Challenges in the Use of Antibiotics in the Elderly

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Geriatric Refresher Day

The Challenges

- Diagnosing Infection in the Elderly
- Antibiotic Overuse
- Antibiotic Resistance
- Dosing of Antibiotics
- Adverse Effects
- Drug Interactions
- Drug Administration
- Compliance Issues

Introduction

Why are the elderly at increased risk for infection?

- decreased immunity
- immunosuppressive drugs
- poor nutrition
- decrease in usual protective barriers (cough, skin)
- chronic illness
- increased exposure to organisms, esp in LTCFs
- increased use of invasive devices

Diagnostic Challenges

- 'Classic' signs and symptoms
  (e.g. fever, incr WBC) may be absent
- Presentation of infection may be non-specific
  - Change in appetite, cognition; decreased functional status, delerium, agitation, lethargy, decreased oral intake, N/V, falls, incontinence, etc.
- Many other reasons for these changes
- Difficulty in interpretation of assessment
  - Lung findings, bacteruria, pyuria
- Impaired communication of symptoms
- Limited availability / use of diagnostic testing

Fever in the Elderly

- May be absent or blunted
- Presence of fever more likely to reflect serious infection
- Baseline often lower than normal

What is Fever?

- Oral temp > 37.8°C (100°F)
- Persistent temp > 37.2°C (oral, TM) or
  > 37.5°C (rectal) (> 2 occasions)
- > 1.1 - 1.3 °C over baseline

= trigger for *evaluation* of infection

Clin Infect Dis 2000; 31:148-51.
Clin Infect Dis 2009;48:149-71.

Challenge No.2: Antibiotic Use / Overuse

- 50-80% of LTCF residents receive an antibiotic every year
- 25% - 75% of antimicrobials prescribed in nursing homes are considered inappropriate
- Incidence of 4.0 to 7.3 antibiotic courses per 1000 resident-days reported in US and Canada

ICHE 1996;17:119-28.
JAMDA 2012;13:568.e1-e13

Antibiotic Use / Overuse

- Point prevalence of antibiotic use in residents of 363 LTCFs in Ontario in 2009
  - 6% of residents rec'd antibiotics on study date (**range 2-11%)**
  - 43% had a claim for MD bedside visit; only 17% for reason related to infection
  - 21% of courses > 90 days

Daneman N. J Antimicrob Chemother 2011;66:2856-63.

Adverse Consequences of Antibiotic Overuse

- Antibiotic resistance
- Risk of allergic reactions
- Adverse effects
- Drug interactions
- Superinfections
  - *Clostridium difficile* infection
  - Yeast

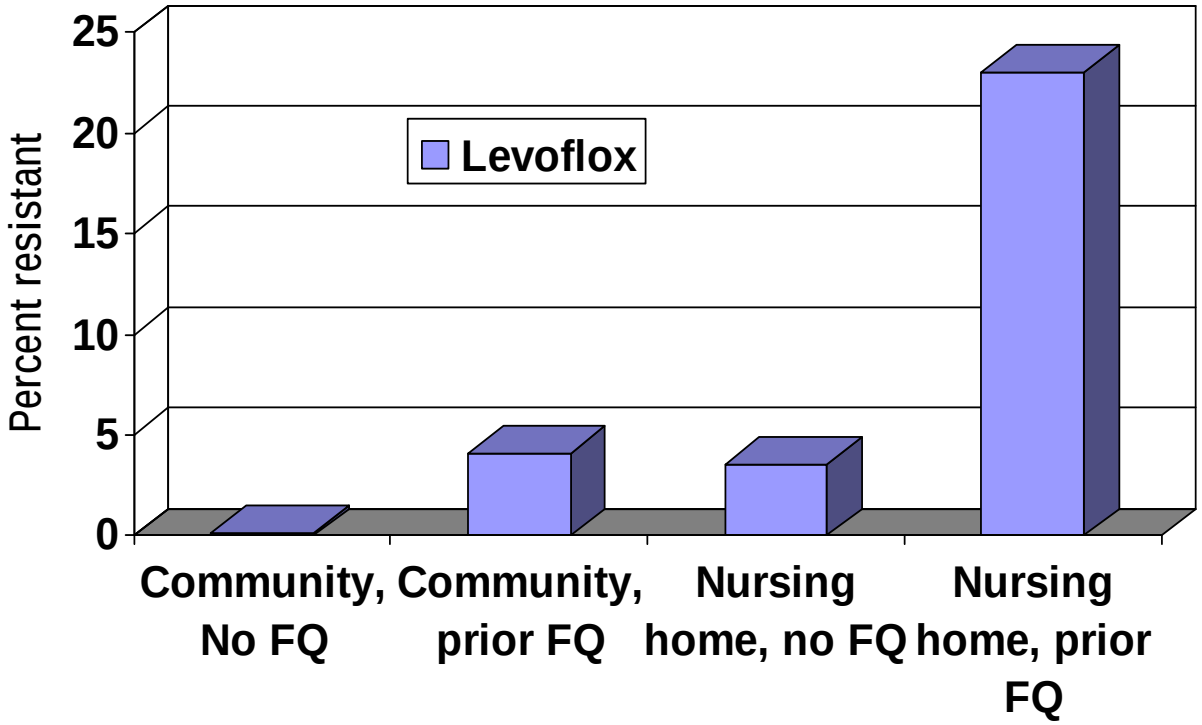
Challenge No.3: Antibiotic Resistance

- Antibiotic resistance
  → a global public health threat
- Particular concerning in LTCFs
- Increased risk of hospitalization, morbidity +/- mortality & healthcare costs
- Most concerning: MRSA, VRE, fluoroquinolone resistance, multi-drug resistant (MDR) gram-negative bacteria

Reasons for Increased Risk of Resistance in the Elderly / LTCF

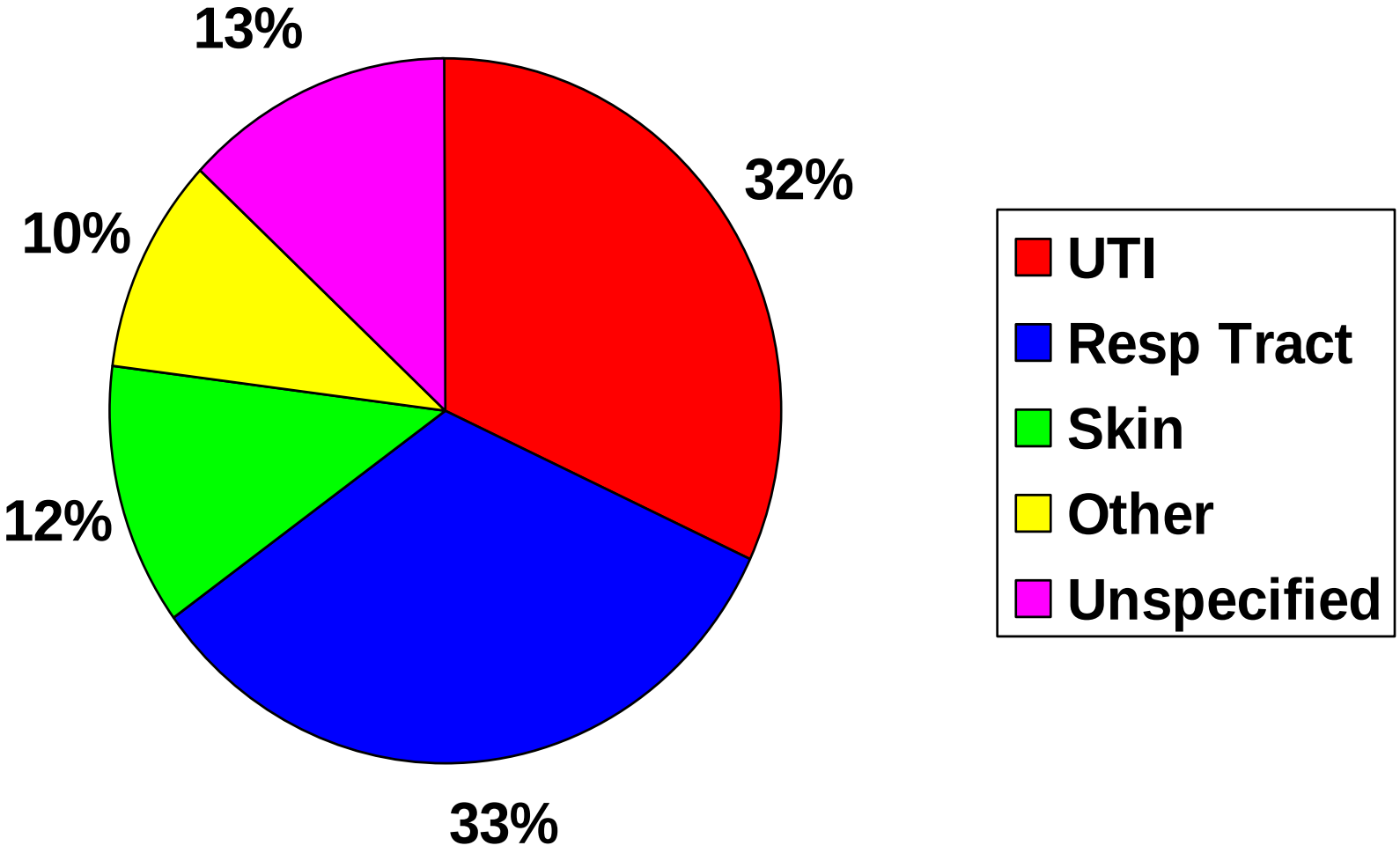
- Increased exposure to healthcare system
- Increased exposure to antimicrobials
- Decreased immune system
- Decreased functional status/hygiene
- Increased use of invasive devices
- Close contact with other residents, medical staff
- Adherence to Infection Control Policies?

Fluoroquinolone Resistance in Pneumococci by Risk Factor



Toronto Invasive Disease Bacterial Network

Most Common Infections in Nursing Home Residents



Adapted from: Benoit et al. J Am Geriatr Soc 2008;56:2039-44.

Challenge: Better UTI Diagnosis

UTI accounts for the largest proportion of inappropriate antibiotic use in LTCFs

UTIs in the Elderly

- Account for ≈ 25% of infections in elderly in the community
- 2nd most frequent cause of infection in LTCFs
- Catheter use associated with increased risk for mortality from UTI

UTI True/False

	True or False
Urine should be cultured if cloudy or if smelly / foul smelling	
The presence of bacteria in the urine is abnormal in the elderly	
An individual with a positive urine culture should always receive antibiotics	
A urinalysis / R&M should always be performed when diagnosing a UTI	
The presence of pyuria (pus) in the urine (WBC or positive leukocyte esterase) means antibiotics should be prescribed	
The absence of pus or bacteria in the urine rules out a urinary tract infection	

UTI True/False

	True or False
In the absence of fever/local symptoms, these are usually a result of dehydration and do not in themselves warrant urine cultures	
10% of elderly men and 20% of women in the community have bacteria in the urine; 30%-50% of frail, LTC residents can have a positive urine culture	
Asymptomatic bacteriuria does not require treatment. Only individuals with symptoms should be treated (local sx in pts without a catheter)	
But a positive dip is not a diagnosis; also need a positive culture with other signs/symptoms	
> 90% of individuals with asymptomatic bacteriuria will have pyuria	
Non-specific and non-localizing signs and symptoms are seldom due to a UTI in the noncatheterized resident	

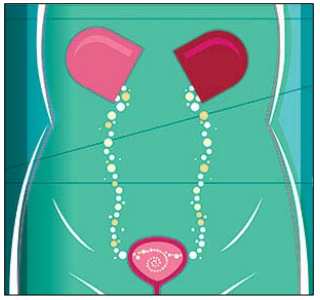
UTI: True/False Catheterized Patients

	True or False
Individuals with a chronic indwelling catheter will always have bacteria in their urine	
Treating these pts with antibiotics will prevent subsequent bacteriuria and/or symptomatic infection	
Presence of urinary catheter increases risk for fever and bacteremia from urine source	
Fever is the most common symptom in catheterized pts with a UTI	
60% of patients with a catheter and fever have a UTI	
Removing/changing the foley catheter before starting antibiotic therapy may be of benefit	

UTI: True/False
Catheterized Patients

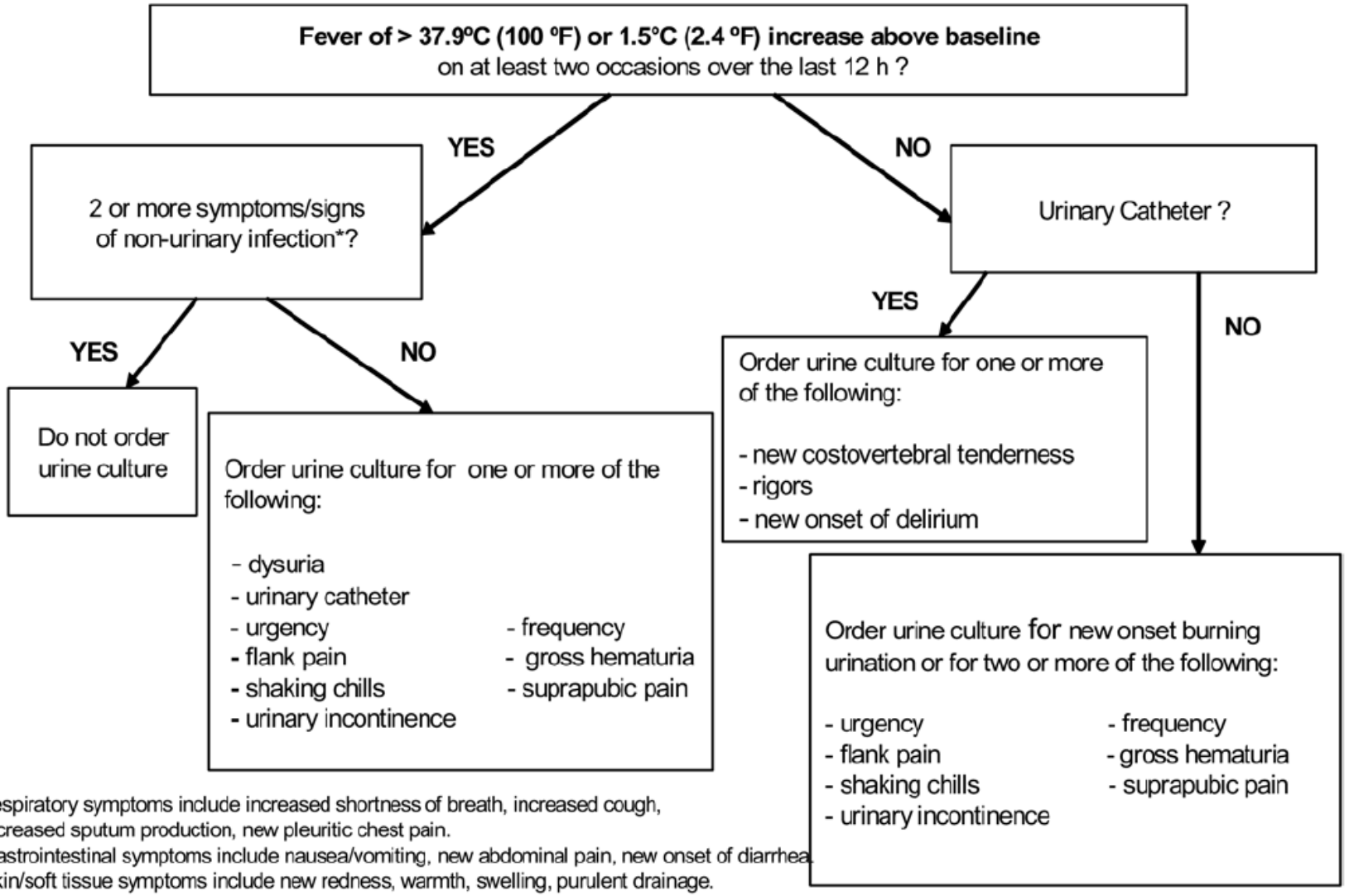
	True or False
Individuals with a chronic indwelling catheter will always have bacteria in their urine	
No benefit to treating bacteria in the urine in the absence of symptoms, but increased risk of resistant bacteria	
Bacteremia is 40 x more common in catheterized individuals than non-catheterized; CAUTI most common source of bacteremia in LTCF	
Fever is the most common symptom in catheterized pts with a UTI	
Fever is due to a UTI in 1/3 of patients with a fever and a catheter	
This may decrease the time to response and/or decrease rate of relapse (removing source of biofilm)	

Principles of UTI Diagnosis



- Presence of bacteria in the urine (positive culture) does not = infection
- A negative culture rules out infection
- Always do a urinalysis / R&M
  - Pyuria (WBC or leucocyte esterase (LE)) does not = infection
  - No pyuria rules out infection (dip neg for LE)
- If inadequate response in 72 h, consider obstruction, complicated disease, resistant organism, or different diagnosis

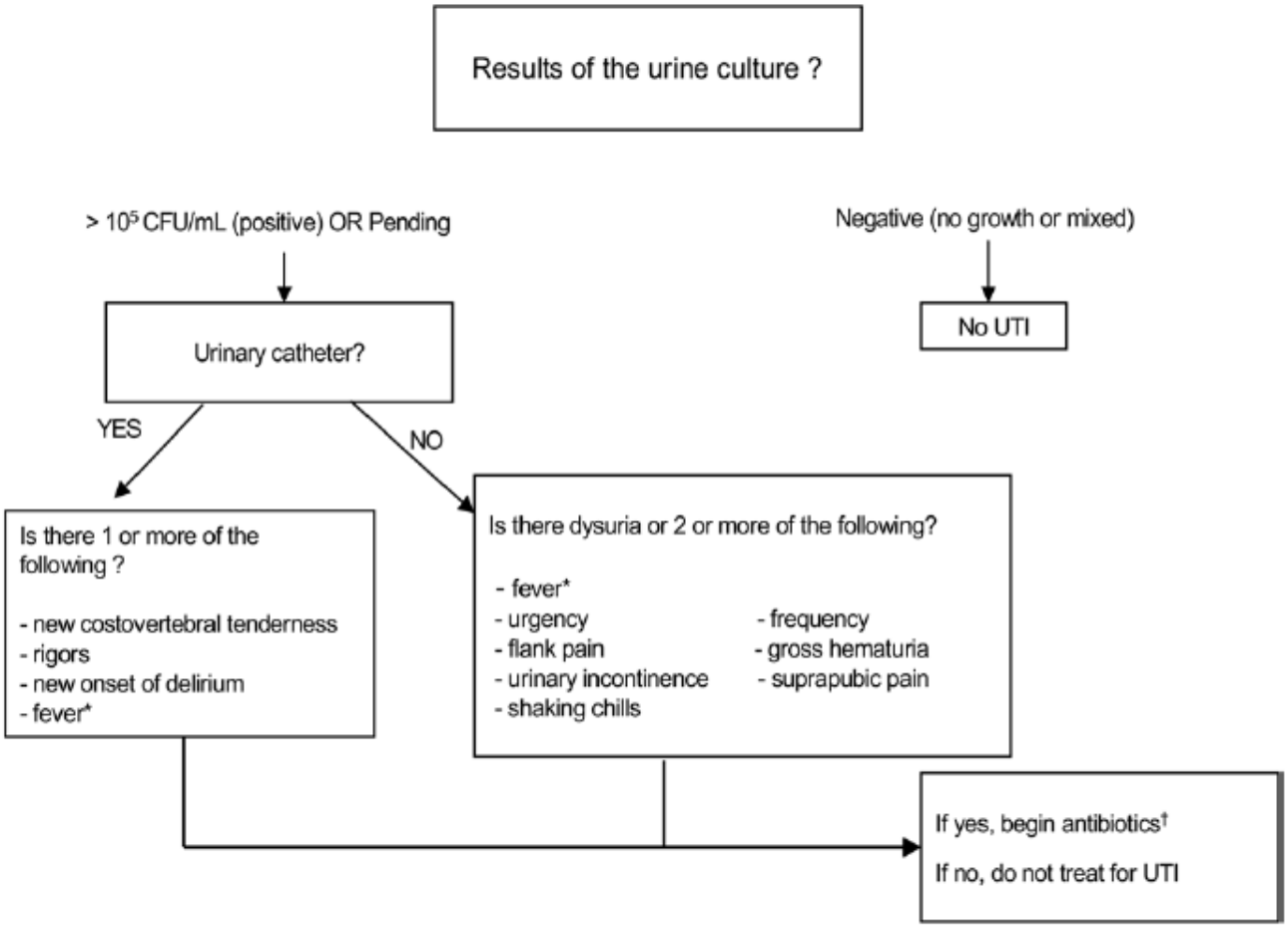
UTI Diagnostic Algorithm



* Respiratory symptoms include increased shortness of breath, increased cough, increased sputum production, new pleuritic chest pain.
Gastrointestinal symptoms include nausea/vomiting, new abdominal pain, new onset of diarrhea.
Skin/soft tissue symptoms include new redness, warmth, swelling, purulent drainage.

J Am Med Dir Assoc 2007;8:477-84.

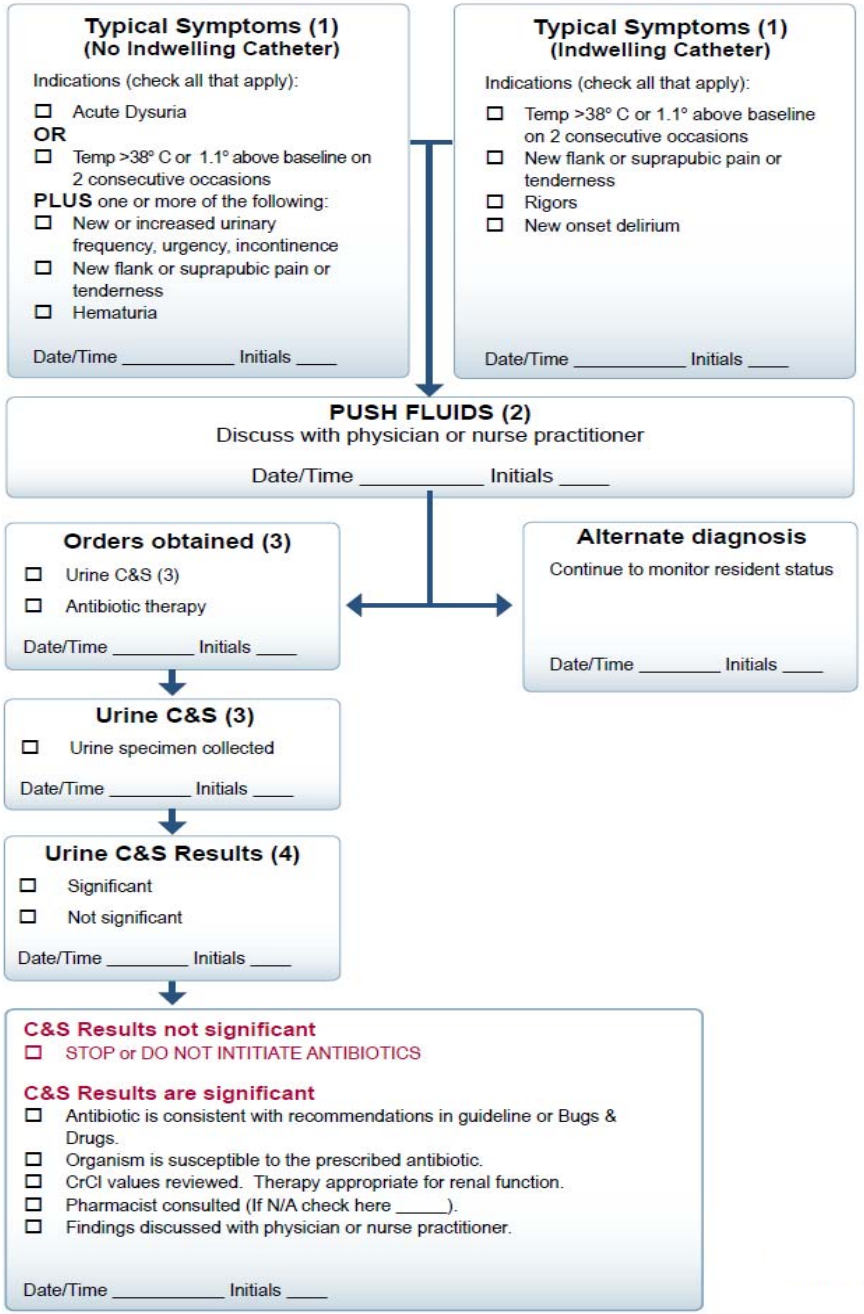
UTI Treatment Algorithm



* >37.9°C (100°F) or 1.5°C (2.4°F) above baseline on 2 occasions over the last 12 h.
† Stop antibiotics if urine culture is negative or no pyuria.

J Am Med Dir Assoc 2007;8:477-84.

UTI Clinical Pathway



TOP Program
Edmonton, Alta

Minimum Criteria for Initiation of Antibiotics in Long-Term Care Residents

Suspected Urinary Infection

- NO indwelling catheter
  need either:
  - Acute dysuria
    or
  - Fever >38.9°C (102°F)
    and at least one of the following:
    - Urgency
    - Frequency
    - Suprapubic pain
    - Hematuria
    - Costovertebral tenderness
    - New onset urinary incontinence

- WITH indwelling catheter
  need at least one of the following:
  - Fever >38.9°C (102°F)
  - New costovertebral tenderness
  - Rigors
  - New onset of delirium

Minnesota Department of Health

Pneumonia in the Elderly

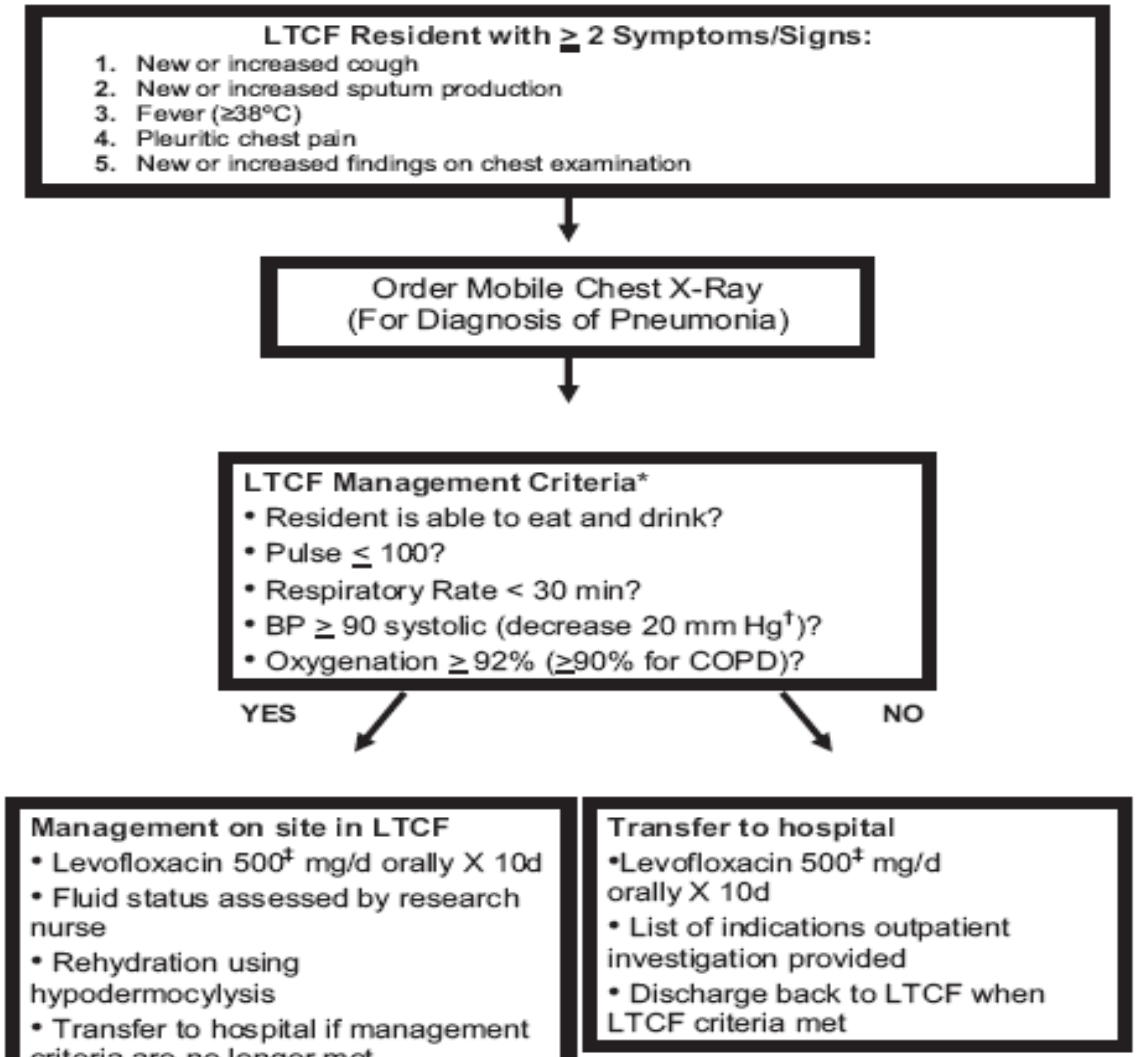
- Higher incidence/mortality rate vs younger pts
- 2nd most frequent cause of hospitalization
- For residents of LTC facilities:
  - pneumonia is 10 times more frequent than healthy ambulatory older adults
  - pneumonia is leading reason for transfer to acute care.
  - leading cause of morbidity and mortality

Am Fam Physician 2004; 70:1495-500.
Clin Chest Med 2007;28:751-71.

Pneumonia Diagnosis

- Symptoms may include fever, new or increased cough w sputum production, dyspnea, new lung findings, increased RR, etc.
- If resp rate >25, check oxygen level (pulse oximetry)
- CXR useful to rule out other diagnosis (e.g., CHF)

Pneumonia Algorithm



J Am Med Dir Assoc 2006;7:271-8.

Pressure Ulcers

- Infectious S/S (prompting cultures)
  - Wound worsening despite appropriate care
  - Purulent drainage
  - Cellulitis (redness, pain, warmth, swelling) of surrounding tissues
- Cultures: from drainage inside wound or tissue at debridement

Diarrhea

- Many causes
  - Drugs (including antibiotics!)
  - Symptoms of remote infections (pneumonia, bacteremia, GI)
  - Viruses
  - Bacteria (food borne) — fever, cramping, WBC or RBC in stool
- If antibiotic tx in last 6 weeks, or if severe, check stool for *C. difficile* toxin

Antibiotic Stewardship in Long Term Care

- Develop/follow guidelines for initiating antibiotics
- Communicate all signs/symptoms (new or worsened) of infection to physician
- Consider non-infectious causes
- Discriminate b/w colonization and infection
- Obtain cultures before antibiotics started
- Preventative measures

Antibiotic Stewardship in Long Term Care

- Obtain/provide history of recent antibiotic use
- Change class of agent when possible and appropriate
  - Esp. fluoroquinolones within previous 3 months, macrolides for respiratory tract infections
  - Consider beta-lactam alternatives, including IM ceftriaxone
- Attention to stop dates / duration of therapy
- Question role of prophylaxis

Challenge No.4: Antibiotic Dosing

- Physiologic changes = unpredictable drug levels and action in body
  - renal excretion most significant
- Elderly usually excluded from studies
- Increase risk of toxicity
- Equations used to estimate renal function not accurate in the elderly
  - uses serum creatinine (from muscle)
  - concern of overestimation

Antibiotic Dosing in the Elderly

- "Start low, go slow" not necessarily better with antibiotics
- Generally, use the usual adult dose regimen
- Adjust for renal function
- Adjust for weight (esp < 45 kg)
- Most antibiotics need dose adjustment in renal dysfunction **except**:
  - cloxacillin, ceftriaxone, azithromycin, doxycycline, moxifloxacin

CID 2005;40:997-1004.

Challenge No. 5: Adverse Effects

- The elderly are at increased risk of adverse drug reactions (ADR)
  - increased exposure due to changes in drug pharmacokinetics
  - increased sensitivity of some organs to drugs
  - polypharmacy
- Antibacterials a frequent cause of ER visits due to ADRs, esp. in elderly
  - 17% of ED visits from ADEs due to antibiotics (Ann Emerg Med **2001**;38:666–71.)
  - Antimicrobial drugs > independent risk factor for an ADE than drugs from many other classes in nursing home residents (Arch Int Med 2001;161:1629-34.)

Esophageal Injury

- “Sticking” of pills in esophagus
- Increased risk in elderly
- Symptoms: sudden onset difficulty swallowing, painful swallowing and/or retrosternal pain
- Transient, self limiting inflammation to severe ulceration / perforation or stricture
- Antibiotics implicated: tetracyclines

  (e.g., doxycycline), clindamycin, rifampin, azithromycin
- Ensure sufficient water and not immediately prior to lying down/bedtime

Challenge No. 6: Drug Interactions

- An estimated 39% of elderly in the community take ≥ 5 meds
- Polypharmacy is even more common in residents of LTCFs
- Pharmacokinetic (change in drug levels) vs pharmacodynamic (effects on action of drug)

FQ = fluoroquinolones (cipro-, levo-, moxi-, nor-, o-floxacin)
Macrolides = erythromycin, clarithromycin, azithromycin*
(* less propensity for interactions)

CID 2005;40:997-1004.

Interacting Drug	Antibiotic(s)	Effect
Warfarin	Macrolides, FQ, metronidazole, septra;	↑ effect of warfarin — monitor INR
Anti-arrhythmics; other drugs that prolong QT interval	Macrolides, FQ	Risk of torsades de pointes; watch electrolytes
Cations (e.g. calcium, Mg++, iron, Al++, zinc)	FQ, tetracyclines	↓ abx levels; adequately space administration
Statins (simvastatin, atorvastatin, lovastatin)	Macrolides	↑ statin levels; muscle toxicity
Serotonergic drugs (e.g. SSRI antidepressants, tramadol)	Linezolid (Zyvoxam®)	Risk of serotonin syndrome (tremor, fever, GI, confusion, delerium, agitation, stiffness)
Digoxin	Macrolides, trimethoprim (in septra), tetracyclines	Possible ↑ digoxin levels; risk of toxicity
Sulfonylureas (e.g. glyburide)	Septra	↑ hypoglycemic effect
Calcium Channel blockers (i.e., diltiazem, verapamil)	Macrolides	↑ effects of CCB; monitor HR, BP
Phenytoin	Metronidazole, septra Ciprofloxacin	↑ phenytoin levels—monitor possible ↓ phenytoin levels

Antibiotic(s)	Interacting Drug
Macrolides	Warfarin, statins (simvastatin, atorvastatin, lovastatin) CCB, drugs that prolong the QT interval, digoxin
Fluoroquinolones	Cations (e.g. calcium, Mg++, iron, Al++, zinc), warfarin, drugs that prolong the QT interval, phenytoin (cipro)
Septra	Warfarin, sulfonylureas, ACE Inhibitors, ARBs, K+ supplements, digoxin, phenytoin
Rifampin	Phenytoin, warfarin, certain steroids, + many many more!! **Always check!**
Linezolid	Serotonergic drugs (e.g. SSRI antidepressants, tramadol)
Metronidazole	Warfarin, phenytoin

CCB: calcium channel blockers (e.g. verapamil, diltiazem)
ARBs: angiotensin blocking agents (“sartans”)
SSRI: selective serotonin reuptake inhibitors (e.g. sertraline, citalopram)

Most Common Antibiotics Prescribed in Ontario LTCFs

Antibiotic name	Number of antibiotic treatment courses (%)
Nitrofurantoin	365 (15.4)
Trimethoprim/sulfamethoxazole	338 (14.3)
Ciprofloxacin	304 (12.8)
Cefalexin	241 (10.2)
Amoxicillin	235 (9.9)
Moxifloxacin	134 (5.7)
Norfloxacin	123 (5.2)
Levofloxacin	105 (4.4)
Clarithromycin	83 (3.5)
Cefuroxime	73 (3.1)
Metronidazole	73 (3.1)
Cloxacillin	59 (2.5)
Tetracycline	56 (2.4)
Azithromycin	47 (2.0)
Clindamycin	36 (1.5)
Cefprozil	22 (0.9)
Penicillin	17 (0.7)
Cefixime	16 (0.7)
Ceftriaxone	12 (0.5)
Ampicillin	10 (0.4)
Erythromycin	10 (0.4)
Vancomycin	≤5 (0.2)
Cefaclor	≤5 (0.1)
Total	2366 (100)

JAC 2011;66:2856-63.

Most Common Antibiotics Prescribed in Ontario LTCF

Antibiotic name	Number of antibiotic treatment courses (%)
Fluoroquinolones: 28%	
Trimethoprim/sulfamethoxazole	338 (14.3)
Ciprofloxacin	304 (12.8)
Beta-lactams (penicillins/cephs): 27%	
Moxifloxacin	134 (5.7)
Nitrofurantoin: 15%	
Clarithromycin	85 (3.5)
Cefuroxime	73 (3.1)
Septra: 14%	
Tetracycline	56 (2.4)
Macrolides (clari, azi): 6%	
Cefprozil	22 (0.9)
Penicillin	17 (0.7)
Cefixime	16 (0.7)
Ceftriaxone	12 (0.5)
Ampicillin	10 (0.4)
Erythromycin	10 (0.4)
Vancomycin	≤5 (0.2)
Cefaclor	≤5 (0.1)
Total	2366 (100)

JAC 2011;66:2856-63.

Fluoroquinolones

Norfloxacin, levofloxacin, moxifloxacin, ciprofloxacin

- Pneumonia (levo, moxi), UTI (norflox, cipro, levo)
- Uncomplicated UTI (cystitis): 250 mg doses
- Cardiac toxicity (QT)
- Tendinitis / tendon rupture
- Hypoglycemia
- CNS: headache, confusion, tremor, dizziness, anxiety, insomnia, hallucinations (esp >80 yo; dose not renally adjusted)

Beta-Lactam Agents

Includes penicillins, cephalosporins, carbapenems

- Well tolerated
- Main side effects: allergy, GI, rash
- Amox/clav: ↑risk diarrhea, liver toxicity
- IM ceftriaxone; IM ertapenem
- Most renally excreted, exc. cloxacillin, ceftriaxone
- 3rd Generation cephalosporins (e.g. ceftazidime, cefepime): concern for non convulsive status epilepticus, esp without dose adjustment

Nitrofurantoin

- Effective for **bladder infections** with *E. coli* and Enterococcus sp.
- Decreased activity with decreased renal function
  - Cutoff: CrCl </= 60 ml/min vs 40 ml/min ??
  - Concern of serious liver, lung toxicity with longer term treatment (e.g., prophylaxis)
  - Peripheral neuropathy
- Only anti-infective on the Beers criteria: 'should generally be avoided in elderly'

J Am Geriatr Soc 2012; 60:616-31.

Septra

- Decreased tolerance in elderly
- Increased risk of rash, liver toxicity, bone marrow toxicity e.g., decrease in WBC, plts
- Hypoglycemia
- Hyperkalemia; esp in pts on ACE inhibitors, K+ supplements
- Adequate hydation
- Interactions (warfarin, sulfonylureas)

Macrolides

- Erthromycin, clarithromycin, azithromycin
- SE: GI** (abnormal taste, nausea, cramping, vomiting, diarrhea)
- Liver
- QT prolongation (azithro less)
- Drug interactions (azithro less)

Aminoglycosides

- Gentamicin, tobramycin, amikacin
- IM or IV only
- Role for seriously ill; MDR UTIs, esp upper UTI
- Increased risk of toxicity vs other agents
- Nephrotoxicity, ototoxicity: inc risk in elderly, dehydration, pre-existing renal dz
- Needs monitoring!! Scr (2-3 x / week), levels
- Renally eliminated; need dosing adjusted; lower doses (1-3 mg/kg daily)

Challenge No.7: Drug Administration

- Limited use of parenteral (IV, IM) routes
- Drugs with good systemic levels include fluoroquinolones (moxi, levo, cipro), septra
- Not macrolides, beta-lactams
- Ceftriaxone, ertapenem IM with lidocaine
- Aminoglycosides IM (e.g., gentamicin)
- Absorption issues: take with food vs empty stomach; interaction with cations

Challenge No.8: Compliance

- Polypharmacy
- Fear of interactions
- Inability to follow directions
- Poor comprehension/memory
- Cost
- Adverse effects
- Unable to open

Summary

- Numerous challenges associated with antibiotic use exist in the elderly
- Antibiotics can be life saving drugs, but also carry significant potential harms
- Risks of adverse effects and antibiotic resistance can be minimized in the elderly by:
  - Appropriate dosing in patients with decreased renal/liver function
  - Attention to drug interactions, esp. in patients on multiple medications
  - Use of guidelines for initiation of antibiotics in LTCFs