# Dealing with #1: Reflections on UTI Treatment

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# Faculty/Presenter Disclosure

- **Relationships with commercial interests:**
  - **No Conflicts to Declare**

# UTI and Fluoroquinolones - Background

- Fluoroquinolones are among the most widely prescribed class of antibiotics
  - directly inhibit bacterial DNA synthesis
  - high bioavailability (70-95%)

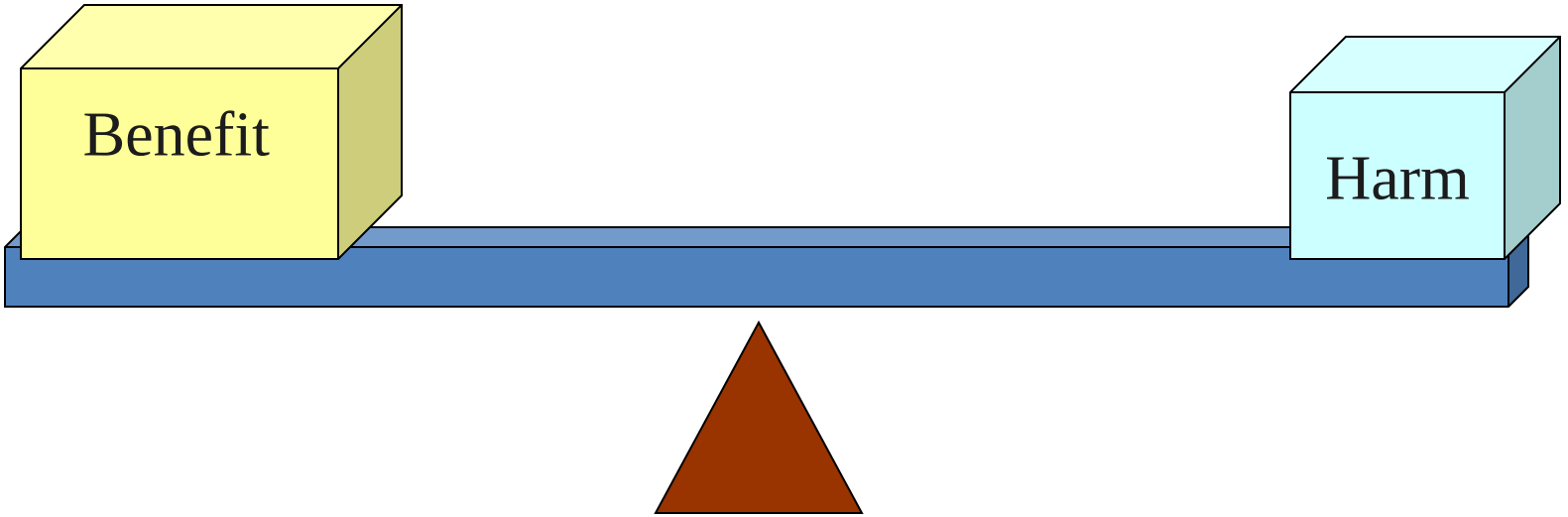
- Use expanded to some milder infections with limited evidence (low value indications)
  - acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis in COPD patients, **uncomplicated UTI**

# Adverse Effects of Fluoroquinolones

- Cardiac
  - torsades de pointes, ventricular tachycardia, and sudden cardiac death
- Musculoskeletal
  - tendinopathy, tendon ruptures, and complications with cartilage, bone, and muscle
  - may be associated with an increased risk of aortic aneurysms
- Myasthenia Gravis Exacerbation
  - symptoms worsened by increased muscle weakness and respiratory problems
- Peripheral Neuropathy
- Retinal Detachment
- Phototoxicity
- Central Nervous System Reactions
- Hypersensitivity Reactions
- Hypo or Hyperglycemia

# FDA & Health Canada

- There is a need to ensure fluoroquinolones use is reserved for indications where there is a clear and proven benefit.
- Health Canada is conducting a safety review of systemic oral fluoroquinolones.



# FDA & Health Canada

## Fluoroquinolone Antibacterial Drugs for Systemic Use: Drug Safety Communication - Warnings Updated Due to Disabling Side Effects

https://www.fda.gov/Drugs/DrugSafety/ucm500143.htm

[Posted 07/26/2016]

Health Canada
www.hc-sc.gc.ca

Drugs and Health Products

**Summary Safety Review - Fluoroquinolones - Assessing the potential risk of persistent and disabling side effects**

January 23, 2017

http://www.hc-sc.gc.ca/dhp-mps/medeff/reviews-examens/fluoroquinolones2-eng.php

# Drug Utilization Review

- Fluorquinolone usage per capita is relatively stable
- Ciprofloxacin represents approximately ½ of fluorquinolone prescribing
- Top Indication for Ciprofloxacin
  - MB 2004 …. UTI
  - MB 2014 … UTI
- Family physicians prescribe the majority of fluoroquinolones in Canada
- SK Nitrofurantoin most commonly used drug
- MB Ciprofloxacin most commonly used drug

# FDA - UTI

**Tables 17 & 18: uUTI: Top drug molecules (oral forms only) by number of drug use mentions associated with broadly defined uncomplicated urinary tract infection* (uUTI) as reported by U.S. office-based physician surveys, stratified by drug, for years 2010 and 2014**

**Table 17**

| 2010 | Uses (000) | Share % | 95% C.I. (000) |
|---|---|---|---|
| Total Market | 22,338 | 100.0% | 21,632 - 23,043 |
| ciprofloxacin | 7,773 | 34.8% | 7,357 - 8,189 |
| sulfamethoxazole/tmp | 5,550 | 24.8% | 5,198 - 5,901 |
| nitrofurantoin | 4,534 | 20.3% | 4,217 - 4,852 |
| phenazopyridine | 1,524 | 6.8% | 1,340 - 1,709 |
| levofloxacin | 1,155 | 5.2% | 994 - 1,315 |
| cephalexin | 502 | 2.3% | 396 - 608 |
| doxycycline | 128 | 0.6% | 74 - 181 |
| cefdinir | 96 | 0.4% | 49 - 142 |
| meth/me bl/salicy/na phos/hyos | 93 | 0.4% | 48 - 139 |
| ampicillin | 89 | 0.4% | 44 - 133 |
| All Others | 894 | 4.0% | 753 - 1,035 |

**Table 18**

| 2014 | Uses (000) | Share % | 95% C.I. (000) |
|---|---|---|---|
| Total Market | 25,177 | 100% | 24,383 - 25,971 |
| ciprofloxacin | 8,100 | 32.2% | 7,649 - 8,550 |
| nitrofurantoin | 5,822 | 23.1% | 5,440 - 6,204 |
| sulfamethoxazole/tmp | 5,610 | 22.3% | 5,235 - 5,985 |
| phenazopyridine | 1,980 | 7.9% | 1,758 - 2,203 |
| levofloxacin | 1,223 | 4.9% | 1,048 - 1,399 |
| cephalexin | 968 | 3.8% | 812 - 1,124 |
| amoxicillin | 226 | 0.9% | 151 - 301 |
| amoxicillin/clav | 165 | 0.7% | 100 - 229 |
| cefdinir | 113 | 0.5% | 60 - 166 |
| cefuroxime | 80 | 0.3% | 35 - 124 |
| All Others | 890 | 3.5% | 741 - 1,040 |

*Source: Encuity Treatment Answers™ with Pain, 2010&2014, Extracted AUG2014, Source File(s): PDDA 2015-896 FQ AC AUG2015*

**uUTI definition was expanded to include acute cystitis (ICD9: 59500.0), cystitis NEC (ICD9: 59589.0), cystitis NOS (ICD9: 59590.0), and urinary tract infection NOS (ICD9 59900.0)*

CNODES
CANADIAN NETWORK FOR OBSERVATIONAL DRUG EFFECT STUDIES

FDA Briefing Document. The Benefits and Risks of Systemic Fluoroquinolones. Nov 5, 2015. http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/anti-infectivedrugsadvisorycommittee/ucm467383.pdf

# OVERVIEW

- **Canadian recommendations**
- **Local resistance data**
- **Emerging resistance trends**
- **Selecting specific therapy & duration**

# MICROBIOLOGY

- ***E. coli* = 75-95%**
- **Most of Remainder**
  - *Staph. saprophyticus* = 0.2% of outpatients; higher in young women
  - *Klebsiella spp. & Proteus spp.*
- **Less common**
  - Other Enteric Gram Negative Rods
  - *Pseudomonas aeruginosa*
  - Grp B & D Streptococci
  - *Enterococcus*

# RECOMMENDED EMPIRIC THERAPY: CYSTITIS

## RX FILES JANUARY 2017 (SASKATCHEWAN)
## BUGS & DRUGS 2012 (ALBERTA HEALTH SERVICES)

| | Preferred | Alternative | Comments |
|---|---|---|---|
| Non-Pregnant Women | • Nitrofurantoin 5 d<br>• *TMP/SMX 3 d* | • Cephalexin 7 d<br>• Cefixime 7 d<br>• Amox/Clav 7 d<br>• Fosfomycin 1 d | **Third Line**<br>• CIP, LEVO 3 d |
| Pregnant Women | • **Nitrofurantoin 7 d**<br>• **Cephalexin 7 d**<br>• **Cefixime 7 d**<br>• **Amox/Clav 7 d** | • Fosfomycin 1 d | • C&S important<br>• ⃠ Nitro 36-42 wk |

# SBGH ANTIBIOGRAM (2016)

**Table 1. In vitro activity of selected anti-infective agents tested against Gram-negative bacilli[a]**

| Organism (number tested): January through December 2015 ▭ = Not tested, not routinely reported, or not recommended | Percent Susceptible | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Ampicillin | Amoxicillin-Clavulanate | Piperacillin-Tazobactam | Cefazolin | Cephalexin[b] | Cefuroxime | Ceftriaxone | Ceftazidime | Meropenem | Amikacin | Gentamicin | Tobramycin | Ciprofloxacin | Trimethoprim-Sulfamethoxazole | Nitrofurantoin[c] |
| *Citrobacter* spp. (47) | | | 79 | | | | 68 | 70 | 100 | 100 | 91 | 98 | 87 | 74 | 92 |
| *Enterobacter aerogenes* (46) | | | 85 | | | | 81 | 83 | 100 | 100 | 100 | 100 | 100 | 100 | |
| *Enterobacter cloacae* complex (101) | | | 76 | | | | 70 | 73 | 99 | 100 | 98 | 97 | 95 | 92 | 42 |
| *Escherichia coli* (190) systemic | 45 | 73 | 90 | 46 | | | 87 | 91 | 99 | 99 | 91 | 88 | 76 | 65 | |
| *Escherichia coli* (854) urine | 51 | 78 | 97 | 58 | 89 | | 91 | 93 | 100 | 100 | 92 | 90 | 77 | 72 | 95 |
| *Haemophilus influenzae* (103)[d] | 71 | n.d. | | | | 97 | | | | | | | | 78 | |
| *Klebsiella pneumoniae* (236) | | 93 | 96 | 81 | n.d. | | 96 | 96 | 99 | 99 | 98 | 96 | 96 | 92 | 33 |
| *Klebsiella/Raoultella* spp. (65)[e] | | 97 | 97 | 5 | | | 97 | 98 | 100 | 100 | 98 | 98 | 98 | 97 | 78 |
| *Morganella morganii* (47) | | | 100 | | | | 94 | 94 | 100 | 100 | 87 | 96 | 77 | 79 | |
| *Proteus mirabilis* (47) | 85 | n.d. | 100 | n.d. | n.d. | | 98 | 100 | 100 | 100 | 94 | 98 | 96 | 77 | |
| *Pseudomonas aeruginosa* (235) | | | 96 | | | | | 94 | 94 | 100 | 94 | 98 | 89 | | |
| *Serratia marcescens* (68) | | | 98 | | | | 98 | 100 | 98 | 100 | 100 | 97 | 99 | 100 | |

**Recent antibiotic use is particularly associated with *E. coli* resistance**

# ESBLS
# EXTENDED-SPECTRUM BETA-LACTAMASES

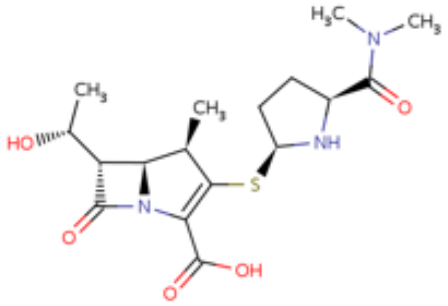
- **Only Gram-negative bacteria**
- **Mostly *E. coli & K. pneumoniae***
- **Increasing reports in other Gram-Negatives**
  - *P. mirabilis & Enterobacter spp.*

# BETA-LACTAMASE CLASSIFICATION

| ESBL | Preferred Target | Inhibited by CA | Genetic Location* |
|---|---|---|---|
| TEM, SHV, CTX-M types | Penicillins, narrow and 3GC, monobactams | Yes | Chromosome or Plasmid |

# ESBL SUBSTRATE PROFILE

| Class | Resistance Pattern |
|---|---|
| Penicillins | Resistant (+/- if combined with a BL-inhibitor) |
| Cephalosporins | Resistant<br>EXCEPT cefoxitin |
| Carbapenems | Active. No resistance to date |




**Meropenem**

**DENISUIK ET AL.**

# RATES OF ESBL *E. COLI* QUADRUPLE IN CANADIAN HOSPITALS

**CANWARD 2007-2014** **ICAAC, SAN DIEGO CA, SEPTEMBER 2015**

## ESBL-Producing *E. coli*

2007: 3% of collected *E. coli* isolates

2014: 12% of collected *E. coli* isolates

- **Bacteremia; lower in UTI…for now!**

| | **ESBL-producing *E. coli* %susceptible (n=403)** |
|---|---|
| Amoxicillin-Clavulanate | 50% |
| Ciprofloxacin | 10% |
| TMP-SMX | 30% |

# NITROFURANTOIN & FOSFOMYCIN RETAIN ACTIVITY

| | **ESBL-producing *E. coli* %susceptible** |
|---|---|
| Nitrofurantoin | >90% |
| Fosfomycin | >90 |

# SELECTING THERAPY: CYSTITIS

- **If active based on MIC/laboratory testing, chose:**
  - least toxic/side effects
  - least collateral damage (normal flora)
    - FQ>>>Nitrofurantoin
- **Empirically, nitrofurantoin has least resistance**

**Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 8th ed.**
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# SELECTING THERAPY: CYSTITIS

- Antibiotic blood levels poorly correlate with outcomes
- Achievable urinary levels & pathogen MIC = outcome
- Nitrofurantoin, fosfomycin PEN/CEPH, FQ
  - **attain urine concentrations ↑↑↑ than MIC**
  - **exception: moxifloxacin - poor levels in urine**

**Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 8th ed.**
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# SELECTING THERAPY: CYSTITIS

- **Renal failure pts may fail to achieve adequate [ ] s in urine for some agents**

- **Agents excreted exclusively by filtration**
  - Sulfonamides, Aminoglycosides

- **Nitrofurantoin**
  - Avoid CrCl < 30 mL/min (Updated BEERS Criteria 2015); previously < 60 mL/min
    - **Poor levels in urine with severe renal impairment**

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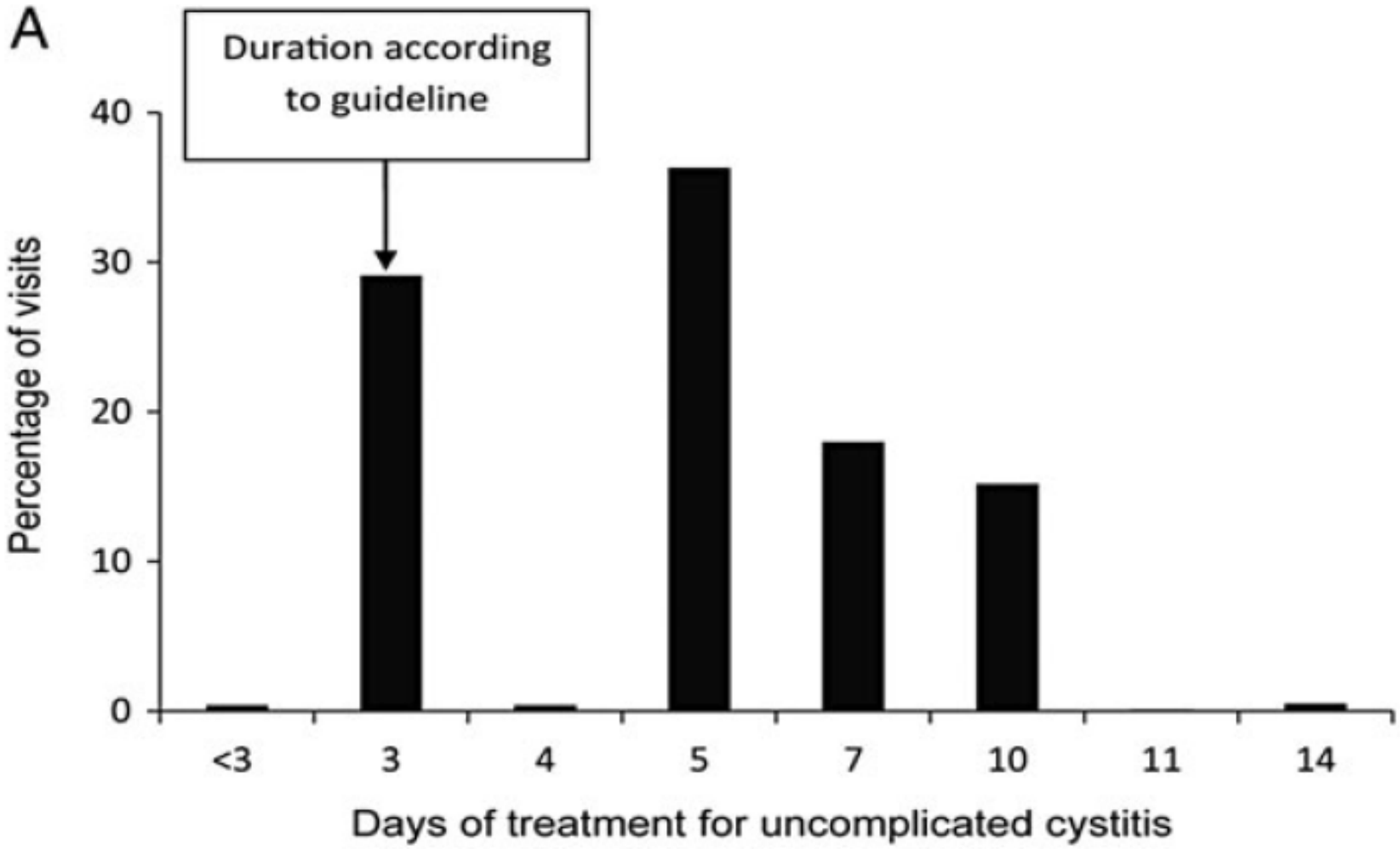
# Low Concordance With Guidelines for Treatment of Acute Cystitis in Primary Care

Larissa Grigoryan,[1] Roger Zoorob,[1] Haijun Wang,[1] and Barbara W. Trautner[2,3]

CID 2016

**Ciprofloxacin or Levofloxacin**



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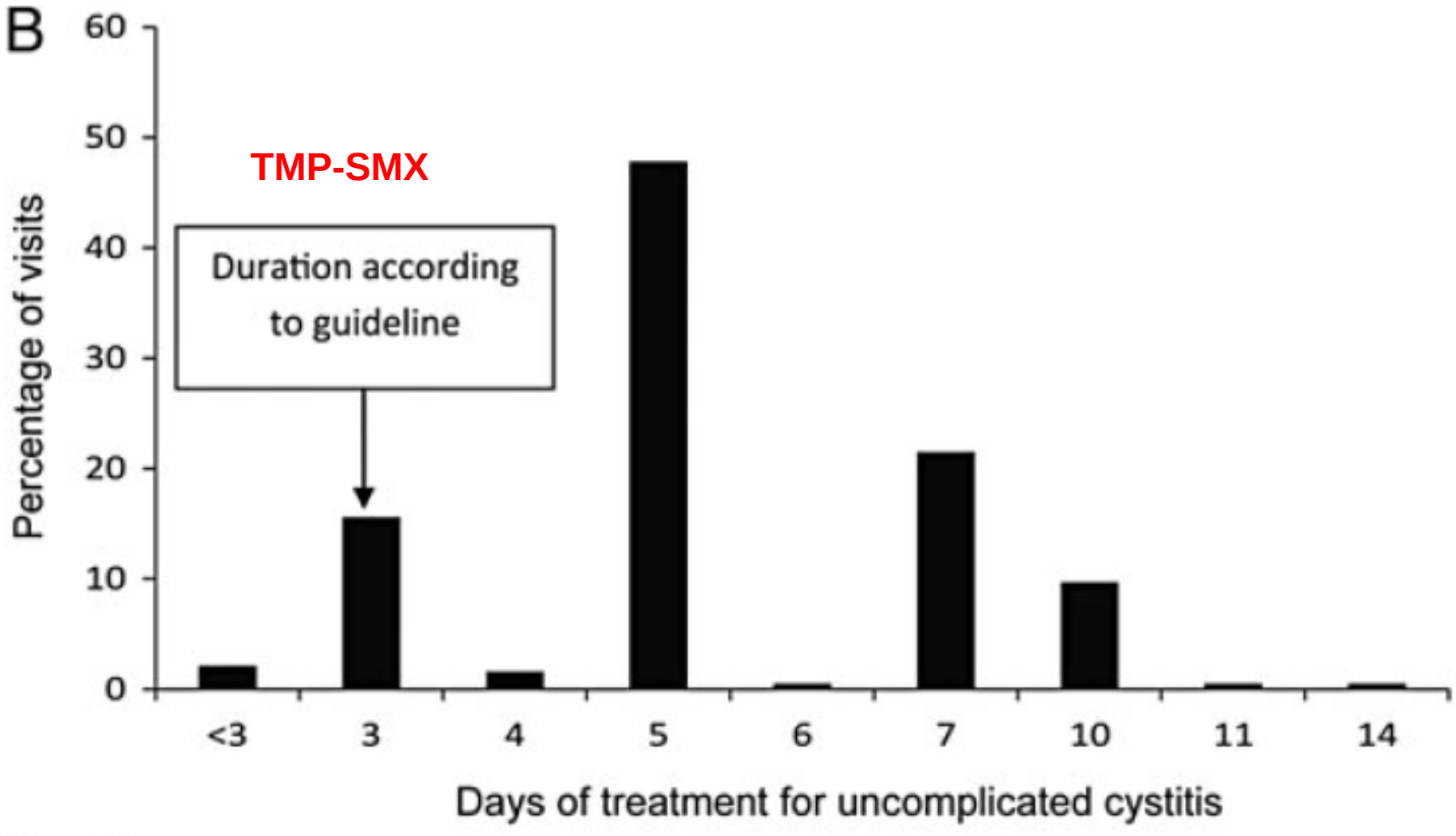

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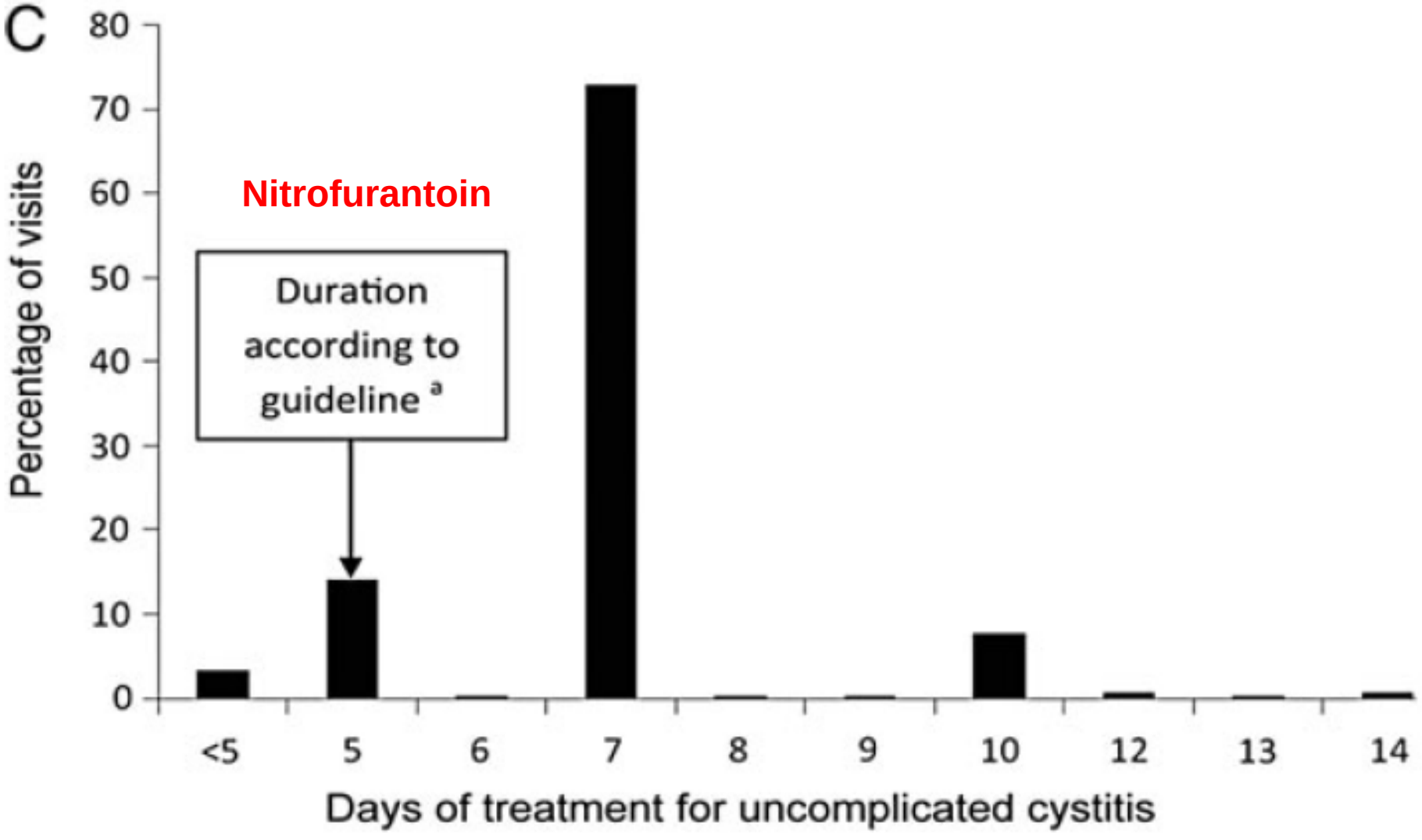

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| Pregnant Women | • **Nitrofurantoin 7 d**<br>• **Cephalexin 7 d**<br>• **Cefixime 7 d**<br>• **Amox/Clav 7 d** | • Fosfomycin 1 d | • **C&S important**<br>• ⃠ Nitro 36-42 wk |

# CONCLUSIONS

- **Nitrofurantoin = first-line therapy in uncomplicated cystitis**
  - Very low resistance; even with ESBL producers
  - Least collateral resistance & damage
  - Least potential for severe toxicities

- **Use β-lactams as alternative therapy**

- **Reserve fluoroquinolones for complicated UTI**

- **Adjust duration of therapy based on drug (& indication)**