Antibiotics "Shorter is Better"

McGill Refresher Course 2022
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Speaker / Disclosures

- Trong Tien Nguyen, MDCM, FRCPC
  - Infectious Diseases & Medical Microbiology
  - St. Mary's Hospital, CIUSSS ODIM

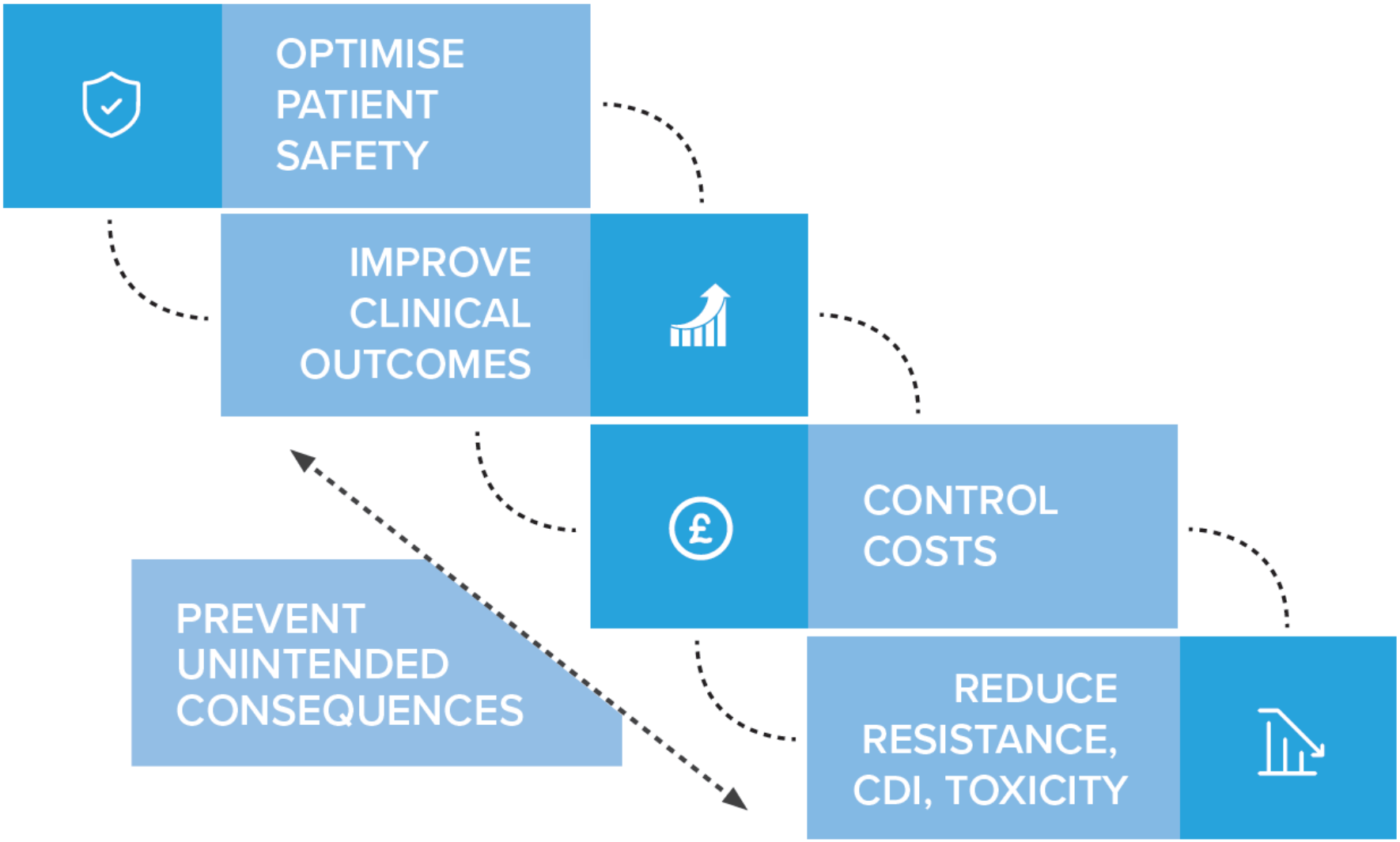
- Speaker has no conflict of interest.

Learning Objectives

As a result of attending this session, participants will be able to:

- Avoid prescribing antimicrobials when they are not clinically indicated.
- Safely shorten antimicrobial courses in order to reduce their adverse consequences.
- Recognize clinical situations when shortening antimicrobials is not warranted.

WHY SHORTER?



Nathwani D. BSAC. 2018

Adverse Drug Events Occur in 20% Patients on Antibiotics

- Common & serious adverse effects
  - Gastrointestinal (42%)
  - Renal (24%)
  - Hematologic (15%)
  - *Clostridium difficile* infection
- Societal burden
  - Drug costs
  - Emergency department visits, hospital readmission
  - Emergence of resistant bacteria

Tamma PD. JAMA Intern Med. 2017

Guidelines recommend many antibiotic options

- Alternatives allow individualized therapy
  - Allergies and intolerances
  - Contraindications
  - Resistance
- If options are equal, select the least harmful
  - Shorter duration
  - Less adverse effects
  - Less frequent dosing
  - Less expensive

(When they are not clinically indicated …)

NO ANTIMICROBIALS IS BEST

“No matter how popular they get, antibiotics will never go viral.”

Influenza	Rarely
Rhinovirus	***B. pertussis***
Adenovirus	***Mycoplasma***
HMPV	***pneumoniae***
Coronavirus	***Chlamydophila***
Parainfluenza	***pneumoniae***
RSV	

Don’t prescribe antibiotics in adults with uncomplicated:

- Bronchitis
- Bronchiolitis
- Acute sinusitis
- Pharyngitis
- Acute otitis media

Choosing Wisely Canada. 2018
College of Family Physicians of Canada
Canadian Association of Emergency Physicians

Antibiotics do not treat viruses

- Don’t use antibiotics for upper respiratory infections that are likely **viral** in origin, such as influenza-like illness, or self-limiting, such as **sinus infections of less than seven days** of duration.
  - College of Family Physicians of Canada

- Don’t routinely use antibiotics in adults and children with **uncomplicated sore throats**.
  - Canadian Association of Emergency Physicians

- Don’t use antibiotics in adults and children with **uncomplicated acute otitis media**.
  - Canadian Association of Emergency Physicians

Acute rhinosinusitis is usually viral

- Resolves within 10-14 days, without treatment
- Consider antibiotics if:
  - Persistent & not improving ≥10 days
  - Severe symptoms ≥ 3-4 days (fever, facial pain, purulent nasal discharge)
  - Worsening or double-sickening ≥3-4 days

>70%, if bacterial

S. pneumoniae

H. influenzae

Rarely

M. catarrhalis

S. pyogenes

S. aureus

INESSS. 2018
Chow AW. Clin Infect Dis. 2012

Bronchitis is usually viral

- Don’t prescribe antibiotics in adults with bronchitis / asthma and children with bronchiolitis.
  - Canadian Association of Emergency Physicians

Influenza

Rhinovirus

Adenovirus

Coronavirus

RSV

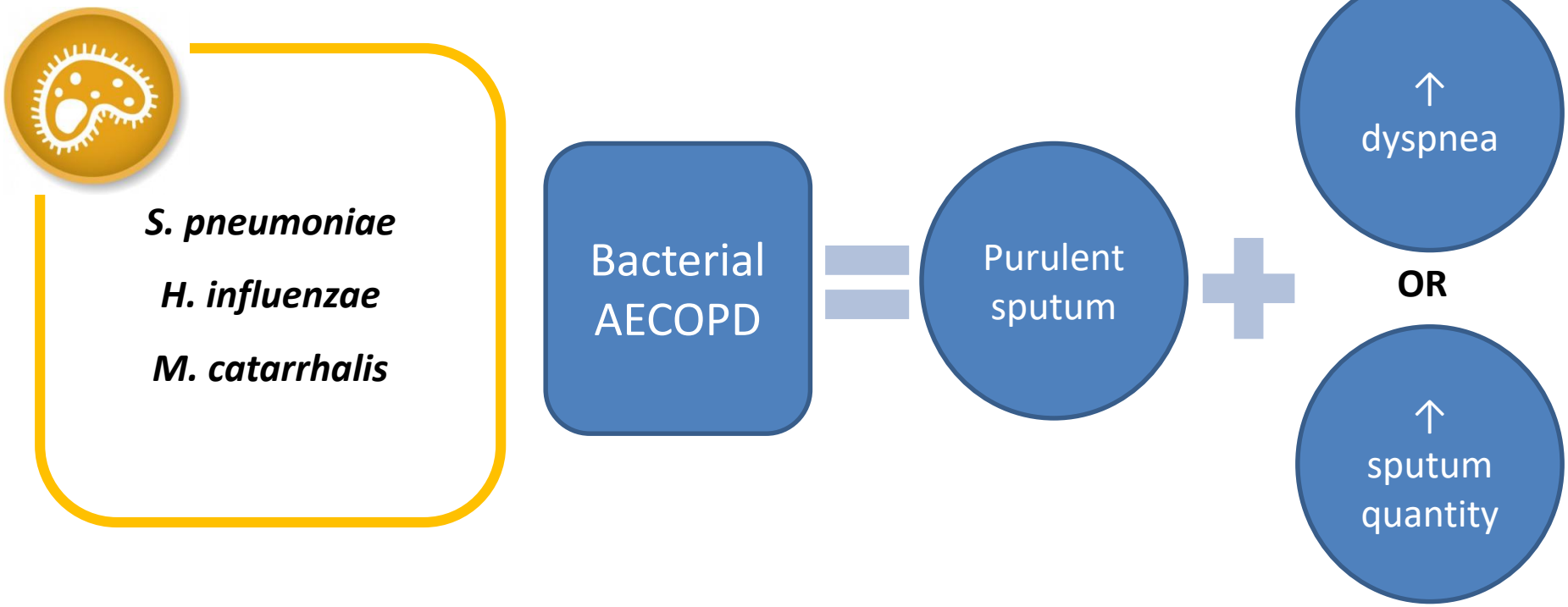
Rarely

B. pertussis

Mycoplasma pneumoniae

Chlamydophila pneumoniae

Simple AECOPD Results in Additional Pharmacologic Therapy



AECOPD Management Does Not Always Require Antibiotics

- GOLD guidelines (2019)
  - Mild: short-acting bronchodilators only
  - Moderate: [mild] + antibiotics +/- corticosteroids
  - Severe: [moderate] + hospitalization
- Cochrane SR/MA (2018)
  - ICU:↓ mortality, ↓ LOS
  - Non-ICU:
    - Inconsistent effect on treatment failure
    - No benefit for mortality or LOS

GOLD. 2019
Vollenweider DJ. Cochrane Database Syst Rev. 2018

Drained minor skin abscesses may not require antimicrobials

- Don’t prescribe antibiotics after **incision and drainage** of uncomplicated skin abscesses unless extensive cellulitis exists.
  - Canadian Association of Emergency Physicians

S. aureus

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S. pyogenes

INESSS. 2017
Choosing Wisely Canada. 2018

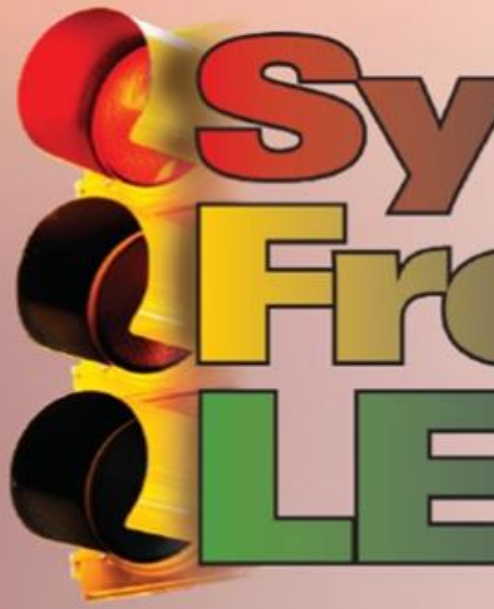
Urinary tract infection diagnosis relies on clinical symptoms

- Fever
- Dysuria
- Frequency
- Urgency
- Suprapubic pain
- Costovertebral pain

- Acute hematuria
- New onset incontinence
- Rigors
- Altered mental status without other cause
- Increased spasticity or autonomic dysreflexia if spinal cord injury

- Cloudy urine
- Foul smelling urine
- Urinary retention
- Perineal pruritus

Hartley S. Infect Control Hosp Epidemiol. 2013



Symptom-Free Pee: LET IT BE

A national initiative to stop inappropriate antibiotic use for asymptomatic bacteriuria in long-term care residents.

For more direction and guidance:

www.ammi.ca

#SymptomFreeLetItBe

AMMI™ Canada

Do Not Screen for or Treat ASB

- "Don't use antimicrobials to treat **asymptomatic bacteriuria**."
  - Canadian Geriatrics Society
  - Canadian Society for Hospital Medicine
  - Canadian Urological Association
  - Canadian Nurses Association
  - American Geriatrics Society
  - Infectious Diseases Society of America
  - Canadian Association of Physical Medicine and Rehabilitation

- "Don't perform **urinalysis or urine culture** unless patients have signs or symptoms of infection."
  - American Academy of Pediatrics
  - Society for Healthcare Epidemiology of America
  - Long Term Care Medical Directors Association of Canada
  - AMDA – The Society for Post-Acute and Long-Term Care Medicine

Choosing Wisely. 2018
Choosing Wisely Canada. 2018

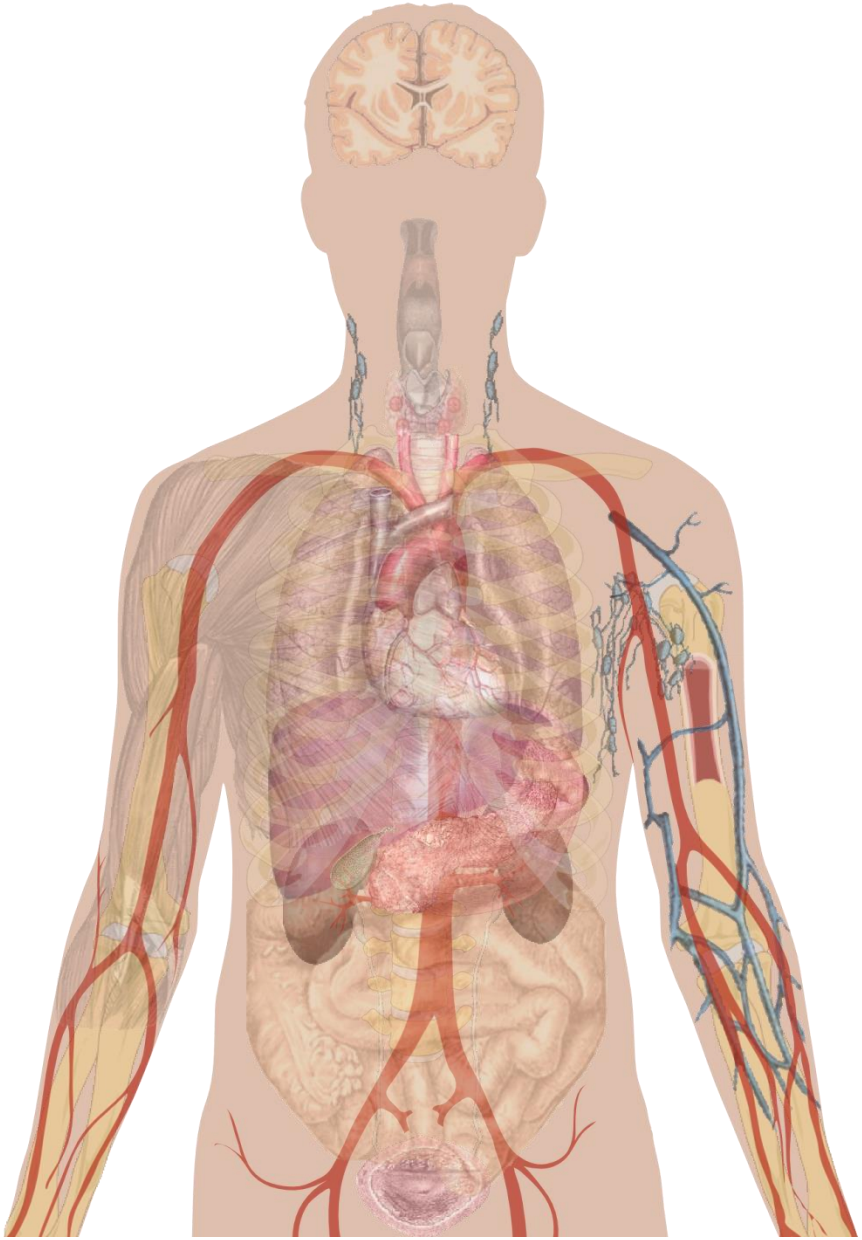
Urine Culture Should Not be Sent for Asymptomatic Bacteriuria (ASB)

- Prospective studies in long-term care facilities[1]
  - Prevalence 10-50%
  - New pyuria/bacteriuria within 4 days of catheter
  - ASB can persist up to 1–2 years
  - No increased morbidity or mortality
- Up to 2/3 patients with ASB still receive antimicrobial therapy[2]

1. High KP. Clin Infect Dis. 2009
2. Leis JA. Clin Infect Dis. 2014

(When they are clinically indicated …)

SHORTER IS BETTER



Upper Respiratory Tract Infection
- Otitis media
- Rhinosinusitis
- Bronchitis

Lower Respiratory Tract Infections
- Pneumonia
- Acute exacerbation of COPD

Skin & Soft Tissue Infection
- Nonpurulent cellulitis
- Purulent cellulitis

Urinary Tract Infection
- Cystitis
- Pyelonephritis
- Prostatitis

Treat Uncomplicated ENT Infections for 5-7 Days

Odontogenic

Penicillin +/- metronidazole

Cephalosporin I/II
Amoxicillin +/- clavulanate
Clarithro-/Azithromycin*
Clindamycin

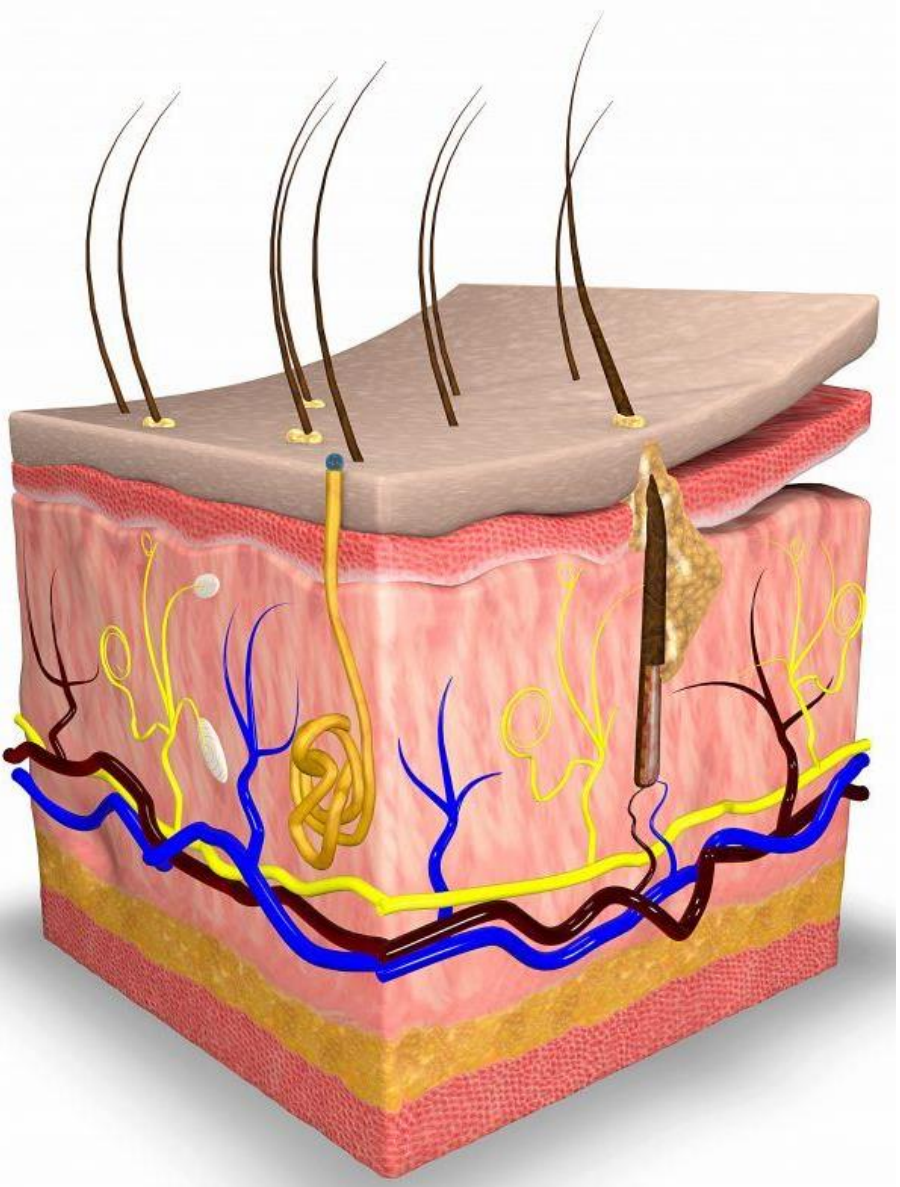
Rhinogenic

Amoxicillin +/- clavulanate

Cephalosporin II
Ceftriaxone
Moxi-/Levofloxacin
+/- Vancomycin

**S. pneumoniae* azithromycin resistance in Quebec is ~20%.

Fairbanks DNF. American Academy of Otorhinolaryngology. 2007
INESSS. 2017
Chow AW. Clin Infect Dis. 2012



Epidermis	• Erysipelas
Dermis	• Cellulitis
Hypodermis	• Abscess
Deeper Soft Tissues	• Fasciitis, tenosynovitis • Pyomyositis • Osteomyelitis

https://www.dreamstime.com/stock-images-skin-layers-consist-two-superficial-epidermis-made-epithelial-tissue-deeper-dermis-made-connective-tissue-image35208934

Treat Uncomplicated SSTI for 5-10 days

Nonpurulent

S. pyogenes

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S. aureus

Purulent

S. aureus

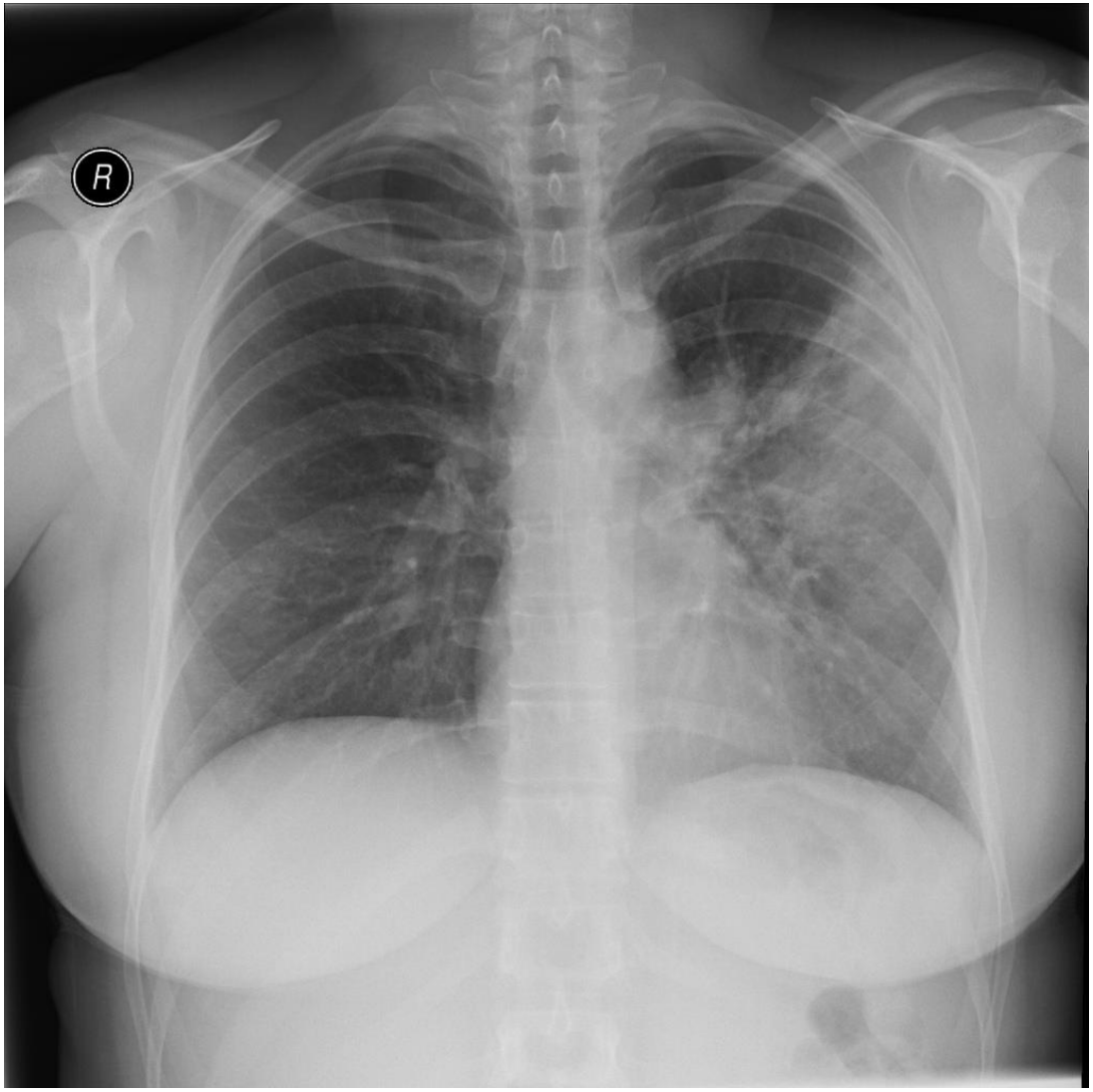
>>>

S. pyogenes

- First-line
  - Cefadroxil
  - Cephalexin
  - Cloxacillin
- INESSS (2017)
  - 5-10 days
- IDSA (2014)
  - 5 days (extend if not improved)

INESSS. 2017
Stevens DL. Clin Infect Dis. 2014
Choosing Wisely Canada. 2019

Lobar pneumonia is usually bacterial



S. pneumoniae

H. influenzae

K. pneumoniae

Legionella

M. tuberculosis

Treatment duration is individualized based on clinical response

- Body temperature ≤ 37.8°C for ≥ 48 hours
- No supplemental oxygen
- ≤ 1 CAP-associated sign of clinical instability
  - HR > 100
  - RR > 24
  - SBP ≤ 90

Mandell LA. Clin Infect Dis. 2007
Uranga A. JAMA Intern Med. 2016

Pneumonia Treatment can Safely be Shortened

- Trend to shorten courses
  - IDSA (2007) ≥ 5 days (stop using clinical criteria)[1]
  - ≤7 days no different than >7 days[2]
  - 3 days no different than 8[3]
- Shorter courses are associated with:
  - ↓ mortality (RR 0.52, 95% CI 0.33-0.82)[4]
  - ↓ adverse events (RR 0.73, 95% CI 0.55-0.97)[4]

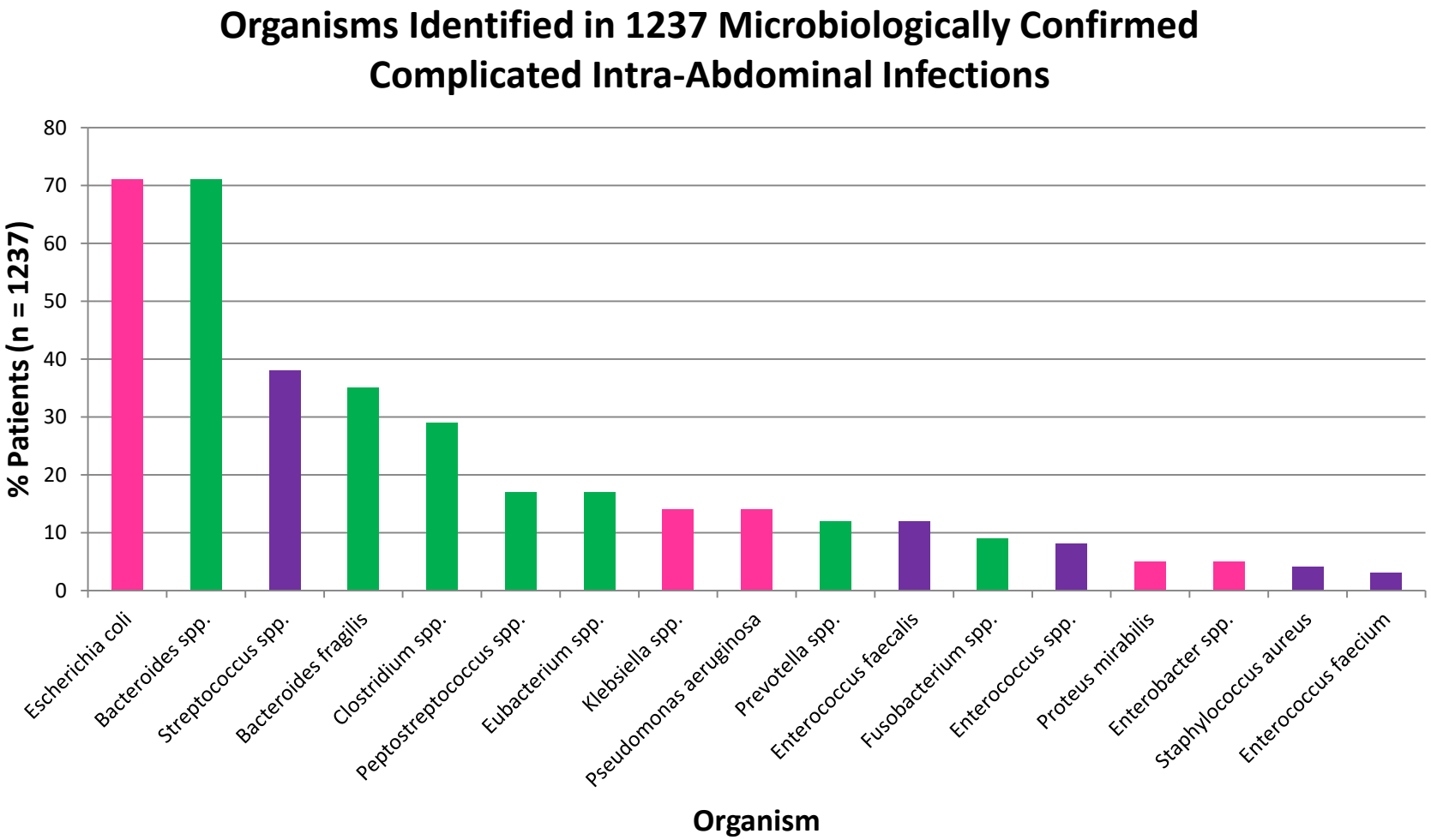
1. Mandell LA. Clin Infect Dis. 2007
2. Uranga A. JAMA Intern Med. 2016
3. el Moussaoui R. BMJ. 2006
4. Tansarli G. Antimicrob Agents Chemother. 2018

Treatment of pneumonia usually requires 5-7 days therapy

	Antibiotics	
First line	Clarithromycin Clarithromycin XL Azithromycin Doxycycline Amoxicillin (1g PO TID)	
First line, if comorbidities	Amoxicillin Amoxicillin/clavulanate	+ Clarithromycin Clarithromycin XL Azithromycin Doxycycline
Second line	Any option in “first line, if comorbidities” Levofloxacin Moxifloxacin	

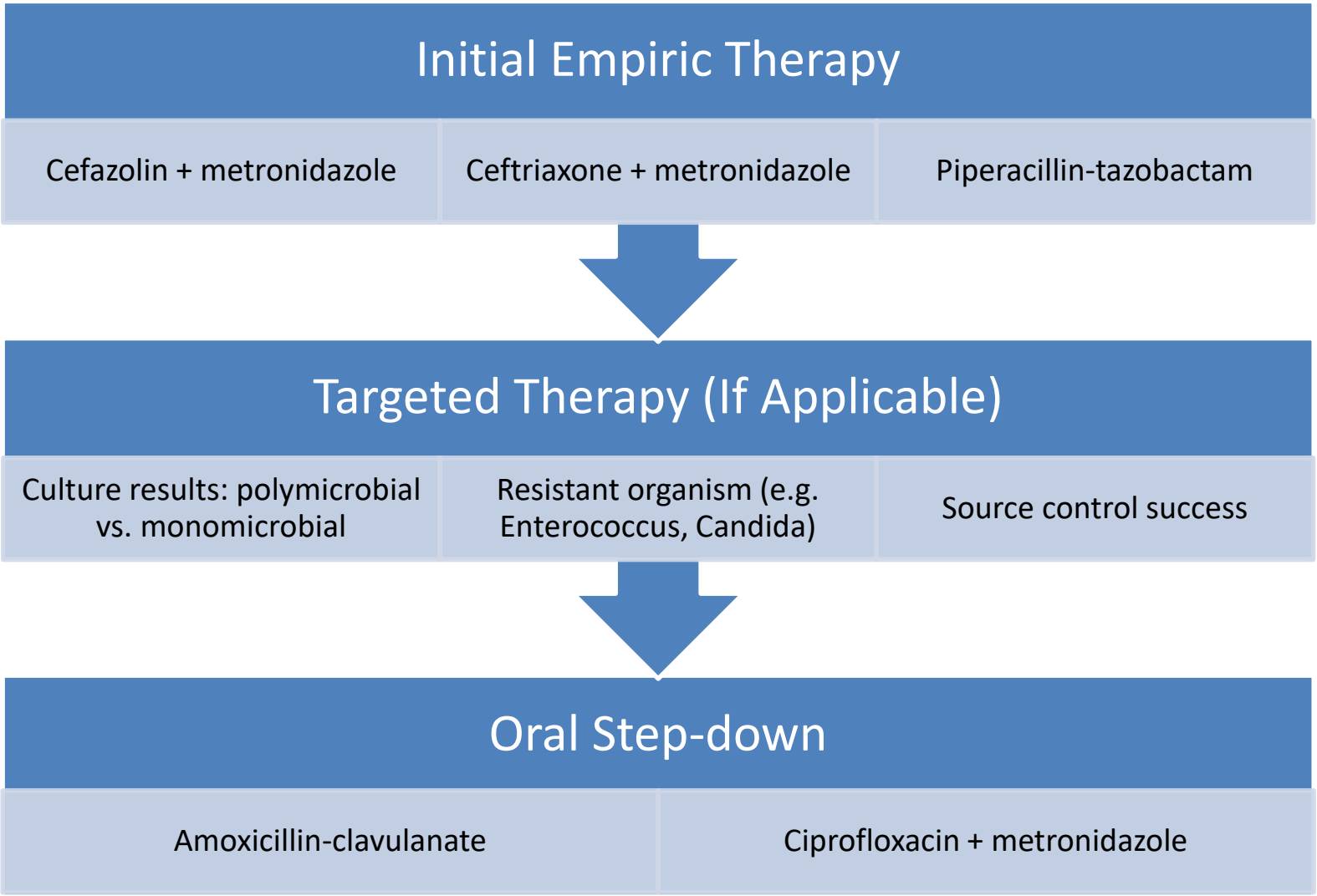
S. pneumoniae azithromycin resistance in Quebec is ~20%.

Community-acquired intraabdominal infections have predictable bacteria



Adapted from Solomkin JS. Clin Infect Dis. 2010
Chow, AW. Can J Infect Dis Med Microbiol. 2010

Reassess Opportunities to Step-Down Antibiotics Throughout Treatment



Shorter Antibiotic Durations Are Safe for Source-Controlled IAIs

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection

R.G. Sawyer, J.A. Claridge, A.B. Nathens, O.D. Rotstein, T.M. Duane, H.L. Evans,

STOP-IT Trial: "Study To Optimize Peritoneal Infection Therapy"

- No difference between 4 days vs. 8 days
- 30-day outcomes: recurrent intraabdominal infection, surgical-site infection, death

Sawyer RG. N Engl J Med. 2015

Uncomplicated Cystitis

Table 1a: E. coli resistance against first-line agents in Quebec

Nitrofurantoin	Fosfomycin
5-10%	<5%

TMP-SMX	Trimethoprim
15-20%	N/A (see TMP-SMX)

Table 1b: E. coli resistance against second-line agents in Quebec

Ciprofloxacin	B-lactams
10-15%	Variable

>75% cases

E. coli

Other agents

E. faecalis

S. saprophyticus

K. pneumoniae

First Line UTI Agents Have Limitations

Nitrofurantoin

- **Ineffective:**
  - Pyelonephritis
  - CAUTI
  - CKD (eGFR <40)
- **Avoid:**
  - T3 pregnancy

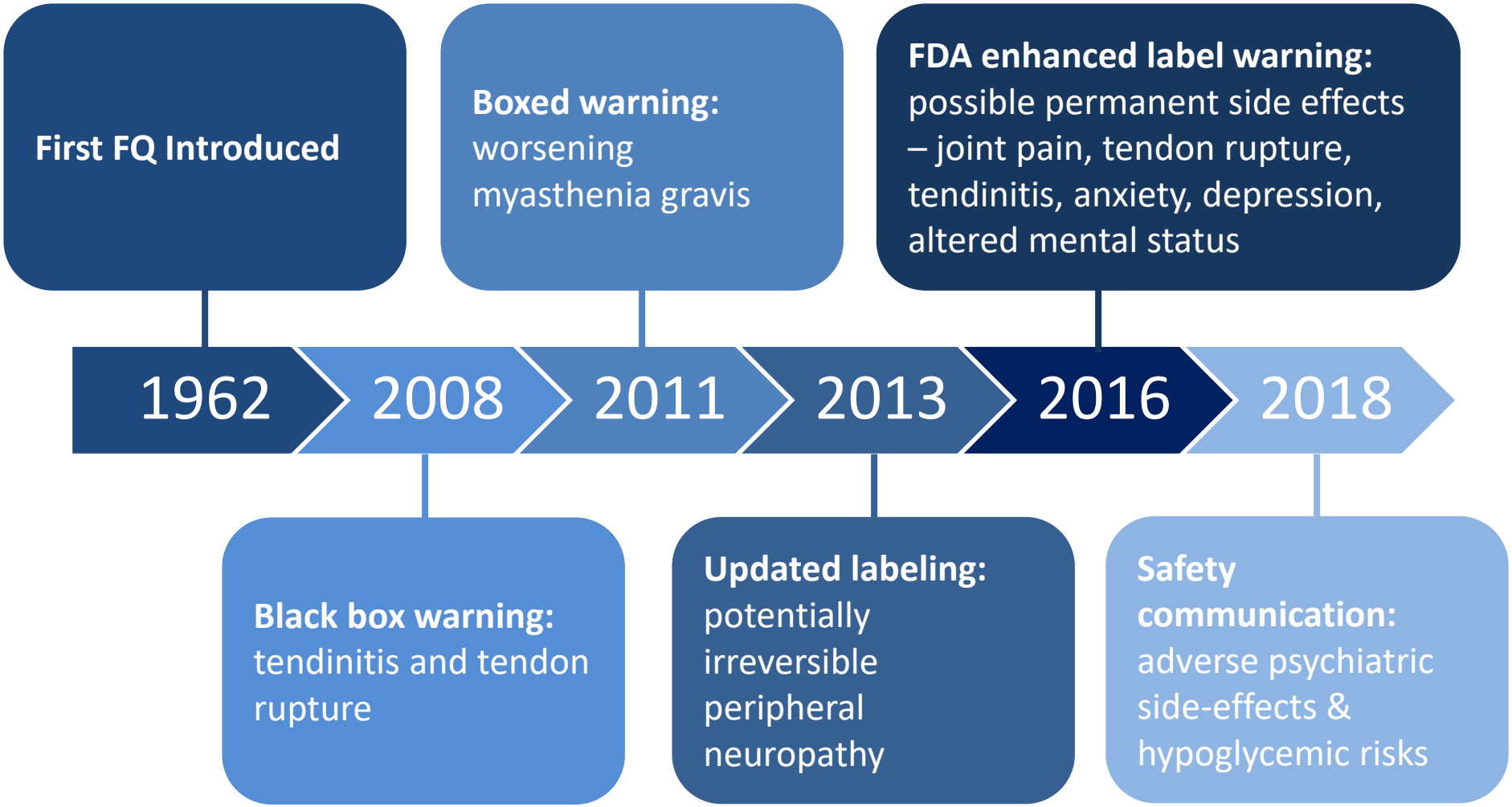
Fosfomycin

- **Ineffective:**
  - Pyelonephritis
  - CAUTI
  - *S. saprophyticus*
- **Limitations:**
  - *E. coli* and *E. faecalis* only
  - Susceptibility testing access

TMP-SMX

- **Ineffective:**
  - Variable local resistance
- **Avoid:**
  - Pregnancy (category C)
  - Rash
  - AKI
  - Hyperkalemia
  - Kernicterus

Fluoroquinolones Are Not Benign



https://www.accessdata.fda.gov/drugsatfda_docs/Label/2016/019537s086lbl.pdf
https://www.fda.gov/downloads/Drugs/DrugSafety/UCM513019.pdf
https://www.fda.gov/downloads/Drugs/DrugSafety/UCM612834.pdf

Shorter Treatment for Uncomplicated Pyelonephritis is Effective

Ciprofloxacin for 7 days versus 14 days in women with acute pyelonephritis: a randomised, open-label and double-blind, placebo-controlled, non-inferiority trial

Torsten Sandberg, Gunilla Skoog, Anna Bornefalk Hermansson, Gunnar Kahlmeter, Nils Kuylenstierna, Anders Lannergård, Gisela Otto, Bo Settergren, Gunilla Stridh Ekman

A Seven-Day Course of TMP-SMX May Be as Effective as a Seven-Day Course of Ciprofloxacin for the Treatment of Pyelonephritis

Miriam T. Fox, BS,[a] Michael T. Melia, MD,[b] Rebecca G. Same, MD,[c] Anna T. Conley, BA,[d] Pranita D. Tamma, MD, MHS[e]

[a]Department of Medicine, [b]Division of Infectious Diseases, Department of Medicine, and [c]Department of Pediatrics, The Johns Hopkins University School of Medicine, Baltimore, Md; [d]Department of Medicine, The University of Maryland School of Medicine, Baltimore; [e]Division of Pediatric Infectious Diseases, Department of Pediatrics, The Johns Hopkins University School of Medicine, Baltimore, Md.

Lancet. 2012 Aug 4;380(9840):484-90.
Am J Med. 2017 Jul;130(7):842-845.

Treat UTI According to Complexity

Uncomplicated cystitis 3-5 days	Uncomplicated pyelonephritis 7 days
Complicated cystitis 5-7 days	Complicated pyelonephritis 7-14 days

(Exceptionally …)

WHEN IS SHORTER NOT BETTER?

Specific infections usually require longer treatment

- Deep-seated infections
  - Source control is key
  - ≥4 weeks for bone, joint, endovascular infections
  - Some RCT evidence (e.g. DAPITO trial, 12 weeks for prosthetic knee infections)
- Chronic infections
  - 2 weeks for acute prostatitis
  - 4 to 6 weeks for chronic prostatitis
- Drug-resistant infections

KEY MESSAGES

Shorter Antibiotic Courses are Safe and Effective

3-5 days	5-7 days	>7 days
• Uncomplicated cystitis • Source-controlled intra-abdominal	• Odontogenic • Rhinogenic • Skin & soft tissue • AECOPD • Pneumonia • Source-controlled intra-abdominal • Complicated cystitis • Uncomplicated pyelonephritis	• Unresolving skin & soft tissue • Unresolving pneumonia • Intra-abdominal, not source-controlled • Complicated pyelonephritis

Choosing Wisely promotes responsible antimicrobial prescribing

- Using antimicrobials only when indicated
  - Don’t treat viruses
- Selecting less C. difficile prone antibiotics
  - Use fluoroquinolones and clindamycin judiciously
- Clarify antibiotic allergies
  - Penicillin allergy de-labelling
- IV-to-PO switch
  - Use oral forms of highly bioavailable agents

Choosing Wisely Canada. 2019
Choosing Wisely. 2019

Guideline & Resource Links

- Choosing Wisely
  - http://www.choosingwisely.org/
  - https://choosingwiselycanada.org/
- INESSS Guidelines
  - https://www.inesss.qc.ca/en/publications/inessss-guides.html
  - https://itunes.apple.com/ca/app/inesss-guides/id1206046869
  - https://play.google.com/store/apps/details?id=com.inesss&hl=fr_CA
- IDSA Guidelines
  - https://www.idsociety.org/practice-guidelines/#/date_na_dt/DESC/0/+/

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- Spectrum, localized antimicrobial stewardship. http://www.spectrum.md/. Accessed November 9, 2018
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