

DIRECTIVES/GUIDELINES

THE LEBANESE SOCIETY OF INFECTIOUS DISEASES AND CLINICAL MICROBIOLOGY Guidelines for the Treatment of Urinary Tract Infections

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ABSTRACT • Urinary tract infection (UTI) is a common condition affecting men and women of all ages. It can have different presentations and can be acute, recurrent or chronic. It mandates prompt management to avoid complications and improve patient's outcome. In an era of increasing antimicrobial resistance and an urgent need for antimicrobial stewardship, national guidelines to standardize care of various infectious diseases have become a priority. Members of the Lebanese Society of Infectious Diseases and Clinical Microbiology (LSIDCM) drafted guidelines for the management of the various forms of UTI. These guidelines serve as a guide for health care workers, specifically primary care practitioners, family physicians, and emergency medicine physicians. They constitute an appropriate starting point before specialist consultation. They take into consideration the available local epidemiological data and the resistance profile of common urinary pathogens in Lebanon.

This document includes the following sections: 1. Rationale and scope of the guidelines; 2. Definition of UTI; 3. Clinical presentation and diagnostic work-up of UTI; 4. Microbiological data of UTI; 5. Management and prevention strategies based on the latest Infectious Diseases Society of America (IDSA) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines, tailored to the microbiological data in Lebanon. It addresses UTI in women (uncomplicated and complicated) and men (acute and chronic). In addition, it covers management of asymptomatic bacteriuria and catheter related UTI. The recommendations in this document were graded based on the strength of the evidence as in the IDSA guidelines.

Keywords : Lebanon; LSIDCM; urinary tract infection; pathogens; antibiotic regimen; complicated; recurrent

RÉSUMÉ • Les infections des voies urinaires (IVUs) sont des maladies courantes qui affectent les hommes et les femmes de tous âges. Elles peuvent avoir des présentations différentes et peuvent être aiguës, récurrentes et chroniques. Elles nécessitent une prise en charge rapide pour éviter les complications et améliorer les symptômes des patients. Face à l'augmentation de la résistance aux agents antimicrobiens et à l'urgence de gérer les antimicrobiens, des lignes directrices nationales pour contrôler les soins des diverses maladies infectieuses sont devenues une priorité. Les membres de la Société libanaise des maladies infectieuses et de la microbiologie clinique (LSIDCM) ont rédigé des directives nationales pour le traitement des diverses IVUs. Ces directives servent de guide pour le personnel soignant, spécifiquement les généralistes, les médecins de famille et les urgentistes. Elles constituent un point de départ approprié avant la consultation de spécialistes. Ces lignes directrices ont pris en considération les données épidémiologiques locales disponibles et le profil de résistance des agents pathogènes des voies urinaires fréquents au Liban. Ce document comprend les éléments suivants: 1. Raison d'être et portée des lignes directrices; 2. Définition de l'IVU; 3. Présentation clinique et bilan diagnostique des infections urinaires; 4. Données microbiologiques des IVUs; 5. Des stratégies de gestion et de prévention basées sur les dernières lignes directrices de l'IDSA et de l'ESCMID et adaptées aux données microbiologiques au Liban. Le document est divisé en IVUs chez les femmes (simples et complexes) et les hommes (aiguës et chroniques). La bactériurie asymptomatique et le traitement des IVUs liées au cathéter y sont également abordés. Les recommandations formulées dans ce document ont été classées selon les récentes directives de l'IDSA basées sur le niveau de preuve scientifique et force des recommandations.

Mots-clés : Liban; LSIDCM; infections des voies urinaires; pathogènes, antibiothérapie; compliquée; récurrente

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INTRODUCTION

Urinary tract infections (UTIs) are among the most common infections in the community as well as in the health-care setting. Resistant bacteria causing these infections, mostly the extended-spectrum β -lactamase (ESBL) producing bacteria and the fluoroquinolone-resistant *Enterobacteriaceae*, pose a great challenge in view of the paucity of available therapeutic options. Moreover, the pipeline for new antimicrobials is drying up which led the IDSA to issue an alarm on “Bad Bugs, No Drugs” [1]. Low adherence to guidelines for the treatment of uncomplicated UTIs in primary care can lead to overuse of fluoroquinolones and excessive duration of treatment, both of which can cause higher antibiotic resistance [2].

Antimicrobial resistance in Lebanon is no exception to the worldwide trend and is rapidly evolving as shown by various studies [3].

Susceptibility to fluoroquinolones in *Escherichia coli* has decreased during the past decade from 73% to 53%, and ESBL production in *Klebsiella pneumoniae* has increased from 12% to 28% [3,4]. Furthermore, the susceptibility of *Enterobacteriaceae* to trimethoprim/sulfamethoxazole has remained consistently low (50%), in addition to the emergence of multidrug-resistant (MDR) *Pseudomonas sp.* and more recently a rapid rise in the incidence of carbapenem resistant *Enterobacteriaceae* (CRE) [3,5]. In view of this crisis, antimicrobial stewardship has become a must to promote judicious use of antibiotics and limit the emergence and spread of further resistance [6].

Clinical practice guidelines for managing UTIs are not available in our country, Lebanon. In this context, the Lebanese Society of Infectious Diseases and Clinical Microbiology (LSIDCM), an official society of the Lebanese Order of Physicians whose members are specialized in infectious diseases (ID) and/or clinical microbiology, has issued these practice guidelines for the management of UTIs in Lebanon. Moreover, the working group has col-

lected local data from different hospitals across the country on the susceptibility of organisms that usually cause UTIs. Several meetings were held with members of the LSIDCM to draft these guidelines. Below are the recommendations based on a consensus among members of the society.

MATERIALS AND METHODS

Organization of Lebanese guidelines-development committee

Contributing members of LSIDCM met to discuss the international guidelines and the local epidemiological data of causative organisms and their resistance. Decisions were based on international guidelines, including the 2010 update by the Infectious Diseases Society of America (IDSA) and the European Society for Microbiology and Infectious Diseases (ESCMID) Guidelines [7], the Infectious Diseases Society of America Guidelines for the Diagnosis and Treatment of Asymptomatic Bacteriuria in Adults [8], and Guidelines on Urological Infections [9]. Then, they chose the best treatment options relying on the above mentioned guidelines, which would fit the microbial ecology in Lebanon, taking into consideration the disease spectrum and the medication cost. Susceptibility profiles in this document are derived from local published literature and microbiology reports of university hospitals. After an agreement between the members of the committee, a subgroup drafted these guidelines and a final version was achieved by a consensus of the guideline development panel. They were then sent to all members of the executive committee for additional comments and suggestions.

Strength of recommendations and quality of evidence

For strength of recommendations and quality of evidence, the methods used in the Lebanese Guidelines for Febrile Neutropenia were adopted and labeled as LSIDCM level of evidence stated in table I.

TABLE I
THE LEBANESE SOCIETY OF INFECTIOUS DISEASES AND CLINICAL MICROBIOLOGY (LSIDCM)
GRADING OF STRENGTH OF RECOMMENDATION AND QUALITY OF EVIDENCE

Category	Definition
1	Based upon high-level evidence with multiple well-designed, controlled, randomized blinded studies and meta-analysis. There is uniform LSIDCM consensus that the intervention is adequate.
2A	Based upon lower level of well-controlled, non-blinded or randomized studies, with retrospective reviews. There is uniform LSIDCM consensus that the intervention is adequate.
2B	Based upon lower level of well-controlled, non-blinded or randomized studies, with retrospective reviews. There is majority LSIDCM consensus that the intervention is adequate.
3A	Based upon any evidence that is less than well-controlled, or randomized, or large sample studies, mostly retrospective. There is uniform LSIDCM consensus that the intervention is adequate.
3B	Based upon any evidence that is less than well-controlled, or randomized, or large sample studies, mostly retrospective. There is no uniform LSIDCM consensus that the intervention is adequate.
3C	Based upon any evidence that is less than well-controlled, or randomized, or large sample studies, mostly retrospective. There is no LSIDCM consensus that the intervention is adequate.
4A	There is any level of evidence from literature against the intervention. There is uniform LSIDCM consensus against the intervention.

Adapted from NCCN Clinical Practice Guidelines in Oncology Prevention and Treatment of Cancer-Related Infections (v.1.2013).
Fort Washington: National Comprehensive Cancer Network, 2013.

In case the same recommendation appeared in another guideline, it would be mentioned with the corresponding level and the name of the guideline.

SCOPE OF THESE GUIDELINES

These recommendations encompass acute uncomplicated bacterial UTI in adult premenopausal non-pregnant women, recurrent uncomplicated UTI in women, complicated UTI in women, asymptomatic bacteriuria in women, acute and chronic bacterial and nonbacterial prostatitis in men, and catheter-associated UTIs in adult patients. UTIs in pediatric patients will not be addressed in this manuscript.

DEFINITION OF URINARY TRACT INFECTION

UTI is an inflammation of the urothelium due to an invasion by a pathogen, usually associated with pyuria and bacteriuria [10]. It is characterized by the presence of a significant number of bacteria in the urinary tract (i.e. $\geq 10^5$ organisms/mL), yet a symptomatic infection can occur with 10^3 organisms/mL [11].

These infections are grouped according to different classification schemes:

Site of infection: Upper (pyelonephritis) or lower (urethritis, cystitis, and prostatitis) urinary tract disease.

- Cystitis describes a clinical syndrome of dysuria, frequency, urgency, occasional suprapubic pain, and/or hematuria. These symptoms, although generally indicative of bacterial cystitis, may also be associated with infection of the urethra or vagina or non-infectious conditions such as interstitial cystitis, bladder carcinoma, or calculi. Conversely, patients may be asymptomatic and have infection of the bladder and possibly the upper urinary tract [12].
- Acute pyelonephritis describes a clinical syndrome of chills, fever, flank pain, with or without nausea and vomiting, accompanied by bacteriuria and pyuria, indicative of an acute bacterial infection of the kidney. It may be difficult to diagnose in elderly patients and patients with spinal cord injury who may be unable to localize the site of discomfort.

Complicated vs. uncomplicated: This classification scheme is based on the host's urinary tract anatomic and urodynamic status and ranges clinically from benign self-limited cystitis to urosepsis [10].

- An uncomplicated UTI is defined as an infection in a healthy patient with a structurally and functionally normal urinary tract. The majority of these patients are women with isolated or recurrent bacterial cystitis or acute pyelonephritis, and the infecting pathogens are usually susceptible to and eradicated by a short course of oral antimicrobial therapy.
- A complicated UTI is defined by the presence of any of the following features: functional or ana-

tomatic abnormality of the urinary tract (reflux, neurologic disease, cystocele, diverticulum, fistula), pregnancy, old age, diabetes mellitus, immunosuppression, presence of an indwelling urinary catheter, urinary tract instrumentation or surgery, hospital-acquired infection, presence of a urolithiasis, symptoms for more than 7 days at presentation, renal failure, renal transplant, and an infection with a pathogen resistant to broad-spectrum antibiotics. Such infections can occur in women or men [12].

Incidence and frequency: Can be labeled as first or isolated, unresolved or recurrent, depending on whether or not the patient had previous episodes of UTI [12]:

- A first or isolated infection is one that occurs for the first time in life or separated by 6 months from other infections.
- An unresolved infection is one that has not responded to antimicrobial therapy within 48 hours after starting the treatment, mainly due to either antimicrobial resistance or presence of two or more bacterial species with different susceptibilities.
- A recurrent infection is one that occurs after documented, successful resolution of an antecedent infection. Recurrence can be early (within 1-2 weeks after complete resolution of previous UTI), usually due to the persistence of bacteria within the urinary tract system, or late (after 2 weeks of complete resolution of previous UTI), mainly due to reinroduction of bacteria into the urinary tract.
- Chronic infection is a vague term that should be avoided in the context of UTI, because the duration of the infection is not defined [12]. Exception to this rule is chronic bacterial prostatitis.

These definitions require careful clinical and microbial assessment and are important because they influence the type and extent of the patient's evaluation and treatment.

DIAGNOSIS

The diagnosis of UTI is based on clinical symptoms and documented pyuria on urinalysis. The diagnosis is usually confirmed by a positive urine culture. Occasionally, early in the infection process, a negative urinalysis and culture may be seen, because the number of bacteria and neutrophils are low or diluted by increased fluid intake [11]. Contamination and colonization can also occur.

Voided and catheterized specimens of urine must be done in a sterile way.

Suprapubic aspiration is least likely to be contaminated but is invasive and has some complications [11].

Furthermore, when patients have urinary symptoms, microscopic urinalysis for bacteriuria, pyuria, and hematuria must be obtained. Five- to 10-mL of the obtained specimen should be centrifuged for 5 minutes at 2,000 rpm and then analyzed [11]. Microscopic bacteriuria is seen in

more than 90% of UTIs with $\geq 10^5$ colony-forming units (CFU) per milliliter of urine and is not detectable in infections with lower colony count (10^2 to 10^4 CFU/mL). On the other hand, bacteria can be seen microscopically in the absence of infection if contamination occurred while obtaining the specimen. This is more commonly seen in female patients. Factors that affect the number of cells seen include the severity of inflammation, the patient's hydration status, the urine collection method, and the volume, speed, and duration of centrifugation together with the volume in which the sediment is resuspended [11].

MICROBIOLOGY

Escherichia coli, other species of *Enterobacteriaceae*, such as *Proteus mirabilis* and *Klebsiella pneumoniae*, and *Staphylococcus saprophyticus* are the most common causative agents of UTIs.

Studies from Lebanon have addressed the bacterial etiology of UTIs. One study by Daoud and Afif investigated retrospectively the etiology of UTIs in a university medical center in Beirut over a 10-year period. The study found that *E. coli* was the most common isolated bacteria representing 60-64% of the total isolates. It was followed by *K. pneumoniae* and *Proteus sp.*, *Pseudomonas aeruginosa*, *Enterococcus sp.*, and *Streptococcus agalactiae* [13]. Another Lebanese study investigated the etiology of UTIs in community acquired versus health care associated infections. It found that *E. coli* was the most common pathogen with more resistance to antibiotics among the health care associated pathogens [14].

Other studies have addressed the issue of antimicrobial resistance of the common uropathogens in the Lebanese population, especially the ESBL-producing pathogens which are steadily increasing especially among *E. coli* and *Klebsiella sp.* A study from Saint George Hospital University Medical Center in Beirut showed that 2% of 4,299 *E. coli* isolates and 20% of 1,248 *K. pneumoniae* isolates collected between 1997 and 2001, produced ESBL [15]. In a study published by Araj *et al.*, 51% of the ESBL-pro-

ducing *E. coli* (n = 150) were resistant to ceftazidime and 54% were resistant to ceftazidime. With respect to ESBL-producing *K. pneumoniae*, 53% of the isolates were resistant to ceftazidime and 82% were resistant to ceftazidime [16]. Recently, a study was conducted to look at ESBL-producing strains of *E. coli* and *K. pneumoniae* isolated from both hospitalized and outpatients in a university hospital in Beirut. It extended over a five-year period from 2005 to 2009 and revealed a significant increase in the percentage of ESBL-producing *E. coli* from 17.8% in 2005 to 30.4% in 2009 and *K. pneumoniae* from 23.7% in 2005 to 31.8% in 2009 [17].

Another study by Moghnieh *et al.* discussed the distribution and trends of resistance of *E. coli* and *Klebsiella sp.* collected from clinical specimens of community-acquired infections. It showed that these organisms are significantly resistant to many antibiotics. Only 69.5% were susceptible to third generation cephalosporins (3GC) and susceptibility to ciprofloxacin was approximately 50% in the 3GC resistant strains. Furthermore, the susceptibility of *K. pneumoniae* to ciprofloxacin was 67%, to 3GC 71%-79%, and to nitrofurantoin and trimethoprim/sulfamethoxazole (TMP/SMX) 59%-62% [18].

A recent study by Baroud *et al.* investigated the molecular etiology of carbapenem resistance among ESBL-producing *K. pneumoniae* and *E. coli* isolates at a tertiary care center in Lebanon. It found that β -lactamase production combined with porin impermeability and/or efflux pump activity was responsible for carbapenem resistance in these organisms. Moreover, the carbapenemase-encoding genes bla_{OXA-48} and the newly emerging bla_{NDM-1} were found in a number of isolates [19].

MANAGEMENT

Acute uncomplicated cystitis in adult premenopausal non-pregnant women (Table II)

Acute uncomplicated bacterial UTIs in adult premenopausal non-pregnant women, including acute cystitis and acute uncomplicated pyelonephritis, are among

TABLE II
RECOMMENDED ANTIMICROBIAL REGIMENS FOR THE TREATMENT OF ACUTE UNCOMPLICATED BACTERIAL CYSTITIS IN ADULT PREMENOPAUSAL NON-PREGNANT WOMEN

Antibiotic	Dose	Frequency	Route	Duration
Microcrystalline Nitrofurantoin monohydrate	100 mg	BID	PO	5 days
Fosfomycin trometamol	3 g	Once	PO	One single dose
Cefdinir	300 mg	BID	PO	3-7 days
Cefuroxime	500 mg	BID	PO	3-7 days
Cefixime	400 mg	QD	PO	3-7 days
Amoxicillin-clavulanate	1 g	BID	PO	3-7 days
Ciprofloxacin	250 mg-500 mg	According to body weight	PO	3-5 days
Ofloxacin	200 mg	BID	PO	3-5 days
Levofloxacin	500 mg	QD	PO	3-5 days
Prulifloxacin	600 mg	QD	PO	3-5 days

BID: twice a day QD: daily PO: per os

the most common infections seen in outpatient clinics all over the world. For most cases of acute cystitis in women, empirical therapy is usually considered. Knowledge of the local antimicrobial susceptibility profile of uropathogens causing uncomplicated UTIs in the Lebanese community should guide therapeutic decisions, and thus dictate our success rate as well as progression of the infection.

In view of the local epidemiology of high resistance rates to fluoroquinolones and trimethoprim/sulfamethoxazole in Lebanon, we recommend:

- Nitrofurantoin monohydrate/macrocrystals (100 mg per os (PO) twice a day (bid) for 5 days) which is an appropriate choice for therapy, as the resistance to it is minimal. (IDSA: A-I) (LSIDCM: 1) (Table I)
- Fosfomycin trometamol (3 g PO as a single dose) is another appropriate choice for therapy, as the resistance is also minimal [7]. (IDSA: A-I) (LSIDCM: 1)
- When other recommended agents cannot be used, β -Lactam agents, including amoxicillin-clavulanate 1 g PO bid, cefdinir 300 mg PO bid or 600 mg PO daily (qd), cefixime 400 mg PO qd, and cefpodoxime-proxetil 200 mg PO bid, for 3-7days [7]. (IDSA: B-I) (LSIDCM: 2A)

Acute pyelonephritis (Table III)

For acute pyelonephritis, treatment should be case specific, based on the antimicrobial susceptibility profile in a timely manner, with an agent that has *in vitro* activity against the causing pathogen, and used for a specific duration to prevent complications.

The antibiotic management of all premenopausal non-pregnant women with acute pyelonephritis should be similar to complicated UTI management even in the absence of urinary obstruction, foreign body, stone, or abscess formation. This is due to the above mentioned epidemiology of 3GCR organisms in Lebanon and the fact that these organisms are prevalent in community

acquired infections, even in patients without classical risk factors.

We recommend:

1. Urine analysis and culture with susceptibility testing. (IDSA: A-III) (LSIDCM: 2A)
2. Empiric treatment should be started immediately pending results of culture and susceptibility testing.
3. The choice of antibiotic therapy depends on whether the patient is hemodynamically stable or not:
 - A. In hemodynamically stable patients with no evidence of sepsis, 3GC (Ceftriaxone 2 g IV/IM, Cefotaxime 2 g q 8 hrs) \pm aminoglycoside is recommended (LSIDCM: 2B) or Aztreonam (1-2 g q 8 hrs) \pm aminoglycoside in case of cephalosporin allergy (LSIDCM: 3A), or Ertapenem 1 g qd IM/IV. (European Society of Urology Guidelines 2015: 1b, Gr B) (LSIDCM: 2B).

These regimens are to be deescalated to 3GC (IDSA: A-I) (LSIDCM: 1) alone/Aztreonam or quinolone (IDSA: A-I) (LSIDCM: 1) in case of evidence of absence of 3GCR, or quinolone resistance and in case of *Enterobacteriaceae* with 3GCR, to continue with Ertapenem IM/IV.

- B. In hemodynamically unstable patients, an anti-pseudomonal carbapenem (European Society of Urology Guidelines 2015: 1b, Gr B) (LSIDCM: 2B) is to be used (Imipenem 500 mg q 6 hrs or 1 g q 8 hrs or Meropenem 1 g q 8 hrs), pending culture results, that will be deescalated after culture results to 3GC in case of absence of 3GCR, or a quinolone in the absence of 3GCR and quinolone resistance, or to Ertapenem in case of absence of evidence of pseudomonas infection, and evidence of 3GCR *Enterobacteriaceae* infection. (LSIDCM: 3A)

Switching to an oral antibiotic therapy is recommended when possible [20,21]. The choice of oral antibiotics depends on the sensitivity result of the isolated organism. These antibiotics include (LSIDCM: 3A):

- _ Amoxicillin 1 g bid (in case of culture positive for

TABLE III
RECOMMENDED ANTIMICROBIAL REGIMENS FOR THE TREATMENT OF ACUTE UNCOMPLICATED BACTERIAL PYELONEPHRITIS IN ADULT PREMENOPAUSAL NON-PREGNANT WOMEN

Antibiotic	Dose	Frequency	Route	Duration
Ceftriaxone	2 g	QD	IV/IM	10-14 days*
Aztreonam*	1-2 g	Q8h	IV	10-14 days*
Amoxicillin-clavulanate	1.2 g	Q8h	IV	10-14 days*
Ertapenem	1 g	QD	IV/IM	10-14 days*
Ciprofloxacin	500 mg	BID	IV/PO	7 days**
Prulifloxacin	600 mg	QD	PO	7 days
Ofloxacin	200-400 mg	BID	PO	7 days
Levofloxacin	500-750 mg	QD	PO/IV	7 days

QD: daily BID: twice a day IV: intravenous IM: intramuscular PO: per os

*IV therapy is continued till the patient is stable and can take oral medication (for a total course of 10-14 days)

**Alternative in case of allergy to β -lactams

- sensitive enterococci or group B streptococci).
- Amoxicillin-clavulanate 1 g bid.
- Trimethoprim/sulfamethoxazole, 1 double-strength tablet bid.
- Ofloxacin 400 mg bid, ciprofloxacin 500 mg bid, prulifloxacin 600 mg qd, levofloxacin 500-750 mg qd.
- Cefixime 400 mg qd or cefdinir 300 mg bid or 600 mg qd.

The treatment duration is 10 to 14 days (IDSA: A-I) (LSIDCM: 1), except for fluoroquinolone therapy where a duration of 7 days would be sufficient (21 days in case of abscess formation). (IDSA: A-I) (LSIDCM: 1)

If the complicating factor(s) were not properly addressed, therapy will be compromised; hence, every effort should be made to correct any underlying urinary tract abnormality and treat host factors that exacerbate the infection [20,22].

Recurrent uncomplicated UTI (RUTI) in women

Definition

RUTI is defined as 3 or more episodes of UTI with at least 3 positive urine cultures in the last 12 months or 2 or more episodes in the last 6 months. Diagnosis is usually made with history and the positive urine cultures. Twenty-five to 30% of women with RUTI experience irritating voiding symptoms which are usually caused by urethral syndrome, interstitial cystitis, or the infection itself [23].

Diagnosis

Work-up for RUTI involves documentation of complete eradication with a urine culture after completion of the antibiotic course and imaging if infection recurs or persists.

A kidney and bladder ultrasound, with pre- and post-void bladder volumes, is needed to rule out a stone or an anatomical abnormality such as hydronephrosis and/or hydroureter. Further evaluation by an intravenous urogram (IVU) or a uroscan may be needed to look for a ureteric stone or congenital anomaly like pelvi-ureteric junction obstruction or ureteric strictures. Sometimes, a hydroureter can be caused by extramural obstruction from adjacent organs like ovarian or uterine pathologies and can present as recurrent infections.

However, absence of obstruction and presence of hydroureter on IVU raises suspicion of vesicoureteral reflux which can be confirmed by a micturating cystourethrogram. In addition, a bladder ultrasound showing a large post-voiding residue can be the cause of RUTIs. This can result in damage to the kidneys if left untreated. Furthermore, uroflowmetry can help ruling out bladder outflow obstruction from urethral stenosis if the post-void residue is more than 100 ml [24].

On the other hand, if there are no signs of obstruction, assessment of the contractility of the detrusor muscles is the recommended next step. If a hypotonic bladder is diagnosed, occasionally seen in poorly controlled diabetic patients, this would require clean intermittent self-

catheterization [23]. A cystoscopy may be performed, in certain cases when other risk factors are not identified, to rule out mucosal lesions or foreign bodies in the bladder. If no risk factors are identified and the UTIs recur, a prophylactic antibiotic, TMP-SMX or nitrofurantoin, is recommended.

In the absence of risk factors with RUTIs, proximity of symptoms to sexual intercourse should be investigated. If this is the case, post-coital antibiotic prophylaxis might be given. Otherwise, when there is no relationship to sexual intercourse, a history of spermicide use, young age when the first UTI occurred, and history of UTI in the mother suggest that genetic and long-term environmental factors might predispose patients to UTIs.

In postmenopausal women, possible utero-vaginal prolapse, urinary incontinence, and post-void residual urine should be ruled out. Other risk factors for RUTIs include: presence of an indwelling catheter, ureteric stent, nephrostomy tube, diabetes mellitus, pregnancy, renal failure, renal transplantation, and immunosuppression [23,25].

Management

Management starts with treating the underlying risk factor if there is one. Prophylactic treatment (European Society of Urology Guidelines 2015: Le 4, Gr A) (LSIDCM: 2A) with trimethoprim/sulfamethoxazole, nitrofurantoin, cephalosporins or fluoroquinolones for 6 to 12 months has proven effective in reducing the number of UTIs, with no significant preference of one antibiotic over the other. However, in view of the escalating resistance to quinolones, we prefer to avoid their use for prophylaxis. If the RUTI is associated with sexual intercourse, post-coital prophylaxis has proven to have similar efficacy to daily prophylaxis. A single post-intercourse dose of cephalexin (250 mg), trimethoprim/sulfamethoxazole (1 tablet), or nitrofurantoin (50 mg) are recommended options [20]. This prophylactic strategy is used for 6 months (LSIDCM: 3A) but if the infection recurs, it can be used for several years [19,26]. (Figure-1)

Other strategies have been used in the management of RUTIs. An oral vaccine with lyophilized *E. coli* (one tablet per day for 3-6 months) has shown to be effective (European Society of Urology Guidelines 2015: 1a, Gr B) (LSIDCM: 2A); moreover, cranberry products have been advocated in order to prevent bacteria from adhering to the bladder wall [9]. (European Society of Urology Guidelines 2015: 1b, Gr C) (LSIDCM: 3A)

When commercially available, it is reasonable to consider the use of intravaginal probiotics that contain *L. rhamnosus* GR-1 and *L. reuteri* RC-14 for the prevention of recurrent UTI [9]. These products can be used once or twice weekly. (European Society of Urology Guidelines 2015: Le 4, Gr C) (LSIDCM: 3B)

In addition, behavioral changes have been found useful as adjuvant measures. They include, but are not limited to, sufficient fluid intake (at least two liters per day), regular voiding and micturition to help wash out bacteria

Symptoms and signs of recurrent urinary tract infections (no fever, no flank pain)

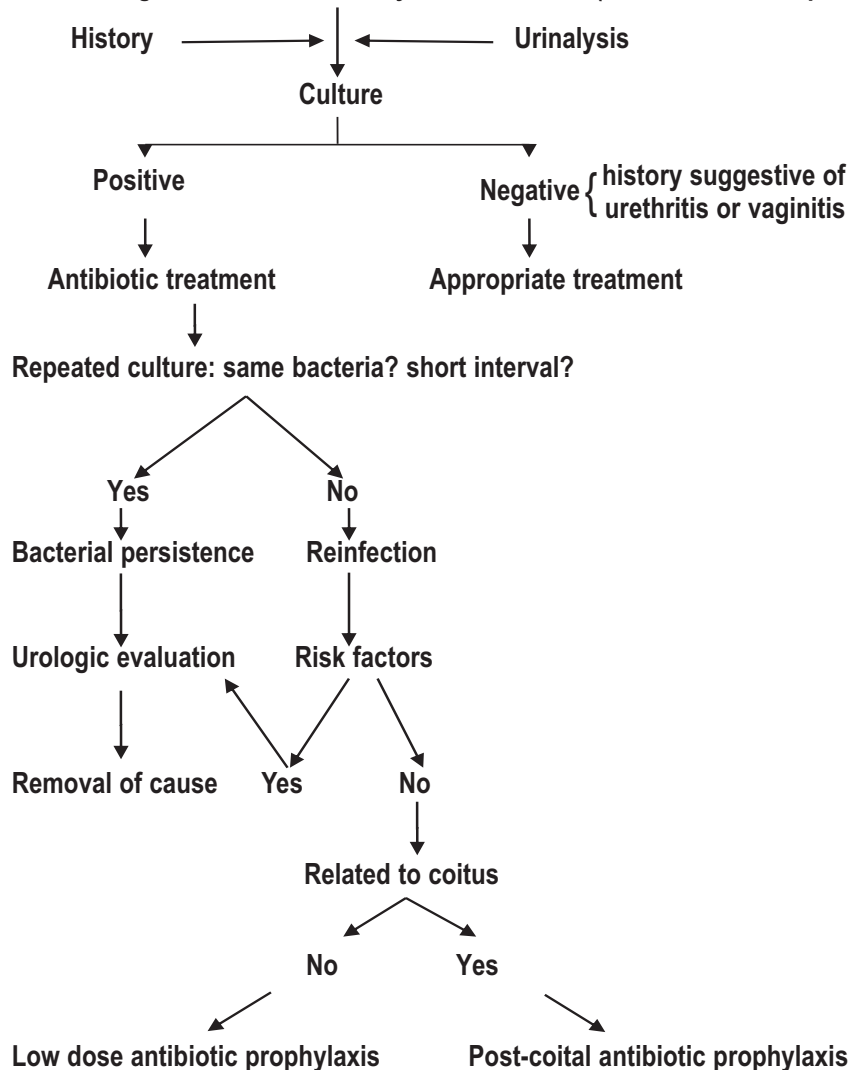


FIGURE 1. Management of recurrent urinary tract infections

especially after sexual intercourse, and avoidance of special genital hygiene, spermicides, and diaphragms use [23]. (LSIDCM: 3B)

In postmenopausal women, vaginal creams containing estrogens normalize the vaginal flora and have been shown to reduce the frequency of UTIs. However, no data is available to recommend a specific type or duration [9]. (LSIDCM: 3B)

Asymptomatic bacteriuria (ASB)

Definition

According to the IDSA 2005 guidelines, the quantitative definition of ASB is the following:

For women, it is the isolation of the same bacterial species with a quantitative count of $\geq 10^5$ CFU/mL in two consecutive voided urine specimens, or isolation of one bacterial species with a quantitative count of $\geq 10^2$

CFU/mL in a single catheterized urine specimen.

For men, it is defined as the isolation of one bacterial species with a quantitative count of $\geq 10^5$ CFU/mL in one voided urine specimen, or isolation of one bacterial species isolated with a quantitative count of $\geq 10^2$ CFU/mL in a single catheterized urine specimen [8].

Treatment

Because of increasing antimicrobial resistance, it is important not to treat patients with ASB unless there is evidence of potential benefit. Pregnant women should be screened for ASB in the first trimester and treated, if present (IDSA: A-I) (LSIDCM: 1). Treatment for ASB is also recommended in men undergoing transurethral resection of the prostate (IDSA: A-I) (LSIDCM: 1) or other urologic procedures with anticipated risk for mucosal bleeding, (IDSA: A-I) (LSIDCM: 1) and in patients prior to implantation of prosthetic valves or joints. (LSIDCM: 3A)

On the other hand, treating ASB in patients with diabetes, elderly women (> 65 years old), patients with or without indwelling catheters, or patients with spinal cord injuries has not been found to reduce the risk of symptomatic episodes [27-30].

Treating ASB in elderly men (> 65 years) does not reduce mortality nor does it significantly reduce symptomatic episodes [31, 32]; on the contrary, it significantly increases the risk of adverse events, such as rashes, *Clostridium difficile* colitis and other gastrointestinal symptoms.

Acute bacterial prostatitis

Definition

Bacterial prostatitis is a clinical disease diagnosed by evidence of inflammation and infection of the prostate.

Bacterial prostatitis accounts for 5-10% of all cases of prostatitis. It can be either acute or chronic according to the duration of symptoms, where symptoms of a chronic infection persist for at least 3 months. An acute infection can be a serious one usually requiring parenteral administration of high doses of a bactericidal antibiotic which may include broad-spectrum penicillin, a 3GC, a carbapenem or a fluoroquinolone according to the local epidemiology. All of these agents can be combined with an aminoglycoside for initial empiric therapy. Since *E. coli*, *K. pneumoniae*, and *K. oxytoca*, which are the most common pathogens causing community-acquired prostatitis, can be resistant to many antibiotics, proper empiric treatment should be guided by the local epidemiology. Moreover, continuous antimicrobial susceptibility surveillance is advisable to track emerging resistance in *Enterobacteriaceae* [9].

Symptoms

Pain at various locations and lower urinary tract symptoms are the predominant symptoms. Acute prostatitis usually presents with fever, general symptoms, and an intense local pain [9].

Clinical findings

In acute prostatitis, prostatic massage is contraindicated but digital rectal examination (DRE) can be done which may show a swollen and tender prostate; otherwise, the prostate is usually normal on palpation. It is important to rule out a prostatic abscess, other urogenital organ disease, and anorectal disorders. Clinical examination should also include evaluation of the pelvic floor musculature [9].

Urine cultures and prostatic secretions

In patients with prostatitis, it is important to evaluate the quantitative bacteriological localization cultures and the microscopy of the segmented urine and of the expressed prostatic secretion (EPS) [33].

Enterobacteriaceae, especially *E. coli*, are the predominant pathogens in bacterial prostatitis. There is uncertainty in the significance of intracellular bacteria, such as *Chlamydia trachomatis*. In immunocompromised patients with HIV infection or other immune deficiencies, pros-

tititis may be caused by fastidious pathogens, such as *Mycobacterium tuberculosis*, *Candida sp.* and rare pathogens, such as *Coccidioides immitis*, *Blastomyces dermatitidis* and *Histoplasma capsulatum* [9].

Treatment

Treatment of acute bacterial prostatitis with antibiotics is life-saving; however, in chronic bacterial prostatitis, treatment is recommended according to results of susceptibility pattern. Initial therapy in acute bacterial prostatitis consists of parenteral high doses of bactericidal antibiotics, such as broad-spectrum penicillin, a 3GC, or a fluoroquinolone, combined with aminoglycoside in case of sepsis or suspicion of ESBL producing Gram negative bacilli. This parenteral regimen is then substituted with oral therapy, after improvement in fever and infection parameters, for a total of 2-4 weeks depending on the antibiogram of the isolated organism and the clinical response [9].

This long duration of treatment is based on the fact that antibiotic penetration into the prostate is limited for drugs other than quinolones and trimethoprim/sulfamethoxazole and on the fear of progression of the symptoms to chronic ones.

Recommended empiric treatment regimens after cultures are taken are as follows:

Septic patients

- Carbapenem (imipenem [500 mg IV q6h or 1 g q8h] or meropenem [1 g IV q8h]) ± amikacin (15 mg/kg/day divided q 12-24 h with a maximum dose of 1 g IV qd). (LSIDCM: 2A)

Patients requiring IV antibiotics but are not septic

- Piperacillin/tazobactam (4.5g IV q8h) ± amikacin (15 mg/kg/day divided q 12-24h with a maximum dose of 1 g IV qd). (LSIDCM: 3B)
- 3GC: ceftriaxone (2 g IV qd) or cefotaxime (2 g IV q8h) ± amikacin (15 mg/kg/day divided q12-24h with a maximum dose of 1 g IV qd). (LSIDCM: 3B)
- Ciprofloxacin (400 mg IV bid) ± amikacin (15 mg/kg/day divided q12-24 h with a maximum dose of 1 g IV qd). (LSIDCM: 3B)
- Aztreonam (2 g IV q8h) (in case of penicillin resistance or intolerance) ± amikacin (15 mg/kg/day divided q12-24 h with a maximum dose of 1 g IV qd).

PO antibiotics according to antibiogram results, if the patient can tolerate oral therapy:

- Trimethoprim/sulfamethoxazole (160 mg/800 mg bid). (LSIDCM: 2A)
- Ofloxacin (400 mg bid), ciprofloxacin (500 mg bid), or levofloxacin (500 mg qd) or plurifloxacin (600 mg qd). (LSIDCM: 2A)
- Cefixime (400 mg bid). (LSIDCM: 3B)

If the isolated organism is ESBL producing and susceptible to piperacillin/tazobactam, it can be used instead of carbapenems, especially for prolonged therapy in order to avoid induction of carbapenem resistance in view of the rising incidence of carbapenem resistant *Enterobacteriaceae* (CRE) [34]. (LSIDCM: 3B)

Chronic bacterial prostatitis

Definition

Chronic bacterial prostatitis is a chronic or recurrent infection of the prostate of at least 3 months duration. It is the most frequent cause of RUTIs in males. Mostly, 50% of men will have at least one episode of prostatitis during their lifetime. Prostatitis (all types) is the most common genito-urinary disease in men between the ages of 18-50 and is the third most common urological diagnosis made in men over the age of 50 years. About 6% of autopsies in males reveal histological prostatitis [35,36]. Usually, culture of prostatic secretions or urine after prostatic massage reveals pathogens, but urine collected before prostatic massage yields no pathogens.

Causative pathogens

Pathogens are similar to those causing acute bacterial prostatitis:

- Most commonly, Gram-negative organisms, in particular *E. coli*.
- Gram-positive organisms, especially *Staphylococcus aureus* and *Enterococcus faecalis*.

The role of other Gram-positive organisms, such as coagulase-negative staphylococci, non-group D streptococci, and diphtheroids is unclear.

Signs and symptoms

Symptoms are present for more than 3 months. The most prominent symptom is pain, most commonly perineal, lower abdominal, penile (especially pain at the tip of the penis), testicular, rectal, and lower back. Ejaculatory discomfort or pain can occur. Urinary symptoms may include dysuria, frequency, hesitancy, urgency, hematuria, and poor stream. Other symptoms include fatigue, arthralgia and myalgia, and on digital rectal exam, the prostate is usually normal or diffusely tender.

Investigations

Urine culture is often negative in chronic prostatitis, but it is worth doing it to exclude UTI as a cause of symptoms. Urethral swabs or first pass urine nucleic acid amplification tests (NAATs) are done to exclude chlamydia and gonorrhea if there is a history of high risk sexual exposure.

Differentiating between chronic bacterial prostatitis and chronic nonbacterial prostatitis depends on testing urine and prostatic secretions for the presence of bacteria and leukocytes. In contrast to chronic bacterial prostatitis, no pathogens are found in prostatic secretions in chronic nonbacterial prostatitis. Leukocytes on the other hand can be either absent (noninflammatory) or present (inflammatory) in chronic nonbacterial prostatitis.

Measurement of serum prostate-specific antigen (PSA) is not indicated as a routine investigation, unless prostate cancer is suspected. Although the PSA level may be raised in prostatitis, it is not specific for prostatitis [35-37]. The different types of chronic prostatitis cannot be differentiated on the basis of signs and symptoms alone. Investigation of prostatic fluid and urine following prostatic massage is required.

Treatment of chronic bacterial prostatitis

Paracetamol and NSAIDs are reasonable for pain relief, although there is no clinical trial data to guide the choice of analgesics.

As for the antibiotics, the choice is usually guided by the results of culture and sensitivity of prostatic secretions, with fluoroquinolones being the most supported by literature. (LSIDCM: 2B). Trimethoprim/sulfamethoxazole is a good alternative if the organism is susceptible and if it is tolerated by the patient. Patients with chronic bacterial prostatitis are treated for at least 6 weeks. Despite negative cultures, most specialists initially try antibiotics to treat possible occult infection [36]; there is no evidence to support this, but a small number of patients seem to gain benefit. However, with increasing antimicrobial resistance, prudent use of antibiotics is highly advisable.

Alpha-blockers are not routinely recommended, but there is weak evidence that α -blockers, added to antibiotic treatment, might improve outcomes. Furthermore, prostatectomy is recommended by some specialists if prostatic calculi are thought to be the cause of recurrent infections. However, since prostatic calculi are common and the effectiveness of surgery has not been adequately investigated, this cannot be recommended outside a clinical trial.

Stress management and referral for psychological assessment might be considered in individuals who are suspected to have a strong psychological component to their symptoms, however, there is no conclusive evidence on the effectiveness of psychological interventions. Furthermore, anxiolytics are not recommended because of the risk of dependence.

Physiotherapy and relaxation techniques may be useful, which suggests that muscle tension may be contributing to the pain in the pelvic floor. Observational data suggests that applying pressure to trigger points in the pelvic floor, in conjunction with relaxation techniques, may be beneficial. However, no randomized controlled trials are done to evaluate the efficacy of these techniques, and treatment may be difficult to access in both primary and secondary care [38].

Other treatments that have been investigated include thermotherapy (transurethral microwave hyperthermia or transurethral microwave thermotherapy), bioflavonoids (quercetin), allopurinol, finasteride, and anti-inflammatory preparations. The evidence supporting these interventions is weak and more clinical trials are needed to confirm their role in treatment [39,40].

Chronic nonbacterial prostatitis/ Chronic pelvic pain syndrome

This entity is not well established. It is recommended for such patients to be followed by a urologist; however, for patients who are sexually active, cyclin or macrolide-based therapy should be considered at appropriate doses for 6 weeks.

An algorithm for the management of patients presenting with prostatitis is suggested in Figure 2.

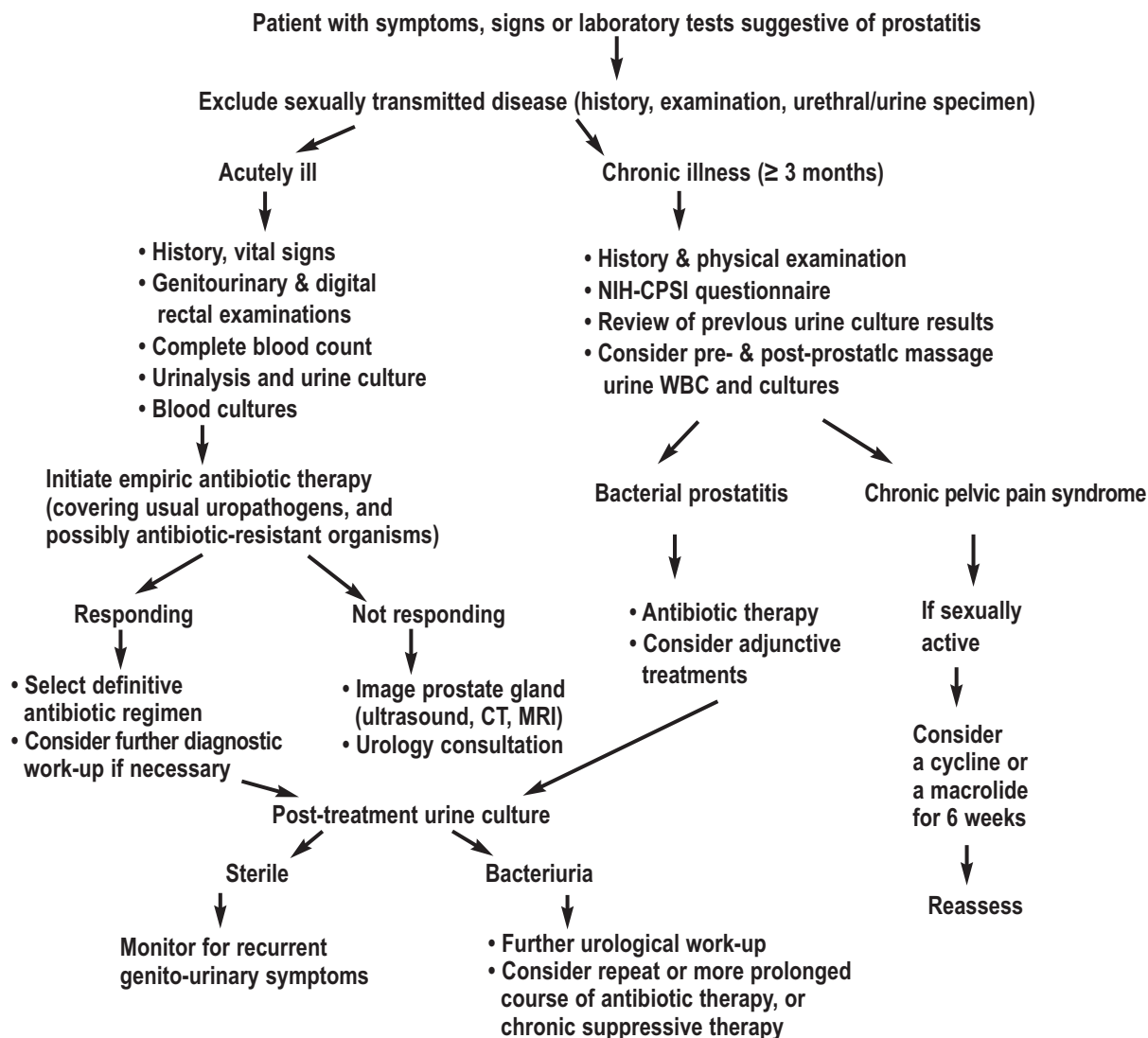


FIGURE 2. Management of prostatitis

Catheter-associated urinary tract infections (CAUTI)

Definition

Bacteriuria can be acquired daily in patients with indwelling catheters (3-10% per day). Hence, patients with a long-term indwelling catheter are all bacteriuric, often with multiple organisms. Moreover, the risk of infection has a strong correlation with the duration of catheterization and for this reason, patients with intermittent catheters have lower incidence of asymptomatic bacteriuria. The higher mortality rate in patients with long-term indwelling catheters, however, has no causative link with urinary tract infections or catheterization [41].

In catheterized patients, UTIs commonly present with fever without any other localizing signs. In addition, UTI is a very common hospital acquired infection (HAI), accounting for 23% of all HAIs and the majority of these are associated with catheters. CAUTI is the source for 8% of hospital-acquired bacteremias [41,42].

Diagnosis

No particular constellation of symptoms or clinical signs (fever or chills, new flank or suprapubic tenderness, change in character of urine, or worsening of mental or functional status) appear to increase the likelihood of a symptomatic UTI in catheterized patients.

The positive predictive value (PPV) of bacteriuria for febrile UTI identified by clinical criteria has been shown to be 11% [43]. The most common symptom, fever, is a nonspecific presenting symptom but its absence does not appear to exclude UTI.

Furthermore, clinical symptoms or signs are not recommended for predicting the likelihood of symptomatic UTI in catheterized patients [44].

Management

After excluding other foci of infection, an appropriately taken urine sample should be cultured when suspecting CAUTI. In a catheterized patient, clinical sepsis

is a stronger indication to request a urine culture compared to urine appearance or smell.

When starting antibiotic therapy, we should take into consideration the risk factors, comorbidities, and severity of symptoms. Furthermore, changing the urinary catheter is recommended.

Antibiotic prophylaxis is not recommended for the prevention of symptomatic UTI in catheterized patients (IDSA: A-II) (LSIDCM: 2A). It may be considered in patients with recurrent or severe infections that permanently affect their daily functions; this may reduce the occurrence of asymptomatic bacteriuria but at the expense of increasing antibiotic resistance [42].

Symptomatic bacteriuria in patients with catheters

Symptoms that may suggest UTI in patients with catheters include fever, flank or suprapubic discomfort, change in voiding patterns, nausea, vomiting, malaise, or confusion. However, the development of abnormalities such as calculi and complications in the kidneys in patients with long term indwelling catheters may present as febrile episodes only [45]. Antibiotic treatment should be given for 7 days once CAUTI is suspected and in patients who have a prompt resolution of symptoms (IDSA: A-III) (LSIDCM: 2B) and for 14 days for those who have a delayed response (IDSA: A-II) (LSIDCM: 2A). Moreover, in the presence of systemic symptoms, such as fever, chills, vomiting, or confusion, catheterized patients should be admitted to the hospital.

Changing the catheter in patients with long-term indwelling catheters having symptomatic UTI will help decrease the duration of fever (IDSA: A-I) (LSIDCM: 1), improve or resolve symptoms after 3 days of antibiotics, and decrease the likelihood of recurrence within one month [45,46]. However, urine should be taken for culture before the catheter is changed and treatment is started. In case of resistant organisms, treatment should be changed according to the susceptibility profile of the isolated organism.

Asymptomatic bacteriuria in patients with catheters

Screening women with asymptomatic bacteriuria after short-term catheterization is not recommended (LSIDCM: 3A). There is inconsistent evidence on the benefit from repeated treatment of asymptomatic bacteriuria, but there is evidence that it increases the risk of colonization by drug resistant bacteria. So, catheterized patients with asymptomatic bacteriuria, whether men or women, should not receive antibiotic treatment [8, 47]. (IDSA: A-III) (LSIDCM: 2B)

CONCLUSION

The LSIDCM members propose these guidelines to help the Lebanese clinicians in the treatment of various UTIs in an era of increasing bacterial resistance.

It is our duty to assume our role in guiding the proper use of antibiotics in various infections including UTIs which are among the most common infections in clinical practice.

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