, 1 superior mortality for oral)	[121–123]

Abbreviations: IV, intravenous; RCT, randomized controlled trial.

› Am J Med. 2022 Mar;135(3):369-379.e1. doi: 10.1016/j.amjmed.2021.10.007. Epub 2021 Oct 27.

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

Noah Wald-Dickler [1], Paul D Holtom [2], Matthew C Phillips [3], Robert M Centor [4], Rachael A Lee [4], Rachel Baden [3], Brad Spellberg [5]

Kelowna General Hospital
Antimicrobial Consumption
2023-2024 - Semi- Annual Report

Cumulative Antimicrobial Consumption

Indicator	2022-2023	2023-2024* KGH	2022-2023-	2023-2024*- RIH
DDD/1000 pt-days	451	466	410	440
DOT/1000 pt-days	392	403	368	398

*April 1, 2023-October 16, 2023

Top 10 Antimicrobial Consumption

Defined Daily Dose (DDD)/1000 Patient-Days†

†Standard Adult Daily Dose Defined by the WHO

Antimicrobial	2022-2023	2023-2024* KGH	% Change	2022-2023-	2023-2024*- RIH	% Change-
ceFAZolin	89.3	90.8	2%	89.9	99.5	11%
cefTRIAXone	79.3	76.4	-4%	72.0	73.4	2%
piperacillin-tazobactam	38.8	38.1	-2%	37.1	38.0	2%
amoxicillin-clavulanate PO	23.0	28.9	25%	18.7	21.1	13%
doxycycline	20.0	23.3	16%	23.9	30.9	29%
vancomycin IV	20.1	21.5	7%	14.6	15.7	8%
ampicillin IV	11.4	14.4	26%	6.8	11.5	69%
cloxacillin IV	9.7	14.2	47%	13.3	8.8	-34%
meropenem	14.4	14.1	-2%	14.8	15.7	6%
cefixime	14.1	12.8	-9%	10.5	10.1	-3%

Days of Therapy (DOT)/1000 Patient-Days

Antimicrobial	2022-2023	2023-2024* KGH	% Change	2022-2023-	2023-2024*- RIH	% Change
cefTRIAXone	78.1	78.0	0%	72.4	79.6	10%
ceFAZolin	49.1	54.9	12%	50.7	59.4	17%
piperacillin-tazobactam	46.1	45.6	-1%	46.8	47.8	2%
amoxicillin-clavulanate PO	20.8	25.9	25%	19.4	21.4	10%
vancomycin IV	20.7	21.7	5%	15.1	15.2	1%
metroNIDAZOLE IV	16.4	16.9	3%	11.2	14.6	31%
cefixime	14.4	13.1	-9%	9.9	9.5	-4%
metroNIDAZOLE PO	11.8	12.2	3%	7.8	8.4	8%
doxycycline	10.2	12.0	17%	13.6	17.4	28%
ciprofloxacin PO	11.6	11.6	0%	5.4	5.4	0%

Stable cumulative consumption (DOT/1000 patient-days ↑ 3%)
-Cumulative consumption similar to RIH
~40% inpatients receiving antimicrobials /day

Stable consumption:
-ceftriaxone - no chg
-ciprofloxacin PO - no chg
-metronidazole IV ↑ 3%
-metronidazole PO ↑3%
-piperacillin-tazobactam ↓ 1%
-vancomycin IV ↑ 5%

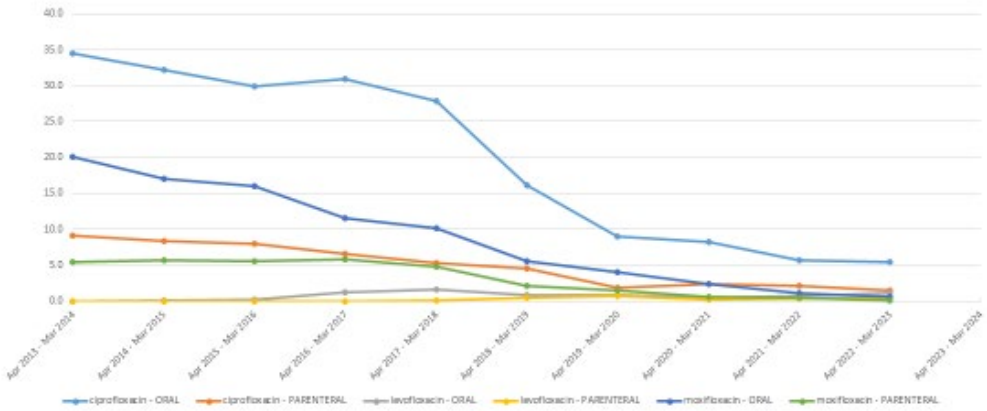
Increased consumption:
-amoxicillin-clavulanate PO ↑25%
-cefazolin ↑ 12%

Decreased consumption:
-cefixime ↓ 9%

Analysis:
- Broad-spectrum antibiotic consumption stable or decreased except for amoxicillin-clavulanate PO
-Cumulative consumption similar to pre-pandemic

RIH – Antimicrobial Stewardship

Fluoroquinolones



RIH penicillin allergy delabelling:

- 25% penicillin allergy inpatients on antibiotics – delabelled
  - 1/3 by history alone
- low-risk allergies eligible for direct oral challenges:
  - 50% delabelled (40% received a direct oral challenge)

cmajOPEN
Research

Interprovincial variation in antibiotic use in Canada, 2019: a retrospective cross-sectional study

Michael Crosby MSc PharmD, Teagan Rolf von den Baumen BSc PharmD, Cherry Chu MSc, Tara Gomes MHSc PhD, Kevin L. Schwartz MD MSc, Mina Tadrous PharmD PhD

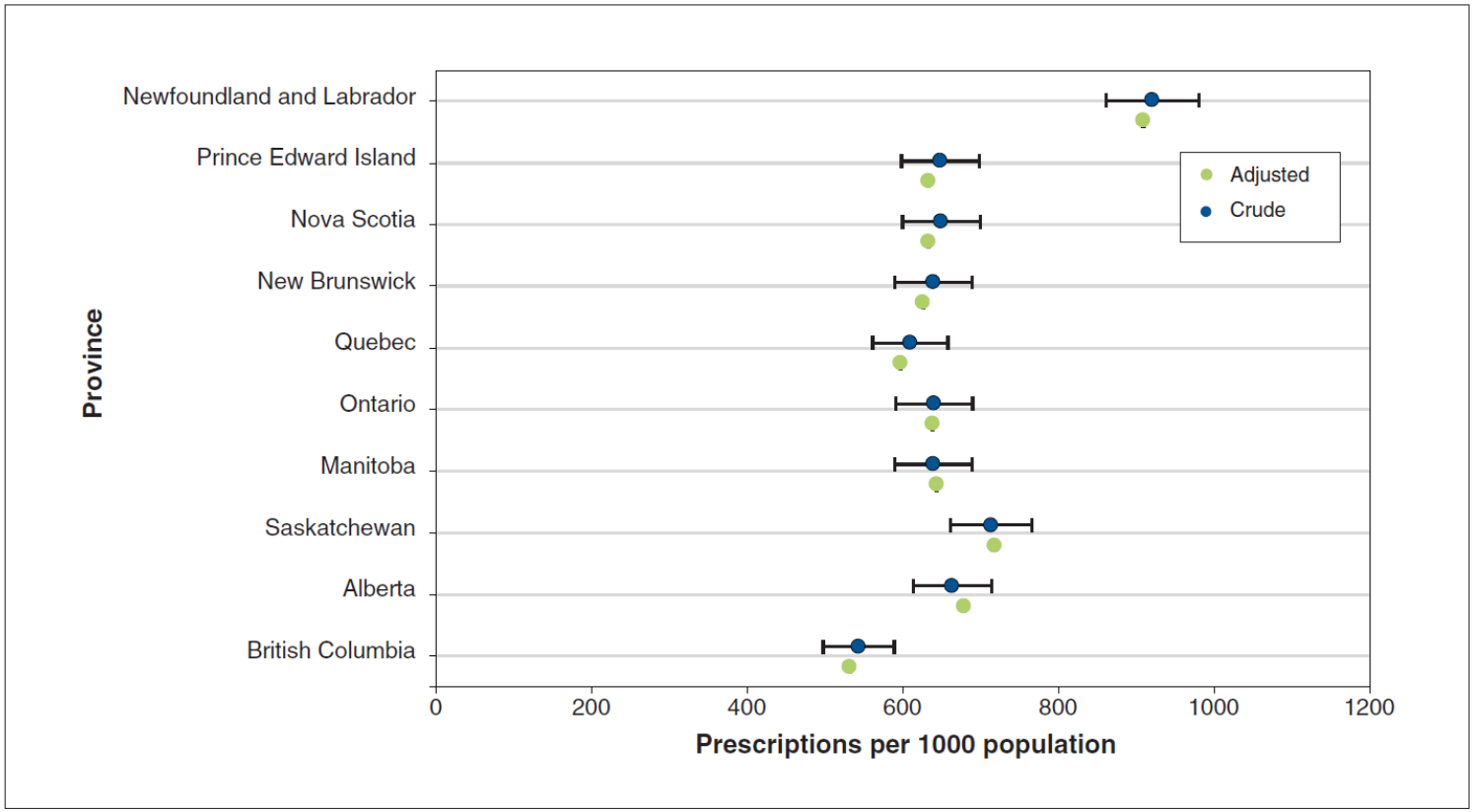
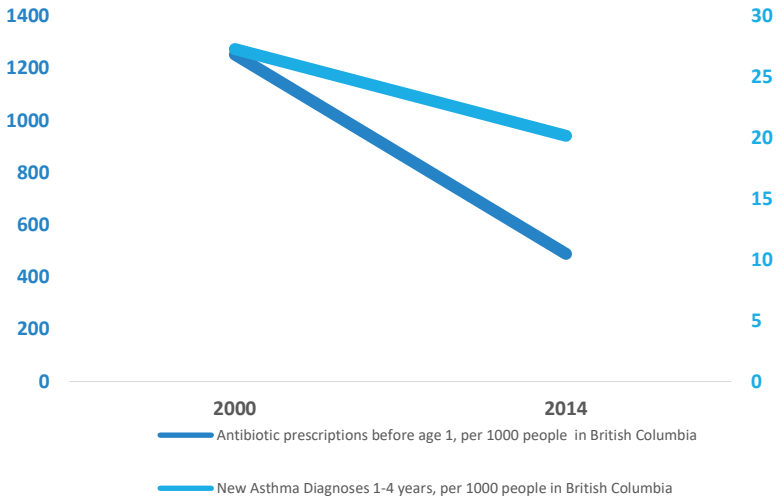


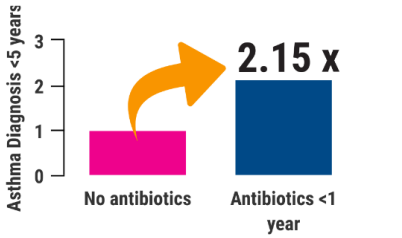
Figure 1: Crude and age-adjusted antibiotic prescription rates per 1000 population with 95% confidence intervals. Poisson model outputs are available in Appendix 2 (www.cmajopen.ca/content/10/1/E262/suppl/DC1).

Preventing Antibiotic Harm | Asthma

Growing evidence:

reducing antibiotics in infancy may significantly reduce childhood asthma.





Children are **2.15 times more likely** to be diagnosed with asthma by age 5 if they take antibiotics before age 1.

Patrick et al. Lancet Respir Med. 2020 Nov;8(11):1094-1105.

Bugs & Drugs

- **Antibiotics**
- **Treatment Recommendations**
- **COVID-19 Treatment Guidelines**
- **Prophylaxis Recommendations**
- **Dental**
- **Infections in Pregnancy**
- **Organisms**
- **References**

What's New

Please ensure you are using the most up-to-date app version of Bugs & Drugs 2.0. You should see a white "2.0" in the orange banner at the bottom of the app icon. The 2.0 app is available free of charge from the Apple app store or Google Play.

Updated January 2024:

1. Treatment Recommendations > Ophthalmic Infections > Endophthalmitis
2. Treatment Recommendations > Adult Patients > Genital > Vulvovaginitis > Candidiasis
3. Infections in Pregnancy > Prevention of Perinatal Infection > Antimicrobial Prophylaxis for Preterm (< 37 weeks gestation) Rupture of Membranes

Updated November 2023:

1. Treatment Recommendations > Culture-Directed Infections > Bacteremia > S. aureus
2. Antibiotics > Antimicrobial Dosing Guide and Daily Costs > Adult Dosing Guide and Daily Costs > Antituberculous Agents ***new***
3. Antibiotics > Adult Dosing

Version 2.0