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ORDER OF PHARMACISTS OF LEBANON

Adherence to International & Lebanese Guidelines for the Treatment of Uncomplicated Urinary Tract Infections in Lebanese Community Pharmacies

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Disclosure Statement

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*****_All authors declare to meeting attendees that there are no financial relationships with any for-profit companies that are directly or indirectly related to the subject of this presentation_

Objectives

- To review the treatment of uncomplicated urinary tract infections (UTI)
- To present the results of a recently conducted study in Lebanon that evaluated the adherence to guidelines for the treatment of uncomplicated UTI in community pharmacies
- To raise awareness about antimicrobial stewardship and overuse of specific antimicrobial agents for the treatment of uncomplicated UTI in the community

Introduction

- Urinary tract infections (UTIs) are considered to be the most common bacterial infections
- Comprise a variety of infections: cystitis, urethritis, pyelonephritis, prostatitis, epididymitis,…
- Accurate diagnosis depends on the presence of symptoms and a positive urine culture

Introduction

- Classification :

  - anatomic site
  - severity (complicated vs uncomplicated)
  - symptomatic vs asymptomatic
  - acute vs recurrent
  - community acquired vs nosocomial

Pathophysiology

- Host defense mechanisms:

  - acidic pH of urine
  - flushing
  - prostatic secretions (PAF) in males inhibit bacterial growth
  - prevention of adherence of bacteria to epithelial cells (urinary slime: glycosaminoglycan)

Risk Factors

- Urinary catheters
- Vesicourethral reflux
- Pregnancy
- Spermicides
- Neurological bladder disease
- Urinary retention
- Urinary tract obstruction

Signs and Symptoms

- Dysuria
- Urinary urgency
- Frequency
- Hematuria, Nocturia
- Fever
- **Flank pain**
- **Costovertebral tenderness**
- Nausea/Vomiting/dehydration

Causative Organisms

- ***Escherichia coli***
- *Klebsiella* species
- *Proteus mirabilis*
- *Enterobacter cloacae*
- *Serratia marcescens*
- *Pseudomonas aeruginosa*
- *Staphylococcus saprophyticus*
- *Enterococcus faecalis*
- Group B streptococcus
- *Candida* species

Causative Organisms

- Community acquired vs nosocomial
- Usually monomicrobial
- Contamination with *Staphylococcus epidermidis*, may need to repeat culture

Diagnosis

- Urine culture → definitive diagnosis

- Urinalysis:
  - Bacteria
  - WBC
  - Nitrite
  - Leukocyte esterase
  - Epithelial cells

Antibiotic Therapy

- Penicillins
- β-lactamase Inhibitor combinations
- Cephalosporins
- Carbapenems
- Aztreonam
- Aminoglycosides

- **Nitrofurantoin**
- **Fosfomycin**
- **Sulfamethoxazole/Trimethoprim**
- Fluoroquinolones

Acute Uncomplicated UTI in Women - Cystitis

- Half of all women will have at least 1 episode

- 1 in 4 will have recurrent episodes

- Most prevalent pathogens include:
  - *E. coli* 85%
  - *Staphylococcus saprophyticus* 5-10%
  - *Klebsiella pneumoniae* & *Proteus mirabilis* > 5%

Acute Uncomplicated UTI in Women– Cystitis Treatment

- Rule out pyelonephritis, check if able to take oral medication
- Resistance patterns and propensity for **“collateral damage”**
- Other factors to consider: allergy history – tolerance – availability – drug concentration in urinary tract – cost

International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases

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Acute Uncomplicated UTI in Women– Cystitis Treatment

- Oral Treatment:

  - Nitrofurantoin

  - Sulfamethoxazole/Trimethoprim

  - Fosfomycin

  - Pivmecillinam

Nitrofurantoin

- Activity against *E. coli, Staphylococcus aureus, Enterococci, Klebsiella* and *Enterobacter* species
- Active primarily in urinary tract, **do not use if pyelonephritis suspected**
- Dose: 100 mg po every 12 hours for 5 days
- Side effects: gastro-intestinal (GI) intolerance, pulmonary and neurotoxicity, brownish urine, hepatotoxicity
- Not recommended in patients with renal impairment

Sulfamethoxazole/Trimethoprim

- Double Strength (800/160 mg) po every 12 hours for 3 days
- Avoid if resistance prevalence is known to exceed 20%
- Avoid if used for UTI in previous 3 months
- SE: rash, urticaria, GI side effects, hemolytic anemia, hyperkalemia
- Do not use in sulfa allergy
- May use trimethoprim 100 mg po every 12 hours for 3 days
- D-D interactions: multiple including warfarin and phenytoin

Fosfomycin trometamol

- Phosphonic acid bactericidal agent
- Active against *E. coli, Citrobacter*, *Enterobacter, Klebsiella* , *Serratia* , and *Enterococcus*
- Mainly for cystitis treatment
- **Do not use if pyelonephritis suspected**
- 3 gram po single dose
- Side effects: transient GI symptoms (nausea, diarrhea), headache

Pivmecillinam

- Penicillin derivative
- Used mainly for cystitis
- Dose: 400 mg po every 12 hours for 5 days
- GI side effects: nausea, vomiting, diarrhea
- **Do not use if pyelonephritis suspected**
- Not widely available

Acute Uncomplicated UTI in Women– Cystitis Treatment

- β-lactams for 3 – 7 days:

  * Avoid ampicillin or amoxicillin alone
  * Can use amoxicillin/clavulanic acid, cefaclor, cefdinir, cefpodoxime, cefixime
  * Lower efficacy than other available agents (require close follow-up)

Acute Uncomplicated UTI in Women– Cystitis Treatment

- Alternatives:

  - Fluoroquinolones for 3 days
    - Norfloxacin 400 mg po every 12 hours
    - Ofloxacin 200 mg po every 12 hours
    - Ciprofloxacin 250 mg po every 12 hours
    - Levofloxacin 250 mg po daily

    - Side effects: GI (nausea/vomiting, diarrhea), tendinopathy, photosensitivity, peripheral neuropathy, central nervous system effects
    - Space from bivalent cations (Fe, Ca, Mg)

Acute Uncomplicated UTI in Women– Cystitis Treatment

- Use of fluoroquinolones has been associated with infection with:

- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Increase in fluoroquinolone resistance in Gram-negative bacilli
- Colonization with multi-drug resistant strains

Lebanese Society of Infectious Diseases and Clinical Microbiology: Guidelines for the Treatment of Urinary Tract Infections

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Lebanese Society of Infectious Diseases and Clinical Microbiology

- The UTI guidelines take into consideration the available local epidemiological data and the resistance profile of common urinary pathogens in Lebanon
- Susceptibility to fluoroquinolones in *E. coli* has decreased during the past decade to ≈ 50%
- Susceptibility of Enterobacteriacae to Sulfamethoxazole/ Trimethoprim has remained consistently low (≈ 50%)
- Extended Spectrum β-lactamase (ESBL) production in *Klebsiella pneumoniae* has increased to ≈ 30%

Lebanese Society of Infectious Diseases and Clinical Microbiology

First-line:

- Nitrofurantoin 100 mg po every 12 hours for 5 days
- Fosfomycin 3 grams po as a single dose

Alternatives:

- β-Lactam agents for 3 - 5 days
  - Amoxicillin-clavulanate 1 gram po every 12 hours
  - Cefdinir 300 mg po every 12 hours or 600 mg po daily
  - Cefixime 400 mg po daily

Adherence to Guidelines for the Treatment of Uncomplicated UTI

- Prospective study conducted in 15 community pharmacies in Lebanon over a period of 1 year
- Adult female patients visiting community pharmacies to purchase an antibiotic prescribed for uncomplicated UTI were interviewed and a questionnaire was filled
- Approved by the Lebanese American University Institutional Review Board

Adherence to Guidelines for the Treatment of Uncomplicated UTI

- Exclusion criteria:

- pregnant women
- patients younger than 18 years
- chronic kidney disease (CKD stages III, IV, V) or structural renal disease
- patients diagnosed with pyelonephritis
- patients diagnosed with a sexually transmitted disease (STD)
- complicated UTI (males, urologic anatomic or functional abnormalities, indwelling catheters or neurogenic bladders, diabetes, immunosuppression)

Adherence to Guidelines for the Treatment of Uncomplicated UTI

Appropriate regimens (drug/dose/duration):

✓Nitrofurantoin 100 mg every 12 hours for 5 days

✓Fosfomycin 3 grams single dose

± Sulfamethoxazole/trimethoprim (appropriate only if culture was done and showed susceptibility)

X All other regimens were considered as inappropriate

Adherence to Guidelines for the Treatment of Uncomplicated UTI

- Statistical analysis
- Data were entered and analyzed using SPSS, version 23.0
- Descriptive analysis: frequency and percentage for nominal and dichotomous variables and mean and standard deviation for continuous variables
- Bivariate analysis: chi square test was used to compare nominal variables between groups
- In all cases, a p-value <0.05 was considered statistically significant

Adherence to Guidelines for the Treatment of Uncomplicated UTI

- Results

Patient population

- N= 376 adult female patients

- Mean age= 38 years (61% of patients are 18-40 years old)

- A urine culture was obtained in 26% of patients

- 18% of patients had recurrent UTI

Adherence to Guidelines for the Treatment of Uncomplicated UTI

Prescribed Antibiotic

- Fluoroquinolone: 39% of patients
  (49% of which is ciprofloxacin)

- Nitrofurantoin: 26% of patients

- Fosfomycin: 5% of patients

- Other antibiotics: 30% of patients

Adherence to Guidelines for the Treatment of Uncomplicated UTI

		Appropriate	Non-Appropriate
Regimen		80 (21%)	296 (79%)
	Drug	131 (35%)	245 (65%)
	Dose	276 (73%)	100 (27%)
	Duration	219 (58%)	157 (42%)

Adherence to Guidelines for the Treatment of Uncomplicated UTI

Bivariate analysis

- Age (≥ 50 years) did not significantly affect the appropriateness of the prescribed antibiotic; p=0.508

- The frequency of attacks (≥ 3) per year was significantly associated with an inappropriate treatment; p=0.025

Adherence to Guidelines for the Treatment of Uncomplicated UTI

- Inappropriate doses were most frequent with fluoroquinolones; 45% vs 22% for nitrofurantoin vs 0% for fosfomycin; $p<0.001$

- Inappropriate duration of therapy was most frequent with fluoroquinolones; 51% vs 41% for nitrofurantoin vs 21% for fosfomycin; $p=0.014$

Adherence to Guidelines for the Treatment of Uncomplicated UTI

- Uncomplicated UTI has a minimal risk of progression to severe disease
- Can be successfully treated with narrow spectrum antimicrobials (nitrofurantoin or fosfomycin) with excellent *E. coli* susceptibility patterns
- Fluoroquinolones have a high risk of “collateral damage” and Gram negative resistance prevalence is continuously increasing

Adherence to Guidelines for the Treatment of Uncomplicated UTI

- The Food and Drug Administration (FDA) conducted a review of placebo-controlled clinical trials and a search of the FDA Adverse Effect Event Reporting System database from November 1997 to May 2015

- 178 identified patients in the United States who developed a disability or a potentially irreversible side effect after the use of a fluoroquinolone

* **FDA safety warning (July 2016): reserve FQ as last line options in uncomplicated infections including cystitis**

Adherence to Guidelines for the Treatment of Uncomplicated UTI

Lack of adherence to the guidelines could be due to:

- low awareness to the international and national recommendations

- physicians' familiarity and preference for certain antibiotics based on their clinical experience

- concern for infectious complications

Adherence to Guidelines for the Treatment of Uncomplicated UTI

Conclusion

- This study demonstrates a high prevalence of inappropriate use of antibiotics for the treatment of uncomplicated UTI in Lebanon
- This is mainly attributable to inappropriate indication, dose and/or duration of therapy with fluoroquinolones
- Interventions that improve prescribing practices through education on appropriate therapy for uncomplicated UTIs are needed

Thank You