Surgical Prophylaxis Update
June 2018

Disclosures

No pharmaceutical / industry relationships / sponsorships

Bugs and Drugs:

- as co-author of Bugs & Drugs I receive nominal payment for my work in updating the content of the application

Objectives

- Discuss new recommendations in surgical prophylaxis
- Discuss the impact of antibiotics on the human microbiome
- Discuss the safety of cephalosporins in patients with penicillin allergy
- Discuss new guidelines for Clostridium difficile infection
- Discuss optimal duration of antibiotic therapy for surgical patients

Clinical Review & Education

JAMA Surgery | Special Communication

Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection, 2017

Sandra I. Berrios-Torres, MD; Craig A. Umscheid, MD, MSCE; Dale W. Bratzler, DO, MPH; Brian Leas, MA, MS; Erin C. Stone, MA; Rachel R. Kelz, MD, MSCE; Caroline E. Reinke, MD, MSHP; Sherry Morgan, RN, MLS, PhD; Joseph S. Solomkin, MD; John E. Mazuski, MD, PhD; E. Patchen Dellinger, MD; Kamal M. F. Itani, MD; Elie F. Berbari, MD; John Segreti, MD; Javad Parvizi, MD; Joan Blanchard, MSS, BSN, RN, CNOR, CIC; George Allen, PhD, CIC, CNOR; Jan A. J. W. Kluytmans, MD; Rodney Donlan, PhD; William P. Schecter, MD; for the Healthcare Infection Control Practices Advisory Committee

GLOBAL GUIDELINES FOR THE PREVENTION OF SURGICAL SITE INFECTION

World Health Organization

SPECIAL ARTICLES

American College of Surgeons and Surgical Infection Society: Surgical Site Infection Guidelines, 2016 Update

Kristen A Ban, MD, Joseph P Minei, MD, FACS, Christine Laronga, MD, FACS, Brian G Harbrecht, MD, FACS, Eric H Jensen, MD, FACS, Donald E Fry, MD, FACS, Kamal MF Itani, MD, FACS, E Patchen Dellinger, MD, FACS, Clifford Y Ko, MD, MS, MSHS, FACS, Therese M Duane, MD, MBA, FACS

Interior Health

Pre-Operative Antibiotic Regimens for Adult Patients

August 2018

Interior Health Surgical Prophylaxis Guidelines

Inside Net: Clinical Resources/Pharmacy/Antimicrobial Stewardship

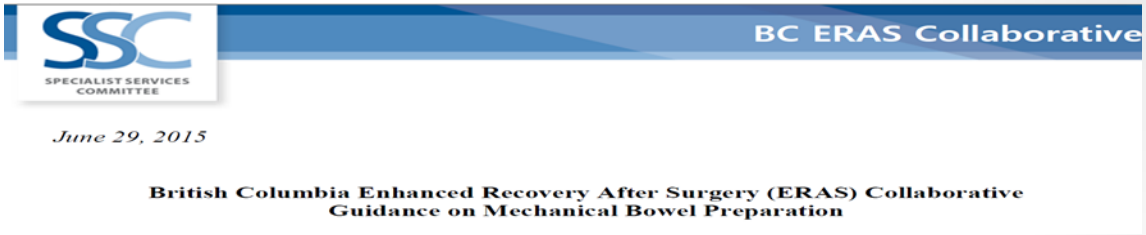
Major changes to IH Surgical Prophylaxis Guidelines

- addition of procedures
- oral decontamination for bowel surgery
- antibiotic prophylaxis for caesarean section
- augmented therapy for prostate surgery/biopsy
- changes for revision arthroplasty
- prophylaxis for MRSA
- diminishing role for post-operative prophylactic antibiotics

Addition of New Procedures

- Breast surgery - high risk
- Gastroesophageal endoscopy - high risk
- Hepatobiliary surgery – high risk
- Urogenital surgery
- Cystoscopy - high risk
- Shock wave lithotripsy - high risk
- Revision arthroplasty

Bowel Surgery



Mechanical bowel preparation /oral decontamination :

reduces surgical wound infections /not anastomotic leak:

- Bellows et al. 2011- MA 16 RCTs
- Roos et al. 2013- MA 8 RCTs
- Nelson et al. 2014- MA 14 RCTs
- Koullouros et al. 2017 - MA 12 RCTs
- Hata et al. 2016 - RCT 579 patients

Add:

mechanical bowel prep and neomycin + metronidazole to current pre-op IV cefazolin + metronidazole

Obstetrics and Gynecology - Caesarean Section

- Tita et al (2016) RCT (n >2000) - azithromycin plus cefazolin :
  - 50% reduction of endometritis / wound infection.

  Generalizability limited by:
  - location: South US -climate markedly different.
  - high obesity (25% BMI ≥35)
  - ethnicity: 65% non-Caucasian /antenatal care
  - baseline post C/S infection of 12% (IH SSI rarely over 2%)
  - neonatal risk:
    - resistance /microbiome
- Boggess K et al. (2017)- highest infection risk:
  - black ethnicity,
  - non-transverse uterine incision
  - membrane rupture > 6 hours
  - surgery > 49 minutes

Urology- Prostatic Biopsy/ Surgery

Augmented therapy

Moderate risk: add ceftriaxone / gentamicin to ciprofloxacin or TMP-SMX

- antibiotics in the last 6 months
- chronic indwelling urinary catheterization
- previous endocarditis
- previous sepsis following prostate biopsy
- previous urine culture with ciprofloxacin resistant organism
- recent international travel (other than South Asia)
- prostate volume ≥ 75 mL/severe voiding disturbances
- diabetes /chronic steroid use /immunodeficiency

High risk: add meropenem to ciprofloxacin or TMP-SMX regimen

- previous urine/blood culture positive for ESBL and /or AmpC
  recent travel (6 months) to South Asia

Yang et al. (2016)

Yamamoto et al. (2016)

MRSA colonization/past infection

For surgeries involving medical devices:

add vancomycin to cefazolin

vancomycin less effective than cefazolin for preventing SSIs due to methicillin susceptible S. aureus (MSSA)

Orthopaedic Surgery

Levy PY et al. (2013) - Systemic Review / Meta-analysis

confirmed nasal carriage of *S. aureus* major risk factor for SSI

Schweizer ML et al. (2015)

nasal screening and decolonization for S. aureus carrier as part of a bundled intervention (included chlorhexidine – gluconate baths)

Pre-operative assessment of nasal culture for S. aureus carriage should be considered. If nasal carrier (MSSA or MRSA): suggest intranasal mupirocin 2% BID for 4 days prior to surgery. No evidence for benefit if not nasal carrier.

Note:

- insufficient evidence to routinely recommend use of antibiotic impregnated cement in primary arthroplasties
- vancomycin alone should be restricted to true cefazolin allergy as it is associated with higher frequency of postoperative infections (including Gram positive infections).

Orthopedic Surgery - Revision Arthroplasty

Withholding prophylactic antibiotics for revision arthroplasty prior to obtaining intraoperative cultures no longer widely recommended.

- Wouthuyzen-Bakker M. et al. (2017)- systemic review -7 studies:

  risk of infection from withholding prophylaxis posed a greater risk, especially if low risk for infection or cultures positive for an organism

- Wouthuyzen-Bakker M. et al. (2017)- retrospective analysis:

  pre-op antibiotics do not reduce culture yield for knee arthroplasty but showed trend toward higher PJI rate in post- op period

- Anagnostopoulos A et al. (2018)- cohort study (n=110)

  showed peri-operative prophylaxis did not negatively influence the microbiological yield in *C. acnes* (previously *P. acnes*)

Post–operative Prophylactic Antibiotics

- Surgical Infection Society (SIS), Infectious Diseases Society of America (IDSA) (2013):
  - no post-operative doses

- Medical Letter (2016):
  - no post-operative doses recommended

- American College of Surgeons and Surgical Society:Surgical Site Infection Guidelines (2016)
  - antibiotics should be discontinued at time of incision closure - no evidence that antibiotic administration after incision closure decreases SSI risk across range of procedures including clean, clean contaminated and contaminated wound classes, but excluding implant-based breast reconstruction, joint arthroplasty, and cardiac procedures.

- WHO – Surgical Site Infections (2016):
  - recommend against prolongation of surgical antibiotic prophylaxis administration after completion of the operation for the purpose of preventing SSIs, except for cardiac and orthognathic procedures. (strong evidence/moderate quality evidence)

- Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection (2017):
  - in clean, and clean contaminated procedures, do not administer additional prophylactic antimicrobial agent doses after the surgical incision is closed in the operating room, even in the presence of a drain (category 1A- strong recommendation; high quality evidence)

Orthopedic Surgery - Post-op antibiotics

Support post-operative prophylaxis:

- American College of Surgeons and Surgical Society Guidelines (2016) antibiotics discontinued at the time of incision closure for all procedures (except joint arthroplasty)

- South Australian Surgical Antimicrobial Prophylaxis Clinical Guideline (2017) recommends post-operative antibiotic prophylaxis with cefazolin 2 g IV Q8H x 2 doses for
  - primary arthroplasty / revision arthroplasty / reoperation
  - internal fixation of large bones
  - lower limb amputation (addition of metronidazole to cefazolin)

Orthopedic Surgery - Post-op antibiotics

Do not support post-operative prophylaxis:

- Thornley P et al. (2015) SR/MA of 4 RCTs > 4000 total hip/knee arthroplasties: Postoperative antibiotics did not reduce the rate of overall surgical site infections compared to placebo

- WHO – Surgical Site Infections Recommendations (2016) recommends against prolongation of surgical antibiotic prophylaxis administration after completion of the operation for the purpose of preventing SSIs

- CDC Guideline (2018) recommends for not to administer additional prophylactic antimicrobial agent doses after the surgical incision is closed in the operating room, even in the presence of a drain

2017 Foundation for Arthroplasty Research and Education

Duke University

Perioperative Antibiotic Prophylaxis in Patients Undergoing Elective Total Knee arthroplasty

Aim- to provide level 1 evidence for or against single versus 24 hour antibiotic prophylaxis for knee arthroplasty

Human Microbiome

Collection of microorganisms in body that exist in mutualistic relationship with the host

Perform essential functions:

- nutrient absorption
- regulate immune system
- protect against pathogens

Disruption- dysbiosis

- nutrient absorption → ? obesity
- inflammation→ ? autoimmune diseases
- damage to cells→ ? cancers

Langdon et al. Genome Medicine (2016) 8:39
DOI 10.1186/s13073-016-0294-z

Genome Medicine

REVIEW Open Access

The effects of antibiotics on the microbiome throughout development and alternative approaches for therapeutic modulation

Amy Langdon[1,2†], Nathan Crook[1,3†] and Gautam Dantas[1,2,4,5*]

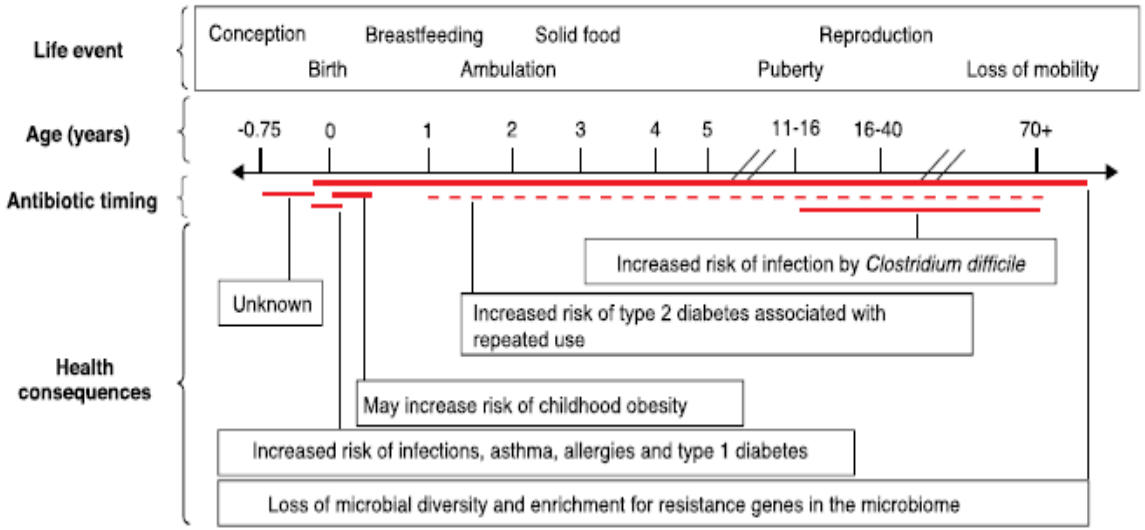


Fig. 1 Health consequences linked to the disruption of human-associated microbiota involving antibiotic use during development and adulthood. *Red lines* indicate that a single dose of antibiotics within the time period has been linked to a health consequence, whereas a *dotted red line* indicates that multiple doses of antibiotics within the time period are required to observe a link

RESEARCH ARTICLE

Same Exposure but Two Radically Different Responses to Antibiotics: Resilience of the Salivary Microbiome versus Long-Term Microbial Shifts in Feces

Egija Zaura,[a] Bernd W. Brandt,[a] M. Joost Teixeira de Mattos,[b] Mark J. Buijs,[a] Martien P. M. Caspers,[c] Mamun-Ur Rashid,[d] Andrej Weintraub,[d] Carl Erik Nord,[d] Ann Savell,[e] Yanmin Hu,[e] Antony R. Coates,[e] Mike Hubank,[f] David A. Spratt,[g] Michael Wilson,[g] Bart J. F. Keijser,[c] Wim Crielaard[a]

UK/Sweden - RCT/placebo controlled study

- single dose clindamycin, ciprofloxacin, amoxicillin or minocycline
- saliva and feces collected at exposure,1, 2, 4, 12 months

Results:

- Salivary microbiome – robust /recovers quickly
- Fecal microbiome - significantly affected microbial community
  - predominantly butyrate producing species
    - inhibit inflammation, carcinogenesis, oxidative stress
  - clindamycin and ciprofloxacin:
    - most impact on butyrate producing microbial community of gut
  - amoxicillin:
    - least effect on microbiome composition
    - highest number of resistance genes

OPEN ACCESS Freely available online

PLoS one

Short-Term Antibiotic Treatment Has Differing Long-Term Impacts on the Human Throat and Gut Microbiome

Hedvig E. Jakobsson[1,2], Cecilia Jernberg[1], Anders F. Andersson[1,3], Maria Sjölund-Karlsson[1], Janet K. Jansson[4,5], Lars Engstrand[1,2]*

1 Department of Bacteriology, Swedish Institute for Infectious Disease Control, Solna, Sweden, **2** Department of Microbiology, Tumor and Cell Biology, Karolinska Institute, Stockholm, Sweden, **3** Limnology/Department of Ecology and Evolution, Evolutionary Biology Centre, Uppsala University, Uppsala, Sweden, **4** Department of Microbiology, Swedish University of Agricultural Sciences, Uppsala, Sweden, **5** Ecology Department, Lawrence Berkeley National Laboratory, Berkeley, California, United States of America

Macrolide treatment:

- reduced bacterial diversity
- 4 years post therapy:
  - disturbed microbiota
  - high levels of macrolide resistance detected

Penicillin Allergy

Clinical Infectious Diseases

MAJOR ARTICLE

The Impact of a Reported Penicillin Allergy on Surgical Site Infection Risk

Kimberly G. Blumenthal,[1,2,3,4] Erin E. Ryan,[5,6] Yu Li,[1,2] Hang Lee,[4,7] James L. Kuhlen,[8] and Erica S. Shenoy[2,4,5,6]

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Clinical Infectious Diseases

EDITORIAL COMMENTARY

The Influence of Reported Penicillin Allergy

E. Patchen Dellinger,[1] Rupali Jain,[2,3] and Paul S. Pottinger[3,4]

Departments of [1]Surgery, [2]Pharmacy, [3]Medicine, and [4]Allergy and Infectious Diseases, University of Washington Medical Center, Seattle

Penicillin Allergy?

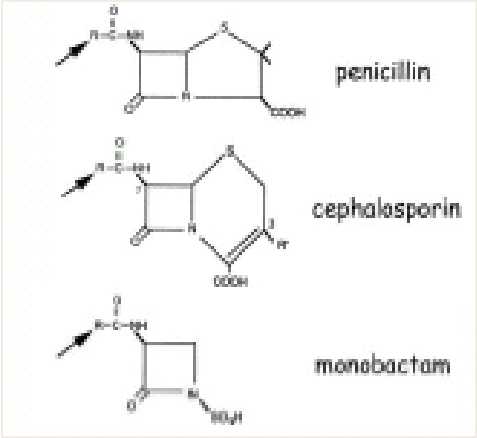
Prevalence of IgE-mediated reaction:

- 0.01-0.05% for penicillin
- 0.0001-0.1% for cephalosporins

https://www.cdc.gov/getsmart/week/downloads/getsmart-penicillin-factsheet.pdf

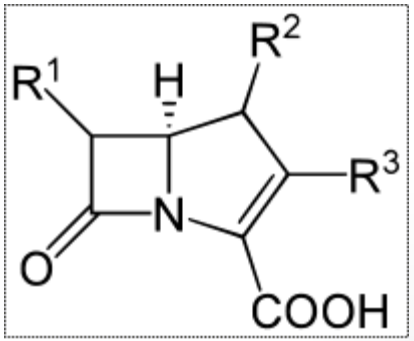
Drug allergy: an updated practice parameter. Ann Allergy Asthma Immunol 2010;105:259-73.

β-lactams



- commonly prescribed
- safe
- risk of adverse effects (AE)
  - 21% - β-lactams
  - 66.8% - alternative antibiotics

Blumenthal KG, et al. J Allergy Clin Immunol Pract 2017;5:616-25



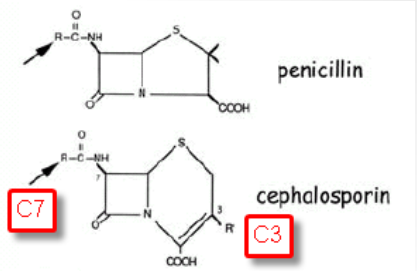
carbapenem

Assessment of β-lactam allergy

- rash due to viral infections common in pediatric patients
- ~ 50% of patients with IgE-mediated penicillin allergy lose their sensitivity after 5 years
    - 80% after 10 years

Drug allergy: an updated practice parameter. Ann Allergy Asthma Immunol 2010;105:259-73.

Cross-reactivity



Cross reactivity between penicillins and cephalosporins :

- related to similarity in side-chain structures rather than β-lactam ring

American Academy of Pediatrics:

"The likelihood of a penicillin-allergic patient reacting to a cephalosporin with a different side chain is similar to that of a non-penicillin-allergic patient".

Pichichero ME. Pediatrics 2005;115:1048-57.

Cross-reactivity

Between penicillins and cephalosporins:

- ~ 1% when penicillin allergy is reported
  - 0.00002% anaphylaxis to cephalosporin
    - similar if no reported penicillin allergy
- 2.55% when penicillin allergy is confirmed

Between penicillins and carbapenems:

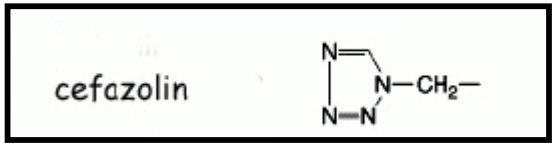
- 4.3% for any type of hypersensitivity reaction
- 2.4% for IgE-mediated reactions

Between cephalosporins or cephalosporins and carbapenems:

- very low
- similar to background allergy rates

Kula B et al Clin Infect Dis 2014;59:1113-22

Cefazolin



Cefazolin does not share a side chain with any other β-lactam and is not expected to cross-react with any other **β-lactam**

http://www.antimicrobialstewardship.com/sites/default/files/asp_simple_messaging_-_beta-lactam_allergy.pdf

Evidence for lack of cross-reactivity with cefazolin

Large retrospective study – evaluation of cephalosporin allergy flag in their chart:

- 622,456 pts exposed to 901,908 courses of PO cephalosporins
- 326,867 pts exposed to 487,630 courses of IV cephalosporins
- 65,915 pts with history of penicillin "allergy" received 127,125 courses of cephalosporins

Results:

Anaphylaxis occurred in:

- 5/901,908 oral courses and 8/487,630 IV courses (0.00055% - 0.0016%)
- no significant difference in anaphylaxis between those with / without listed penicillin or cephalosporin "allergy"

Macy et al. Adverse reactions associated with oral and parenteral use of cephalosporins: a retrospective population-based analysis. J Allergy Clin Immunol 2015;135: 745-52

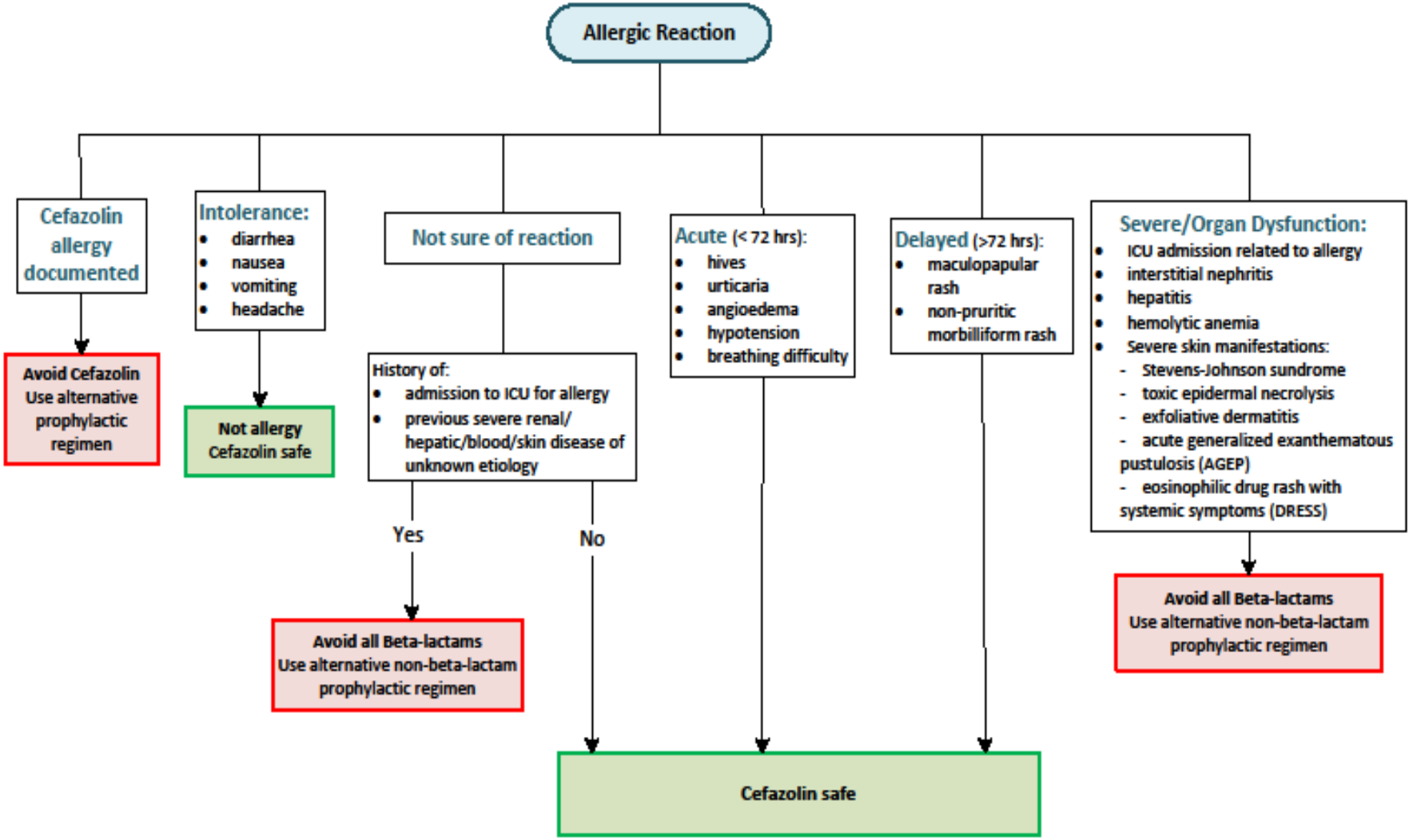
Evidence for lack of cross-reactivity with cefazolin

Prospective study of 41 patients with confirmed penicillin allergy

- skin tested
- given progressive test doses of 3 cephalosporins with side chains dissimilar to penicillin (cefazolin, cefuroxime, ceftriaxone)
- all patients tolerated skin testing and all test doses

Novalbos et al.Clin Exp Allergy 2001;31:438-43

Safety of Cefazolin for Surgical Prophylaxis in Penicillin Allergic Patient



Beta-lactam Cross-Allergy Chart

Beta-lactams	AMOXICILLIN*	AMPICILLIN	CLOXACILLIN	PENICILLIN	PIPERACILLIN*	CEFADROXIL	CEFAZOLIN	CEPHALEXIN	CEFOXITIN	CEFPROZIL	CEFUROXIME	CEFIXIME	CEFOTAXIME	CEFTAZIDIME	CEFTRIAXONE	ERTAPENEM	IMIPENEM	MEROPENEM
AMOXICILLIN*		X	X	X	X	X	✓	X	✓	X	✓	✓	✓	✓	✓	✓	✓	✓
AMPICILLIN	X		X	X	X	X	✓	X	✓	X	✓	✓	✓	✓	✓	✓	✓	✓
CLOXACILLIN	X	X		X	X	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
PENICILLIN	X	X	X		X	✓	✓	✓	X	✓	✓	✓	✓	✓	✓	✓	✓	✓
PIPERACILLIN*	X	X	X	X		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
CEFADROXIL	X	X	✓	✓	✓		✓	X	✓	X	✓	✓	✓	✓	✓	✓	✓	✓
CEFAZOLIN	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
CEPHALEXIN	X	X	✓	✓	✓	X	✓		✓	X	✓	✓	✓	✓	✓	✓	✓	✓
CEFOXITIN	✓	✓	✓	X	✓	✓	✓	✓		✓	X	✓	✓	✓	✓	✓	✓	✓
CEFPROZIL	X	X	✓	✓	✓	X	✓	X	✓		✓	✓	✓	✓	✓	✓	✓	✓
CEFUROXIME	✓	✓	✓	✓	✓	✓	✓	✓	X	✓		✓	X	X	X	✓	✓	✓
CEFIXIME	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	X	✓	✓	✓	✓
CEFOTAXIME	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	X	✓		✓	X	✓	✓	✓
CEFTAZIDIME	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	X	X	✓		✓	✓	✓	✓
CEFTRIAXONE	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	X	✓	X	✓		✓	✓	✓
ERTAPENEM	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		X	X
IMIPENEM	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	X		X
MEROPENEM	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	X	X	

* Applies to beta-lactamase inhibitor combinations i.e. amoxicillin-clavulunate and piperacillin-tazobactam

Avoid all Beta-lactam antibiotics if history of:

- ICU admission related to allergy
- interstitial nephritis
- hepatitis
- hemolytic anemia
- severe skin manifestations:
  - Stevens-Johnson syndrome
  - toxic epidermal necrolysis
  - exfoliative dermatitis
  - acute generalized exanthematous pustulosis (AGEP)
  - eosinophilic drug rash with systemic symptoms (DRESS)

LEGEND:	
Penicillins	
1st Generation Cephalosporins	
2nd Generation Cephalosporins	
3rd Generation Cephalosporins	
Carbapenems	
X	Similar structure. Do not prescribe.
✓	Different structure. Safe to prescribe.

Harm of a Penicillin Allergy Label?

Alternatives to β-lactams:

- more broad spectrum
- more adverse effects
- less effective
- more likely to lead to colonization or infection with multidrug-resistant organisms (VRE, MRSA, MDRGN)

Potential for:

- increased hospital length of stay
- increased re-admission
- increased *C. difficile infection* rates

Macy E, Contreras R. J Allergy Clin Immunol 2014;133:790-6.
MacFadden DR, et al. Ann Allergy Asthma Immunol 2010;105:259-73.

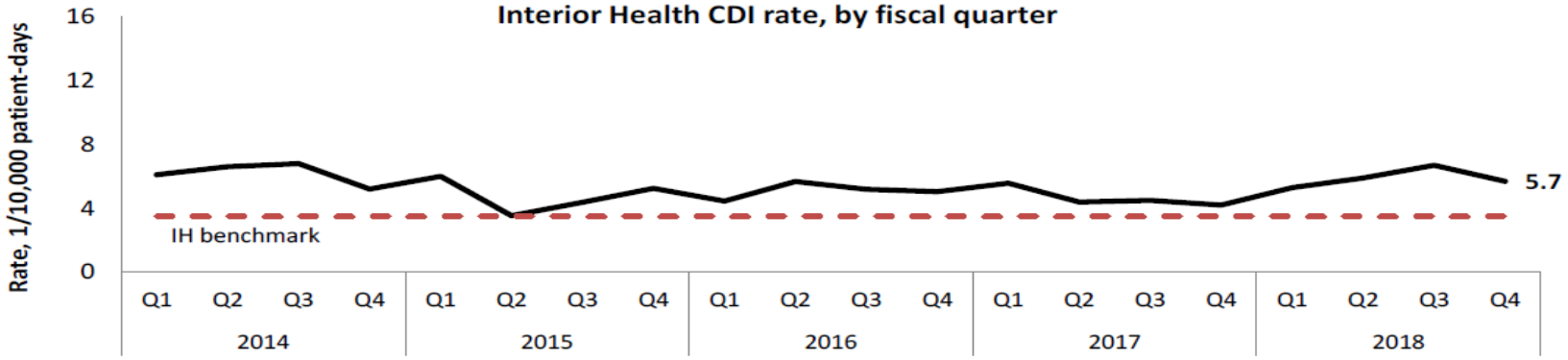
Clostridium difficile

CDI in Interior Health

Infection Prevention and Control Report
Interior Health

Fiscal Year 2018, Quarter 4 Update

***Clostridium difficile* Infection (CDI)**



Analysis: The CDI rate in Quarter 4 was the highest among all Q4 rates in past 5 years. The decrease compared to Quarter 3 was not statisically significant.

Highlight/Actions: Various actions were taken at individual acute care units where CDI cases were more frequent than usual. Investigations of factors possibly impacting CDI rates has started.

Data extract 19 Apr. 2018

Interior Health
Every person matters

CDI rate – BC and IH

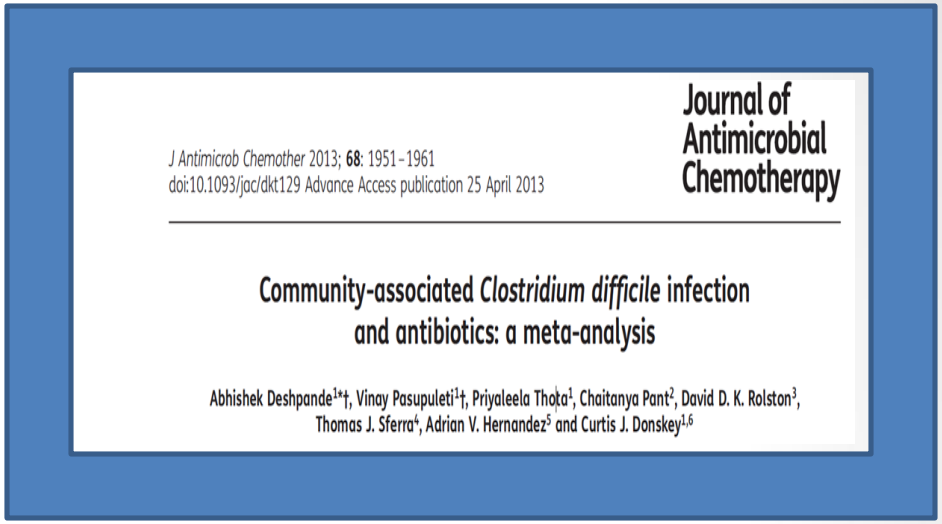
		Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
		2013/14				2014/15				2015/16				2016/17				2017/18			
BC	● Rate per 10,000 inpatient days	5.4	4.4	4.3	4.2	4.1	3.7	3.6	4.9	5.2	5.1	4.5	4.8	4.7	3.8	3.9	4.1	4.2	3.5	4.0	
IH	● Rate per 10,000 inpatient days	6.1	6.6	6.3	4.7	5.3	3.0	4.3	4.9	3.9	5.3	4.9	4.6	5.4	4.3	4.3	3.9	5.5	5.4	6.1	

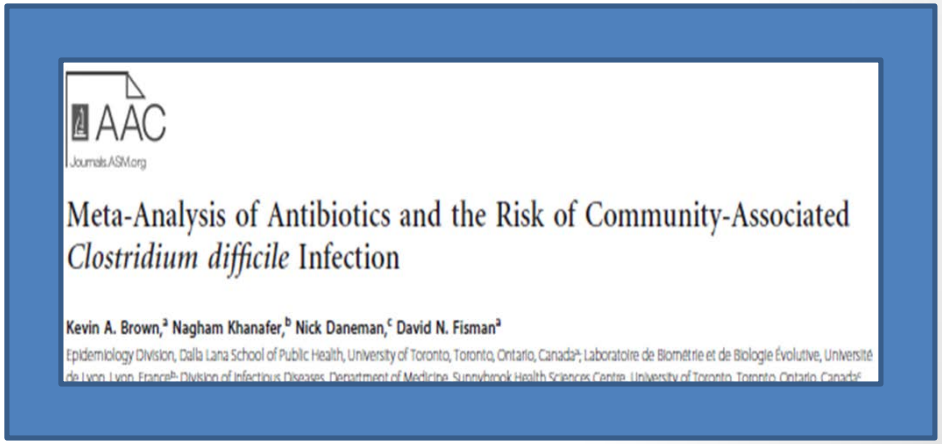
KGH, PRH, RIH, EKH - more CDI cases

Antibiotics at Highest Risk to Cause CDI

- clindamycin
- fluoroquinolones
- broad-spectrum cephalosporins
- broad-spectrum penicillins:
  - amoxicillin-clavulanate
  - piperacillin-tazobactam
- carbapenems

Duration/repeat courses





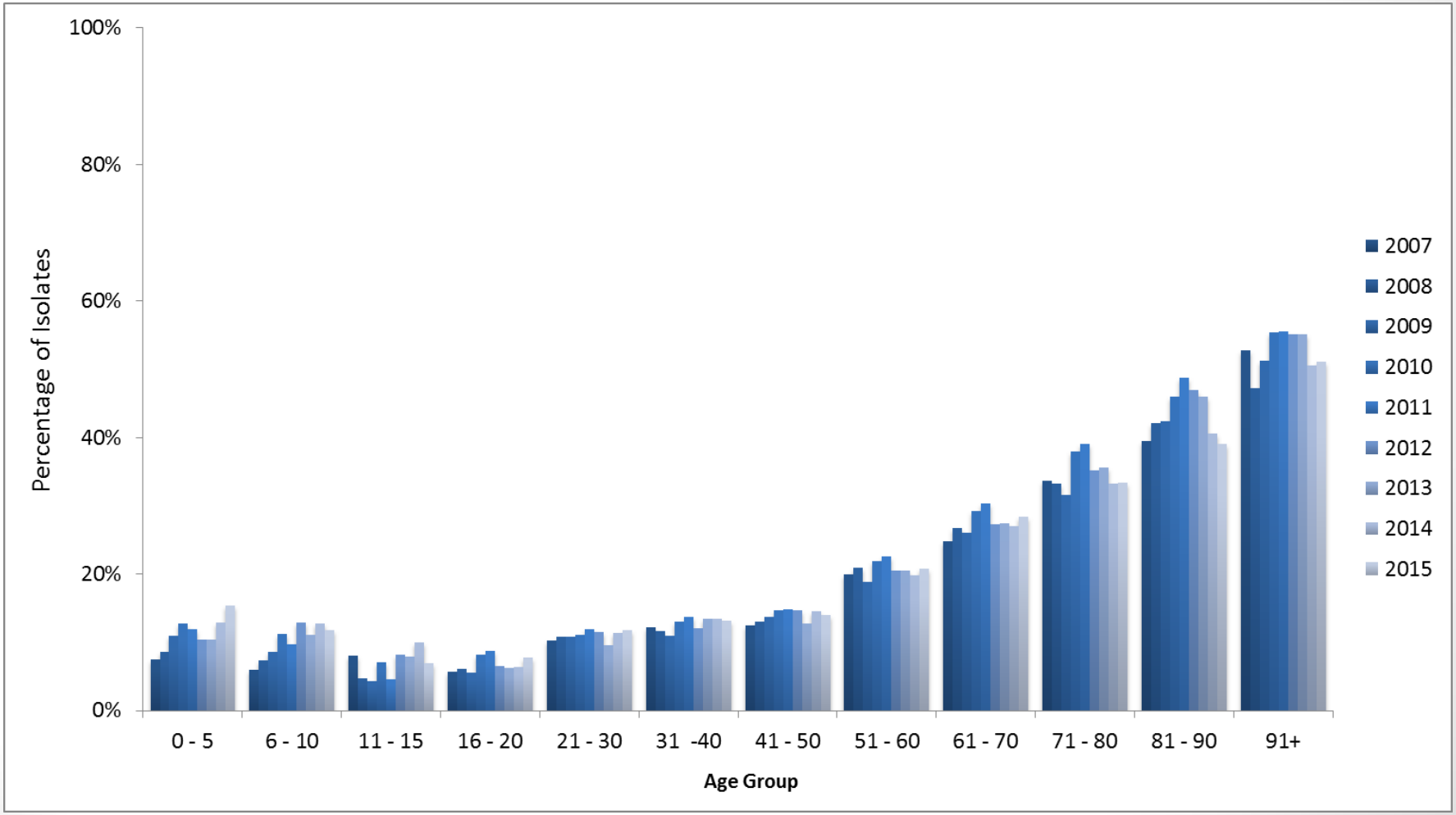
Ciprofloxacin Consumption (2017-2018)

Ciprofloxacin	Oral DDD/1000 patients	IV DDD/1000 patients
KGH	22.2	9.0
RIH	26.2	7.9
EKH	19.1	18.1
KBH	19.7	14.1
PRH	32.4	11.1
VJH	19.5	10.6

Moxifloxacin Consumption (2017-2018)

Moxifloxacin	Oral DDD/1000 patients	IV DDD/1000 patients
KGH	2.9	1.4
RIH	10.3	4.8
EKH	6.1	1.4
KBH	4.3	1.2
PRH	20.1	4.3
VJH	3.3	2.9

E.coli isolates non-susceptible to ciprofloxacin by age group (2007-2015)



Source: LifeLabs Medical Laboratory Services (BC Biomedical Laboratories data)

Health Canada January 2017

serious disabling/ potentially permanent side effects outweigh benefit

- tendons, muscles, joints
- peripheral and central nervous system and neuropsychiatric
- cardiovascular, serious arrhythmias, QT interval prolongation
- acute liver injury
- retinal detachment ?
- aortic aneurysm and dissection

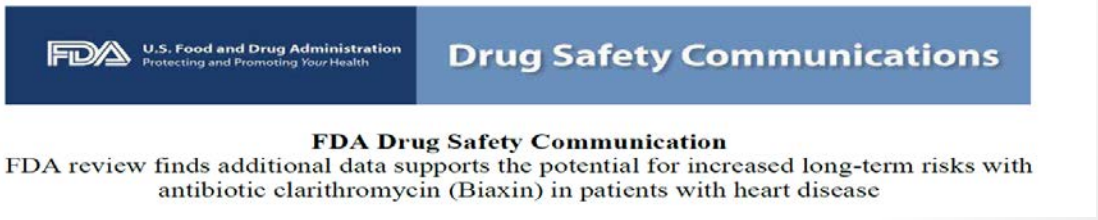
Infectious diseases
Research

Fluoroquinolones and collagen associated severe adverse events: a longitudinal cohort study

Nick Daneman[1, 2, 3, 4], Hong Lu[1], Donald A Redelmeier[1, 2, 3, 5]

FQ restriction- NOT recommended 1st line for:

- acute sinusitis
- acute exacerbation on chronic bronchitis
- uncomplicated urinary tract infection



Probiotics

IH Formulary Probiotic Products*

Probiotic Product	Probiotic organisms/capsule	Suggested dose	Indication(s)
Flora Baby® Probiotic Powder	2 billion CFU/500 mg: *Bifidobacterium bifidum* *Bifidobacterium breve* *Bifidobacterium infantis* *Bifidobacterium longum* *Lactobacillus rhamnosus*	500 mg mixed with fluid up to TID	Restricted to pediatrics (neonates) for the prevention of necrotizing enterocolitis
Bacid® capsules	1 billion CFU/capsule: *Lactobacillus rhamnosus* 0.3 billion Lactobacillus acidophilus 0.7 billion	2 caplets QID (8 billion CFU/day)	Modification of gut flora
Culturelle® capsules	*Lactobacillus rhamnosus* 10 billion/capsule	1 capsule daily	Restricted to treatment prevention of antibiotic-associated diarrhea (not *C. difficile*)

*http://isappscience.org/wp-content/uploads/2016/01/clincial-guide-canada.pdf

Non-Formulary Probiotics

Probiotic Product	Probiotic organisms/capsule	Suggested Dose	Indication(s) (AAD, CDI or NEC)
BioGala® Drops	*L. reuteri protectis* 100 million/5 drops	5 drops daily	**NEC** AAD prevention
BioGala® Chew tablets	*L. reuteri protectis* 100 million/tab	1 tablet daily	AAD prevention
Bio K+® CL capsules	*L. acidophilus* *L. casei.* *L. rhamnosus* 12.5, 25, 30, 50 billion CFU/capsule	1-2 capsules daily	AAD **CDI prevention**
Florastor® capsules	*S. boulardii* 5 billion CFU/capsule	1-2 capsules daily	AAD **CDI prevention**
TuZen® capsules	*L. Plantarum* 10 billion CFU/capsule	1-2 capsules daily	AAD prevention

http://isappscience.org/wp-content/uploads/2016/01/clincial-guide-canada.pdf

Probiotics for Prevention of CDI

- 6 meta-analyses of RCTs
- 2 RCTs
- 1 health technology review of meta-analyses

Summary:

- probiotics inconsistently protect from developing CDI in patients taking antibiotics
- CDI mortality/ length of stay - same as placebo/no treatment

Probiotics to Treat CDI

2010 Cochrane review

probiotics vs. placebo in combination with metronidazole or vancomycin to treatment CDI:

- insufficient data to recommend probiotics to treat CDI

Proton Pump Inhibitors

Multiple studies (USA, Australia, UK):

- 40-65% hospitalized patients taking long term PPIs
- 40-55% primary care outpatients - no documented reason for PPI

BC

- 34% residential care patients – no documented indication for PPI

Evidence from RCTs:

- 8-12 weeks therapy effective for GERD and PUD
  - patients treated effectively do not require chronic acid suppression
- long term PPI appropriate for severe relapsing erosive esophagitis
- NO PPI superior for GERD or PUD symptoms

Proton Pump Inhibitors

Proton Pump Inhibitors

Observational studies on adverse events of PPIs

- C. difficile infection/other enteric infections
- spontaneous bacterial peritonitis
- fractures
- hypomagnesemia
- acute interstitial nephritis
- iron deficiency
- B_{12} deficiency
- gastric polyps/gastric cancer
- ? increased incidence of pneumonia

Proton Pump Inhibitors and C difficile Infection

Meta-analyses:

- PPIs - 1.5-2 X risk of developing CDI

One meta-analysis:

- PPIs - increase odds of recurrence 2.5 fold
  - not confirmed in subsequent studies
- PPIs augment antibiotic exposure CDI risk by 19%
  - high study heterogeneity, unspecified confounders, and other methodological flaws associated with observation data, limit the applicability of the results

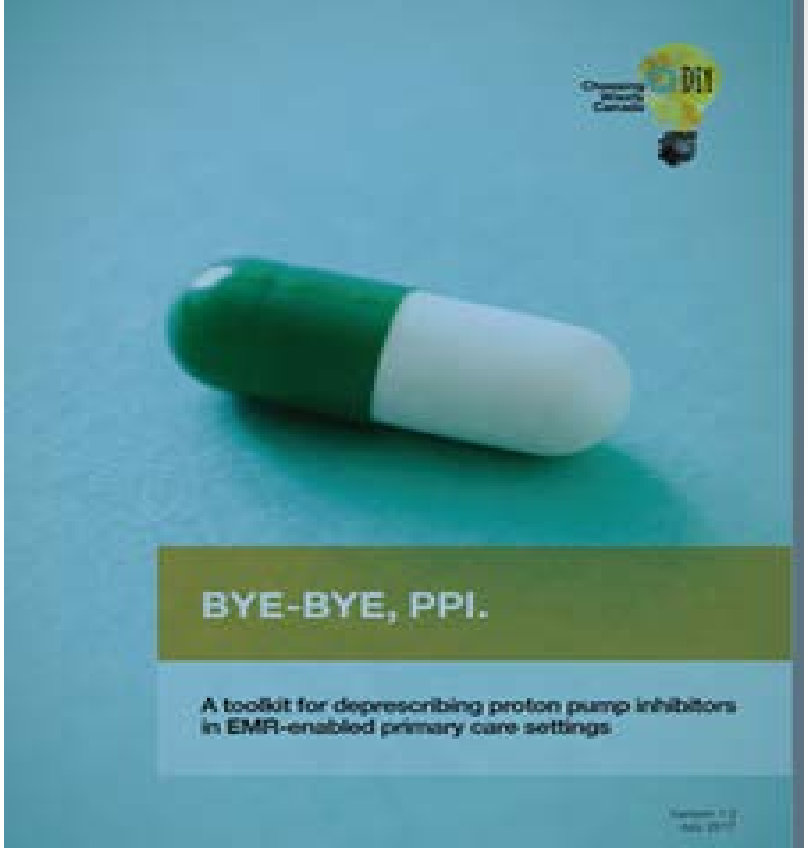
IDSA 2017 CDI Guidelines:

- unnecessary PPIs should be discontinued
- insufficient data to recommend discontinuation of **PPIs as a measure for prevention CDI**
- lack of evidence that PPI increases likelihood refractory/relapsing CDI

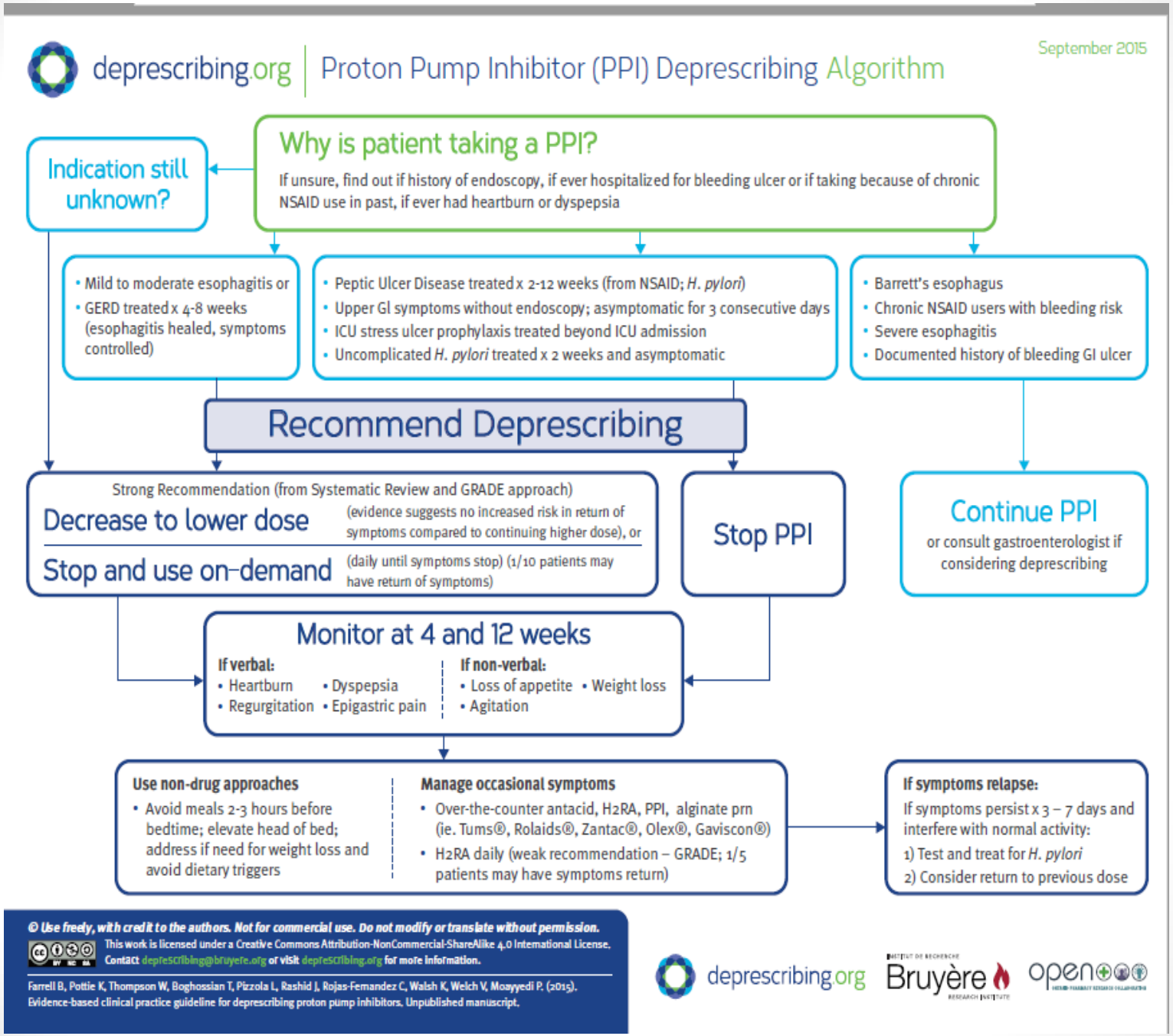
PPIs and CDI

Choosing Wisely Canada

PPI De-prescribing Toolkit



"Don't maintain long-term PPI therapy for GI symptoms without an attempt to stop / reduce PPI at least once a year in most patients."



Farrell B, Pottie K, Thompson W, Boghossian T, Pizzola L, Rashid J, Rojas-Fernandez C, Walsh K, Welch V, Moayyedi P. (2015). Evidence-based clinical practice guideline for deprescribing proton pump inhibitors. Unpublished manuscript.

deprescribing.org Bruyère Research Institute open

thebmj

BMJ 2017;358:j3418 doi: 10.1136/bmj.j3418 (Published 2017 July 26)

ANALYSIS

The antibiotic course has had its day

With little evidence that failing to complete a prescribed antibiotic course contributes to antibiotic resistance, it's time for policy makers, educators, and doctors to drop this message, argue **Martin Llewelyn and colleagues**

Martin J Llewelyn *professor of infectious diseases*[1 2], Jennifer M Fitzpatrick *specialist registrar in infection*[2], Elizabeth Darwin *project manager*[3], SarahTonkin-Crine *health psychologist*[4], Cliff Gorton *retired building surveyor*[5], John Paul *consultant in microbiology*[6], Tim E A Peto *professor of infectious diseases*[7], Lucy Yardley *professor of health psychology*[8], Susan Hopkins *consultant in infectious diseases and microbiology*[9], Ann Sarah Walker *professor of medical statistics and epidemiology*[3]