UAA-AAUS Guidelines for

Urinary Tract Infections and Sexually Transmitted Diseases

(2016, 1st Edition)

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(2016, 1st Edition)

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Foreword

From AAUS

The Asian Association of UTI and STI (AAUS) was founded in 2003 and has been expanding their activities. The aim of AAUS is to clarify etiology and pathology, treatment and prevention of urinary tract infections (UTIs) and sexually transmitted infections (STIs); develop research of causative organisms and surveillance of drug susceptibility and attempt to publish these.

The Urological Association of Asia (UAA) has planned to develop the Asian guidelines for all urological fields and the first guidelines for lower urinary tract symptoms were published in 2013. The field of UTIs and STIs is the second project of UAA guideline development, which is organized by AAUS. The first meeting for this project was held on September 20th 2013 in Macau. And then, the "Guideline Development Group" was set up by AAUS.

In May 2014, The Guideline Development Group successfully had the first forum in Seoul, Korea and kicked off the project of guideline development. The Group met again in the UAA Congress AAUS Symposium in Kish Island, Iran in December 2014. The Group eventually drafted the document of the Guidelines.

The UAA Congress AAUS Symposium 2014 in Kish Island, Iran.

The last consensus forum was held in Seoul on May 3rd 2015. The forum aimed to review the draft of the guidelines. The Group discussed and evaluated the 1st version of guidelines with external peer reviewers. Finally, the 1st Asian guidelines for UTIs and STIs, supported by UAA, were developed in 2015.

The Asian UTI & STI Forum 2015 in Seoul, Korea.

On behalf of UAA and AAUS, we would like to thank the Guideline Development Group, the external reviewers, and Ms. Angie See Beng Guek, Executive Secretary of UAA Central Office. We also would like to thank Prof. Kurt G Naber and Prof. Florian Wagenlehner from EAU for their kind advices.

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Preface

From AAUS

Overall objectives

This guideline provides recommendations based on current evidence for best practice in the management of adults and children with urinary tract infections (UTIs), genital tract infections (GTIs) and sexually transmitted infections(STIs). It includes adult women (including pregnant women) and men of all ages, patients with indwelling catheters, patients with comorbidities such as neurogenic bladder, urinary tract obstructions and diabetes. It also includes children and patients with urogenital tract tuberculosis. The infections of genital tract and sexually transmitted infections including skin diseases are additional subject of the guideline. The guideline does not address prophylaxis to prevent UTI after instrumentation or surgery.

Target users

This guideline will be of interest to urologists, healthcare professionals in primary and secondary care, officers in charge of residential and care homes, antibiotic policy makers, clinical effectiveness leads, carers and patients. Additional information and discussion of this guideline are available on the AAUS website http://www.aaus.info.

Ownership

Urological Association of Asia (UAA)

Asian Association of UTI and STI (AAUS)

Conflict of Interest (COI)

From AAUS

All members of the guideline development group have provided disclosure statements on all relationships that they have and that might be perceived to be a potential source of conflict of interest. This information is kept on file in the Urological Association of Asia (UAA) Central Office database. These guidelines document was developed with the financial support of the UAA. No external sources of funding and support have been involved.

The UAA is a non-profit organization and funding is limited to administrative assistance and travel and meeting expenses. No honorarium or other reimbursements.

Methodology

From AAUS

1. The Guidelines for urinary tract infections (UTIs) and sexually transmitted infections (STIs) have been developed by the Guideline Development Group organized by the Asian Association of UTI and STI (AAUS).

2. The members have meticulously reviewed relevant references, retrieved via the PubMed and MEDLINE databases, published between 2009 through 2015. Furthermore, the International Consultation on Urological Diseases (ICUD) book of "Urogenital Infections" (2010)[1] covering the topic UTIs and STIs have been looked through for systematic literature searches performed until 2008 or 2009.

3. The information identified through the literature review of other resources was supplemented by the author.

4. Level of Evidence & Grade of Recommendation for each management was made according to the following strategy. References used in the guidelines have been assessed according to the level of scientific evidence involved and guideline recommendations have also been evaluated according to the Agency for Health Care Policy and Research.[2]

5. For each subsection, the conclusion(s) drawn from the relevant articles and evidence levels have been judged using a Grade of Guideline Recommendation.

LEVELS OF EVIDENCE

Level	Type of evidence
1a	Evidence obtained from meta-analysis of randomized trials
1b	Evidence obtained from at least one randomized trial
2a	Evidence obtained from one well-designed controlled study without randomisation
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study
3	Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports
4	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities

GRADES OF GUIDELINE RECOMMENDATIONS

Grade	Nature of recommendations

A	Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomized trial
B	Based on well-conducted clinical studies, but without randomized clinical trials
C	Made despite the absence of directly applicable clinical studies of good quality

1. European Association of Urology. Urogenital Infections. Edition 2010. http://www.icud.info/urogenitalinfections.html
2. Clinical Practice Guidelines Development: Methodological Perspectives. Washington DC: US Department of Health and Human Services, Public Health Service; 1992, pp. 115-127

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Acute uncomplicated cystitis

From AAUS

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Executive summary

Epidemiology and pathogenesis

1. Acute uncomplicated cystitis (AUC) frequently occurs in young sexually active as well as postmenopausal, women without relevant structural or functional abnormalities within the urinary tract (LE: 2b).

2. *Escherichia coli* is the predominant pathogen isolated most frequently (approximately 75%) during episodes of AUC, followed by *Staphylococcus saprophyticus* (LE: 2a). Occasionally, other pathogens, such as *Enterococcus faecalis*, *Klebsiella pneumoniae*, and *Proteus mirabilis*,are involved (LE: 2a).

Diagnosis

1. Diagnosis of AUC can be made with a high probability based on a history of urinary irritative symptoms, absence of fever, and physical examination findings in women who have no risk factors for complication with a urinary tract infection(UTI) (LE: 2a, GR: B).

2. A urine dipstick test is useful for diagnosis of AUC. Microscopy of urine sediment is recommended,not only to secure the diagnostic accuracy, but also to distinguish between coccus- and coli-forms(LE: 2a, GR: B).

3. A urine culture is recommended prior to treatment for patients with a high risk for drug resistance (LE: 4, GR: B) in order to avoid an inappropriate choice of antimicrobials.

4. A colony count of ≥ 10^3 colony-forming units (cfu)/mL of uropathogensis required for microbiologic diagnosis in patients presenting with symptoms of AUC (LE: 2, GR: B).

Treatment

1. The standard antimicrobial drugs for treatment of AUC are fosfomycin trometamol (LE: 1a, GR: A), nitrofurantoin macrocrystals (LE: 1a, GR: A), trimethoprim-sulfamethoxazole (TMP/SMX) (LE: 2a, GR: B), and β-lactams, including cephalexin, cefaclor,and amoxicillin/clavulanate (LE: 1a, GR: A).

2. If Gram-positive cocci are present amoxicillin/ clavulanate could be recommended, because the drug is active against *enterococci* and *staphylococci*(LE: 1a, GR: A).

3. Fluoroquinolones should be considered only as alternative choice in young sexually active women with *S. saprophyticus* (LE: 3, GR: B), but not as the first choice for treatment of AUC (LE: 1a, GR: A).

4. Third generation oral cephalosporins, including cefdinir, cefcapene-pivoxil, and cefpodoxime-proxetil, are alternative choices when other recommended agents cannot be used, but should not be prescribed if cocci are present (LE: 1a, GR: A).

5. Amoxicillin or ampicillin should not be prescribed for empirical treatment because of high prevalence of antimicrobial resistance to these agents worldwide (LE: 2a, GR: B).

6. It should be noted that in some Asian countries the resistance of E. coli against TMP/SMX, β-lactams, and fluoroquinolones might be above 20%, a recommended threshold for empiric therapy.

Pregnant women with asymptomatic bacteriuria / AUC

1. Pregnant women with AUC or asymptomatic bacteriuria should be treated with the standard regimen of antimicrobials (LE: 1b, GR: A).

2. Fluoroquinolones, tetracycline, and TMP/SMX should be avoided because of their associated toxicity in newborns (LE: 1b, GR: A).

Introduction

Acute uncomplicated cystitis (AUC) accounts for the greatest number of urinary tract infections (UTIs), particularly among young sexually active[1] and postmenopausal women, and should be treated with an effective antimicrobial agent. Recently,the emergence of antimicrobial resistant bacteria has made empiric antibiotic therapy increasingly more difficult for treatment of AUC and several reports have indicated increased isolation of fluoroquinolone-resistant or ESBL-producing gram-negative bacilli in patients with AUC throughout the world[2][3][4][5]. Therefore, it is important for physicians to be aware of regional resistance ratios before initiating empiric antimicrobial therapy for treatment of AUC.

AUC is a frequently encountered problem in primary care, and its condition is diagnosed and treated by all types of physicians, including urologists and gynecologists, as well as other medical and health care providers. Therefore, appropriate guidelines for diagnosis and treatment of AUC should be provided and constantly renewed based on reviews of epidemiological, pharmacological and clinical investigations.

Definition

Acute cystitis, frequently occurs in adult women, is considered to be uncomplicated if it is sporadic and a community-acquired episode in otherwise healthy individuals if the patient is not pregnant or elderly, there has been no recent instrumentation or antimicrobial treatment, and there are no known structural and functional abnormalities of the genitourinary tracts[6][7](LE: 2b).

Characterization (Etiology/Epidemiology)

AUC is of significant importance in the community due to its high prevalence, particularly among young sexually active and postmenopausal women. A previous cohort study showed that the incidence of AUC accounts for 0.5-0.7 per individuals per year among young women[1], while more than half of all women experience at least one UTI in their lifetime[8].

The microbial etiology of AUC is regarded to be well established and reasonably consistent. *Escherichia coli* is the predominant pathogen isolated most frequently (approximately 75%) in episodes of AUC, followed by *Staphylococcus saprophyticus* (5-15%), mainly in young sexually active women[9][10][11](LE: 2a). Occasionally, other pathogens such as *Enterococcus faecalis*, *Klebsiella pneumoniae*, and *Proteus mirabilis* are involved[3][4][12](LE: 2a). In a recent study conducted in Japan, *E. coli* was detected in 77.8% of 387 AUC cases, followed by *S. saprophyticus* in 5.2% (Fig. 1)[13].

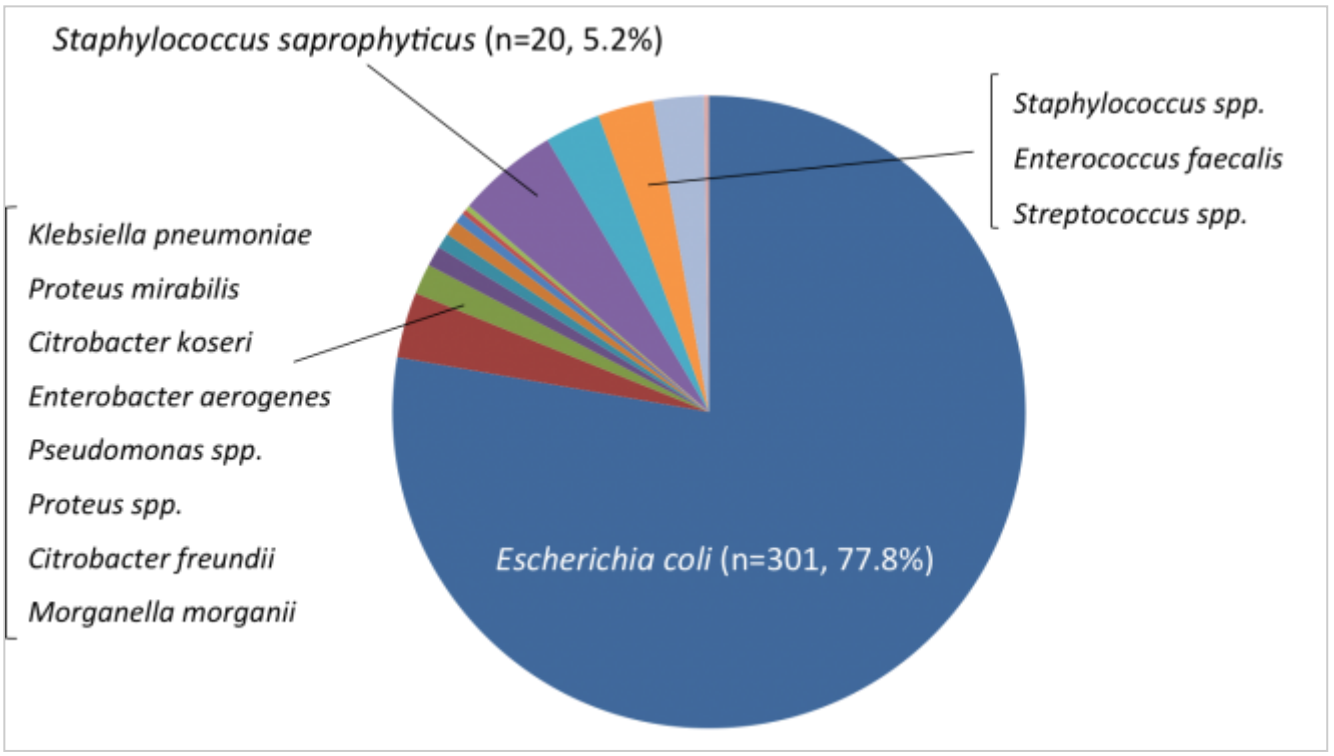

Figure 1. Pathogens isolated from 364 patients with acute uncomplicated cystitis in Japan from 2009 to 2010[13]

The fecal-perineal-urethral hypothesis is widely recognized to explain the cause of increasing UTIs, in which uropathogenic organisms reside in individual rectal flora and serve as a reservoir for UTIs[14][15](LE: 2a).

Risk factors

The most important risk factors for AUC in young women are a history of previous episodes of cystitis and frequent or recent sexual activity[16]. Physiological changes associated with menopause, such as decreased vaginal glycogen and increased pH, are also considered to be risk factors for developing a UTI. Another study reported that insulin-treated diabetes and a lifetime history of UTI are risk factors for AUC among postmenopausal women, whereas AUC was not found to be associated with sexual activity, urinary incontinence, parity, postcoital urination, vaginal dryness, consumption of cranberry juice, vaginal bacterial flora,orpostvoid residual bladder volume[17].

Diagnosis

Symptoms (physical examination)

The signs of AUC are generally urinary irritative symptoms, such as dysuria, frequency, micturition pain, and urgency, and not associated with signs or symptoms of upper UTIs, such as fever, chills, or flank pain[18]. When a woman previously affected by cystitis has symptoms suggesting recurrence, there is an 84% chance that an infection is present[19].

Laboratory tests (radiological investigation, Others)

A diagnosis of AUC can be made with high probability based on a history of urinary symptoms and physical examination findings in women who have no risk factors for complication with a UTI[20](LE: 2a, GR: B).

A urine dipstick test, microscopy of urine sediment, and a counting chamber are reasonable tools to urinalysis for diagnosis of AUC[21][22](LE: 2a, GR: B). Of those, a microscopy of the urine sediment with or without Gram-stainis recommended,not only to securethe diagnostic accuracy, but also to distinguish between coccus- and coli-forms. Flow cytometry may take the place of microscopic examination, because the system discriminating between Gram-positive and negative bacteria is now under development and would be available in the near future.

A urine culture testing is recommended prior to treatment for patients at high risk for drug resistance in order to avoid an inappropriate choice of antimicrobials. Also, that is warranted to identify unusual or resistant organisms in patients whose symptoms either do not abate or recur within 2 to 4 weeks after the completion of treatment[18](LE: 4, GR: B).

A colony count of $\geq 10^3$cfu/mLof uropathogensis considered to represent the compromised threshold for microbiological diagnosis in patients presenting with symptoms of AUC[23](LE: 2b, GR: B).

Treatment (medication/surgery/alternative/prevention)

Overview of treatments for AUC

Antibiotic therapy is recommended for women with AUC because clinical success was found to be significantly more likely as compared to those treated with a placebo[24](LE: 1a, GR: A). Since the resistance patterns of pathogens causing AUC vary considerably between regions and countries, it is difficult to recommend a specific treatment that is universally acceptable for all areas. To appropriately select an antimicrobial agent, it is important for physicianto understand the susceptibility profile of the causative bacteria, particularly the local antimicrobial susceptibility of E. coli, because of resistance to antibiotics in the pathogens of AUC is increasing worldwide[2][3][4][5].

In general, fosfomycin trometamol, nitrofurantoin macrocrystals, trimethoprim-sulfamethoxazole (TMP/SMX), and β-lactams, including cefaclor, cephalexin, and amoxicillin/ clavulanate,are considered to be the drugs offirst choice in Asian countries. In addition, pivmecillinammay be a good candidate for treatment of AUC, though this agent is unavailable in most of Asia. Third generation oral cephalosporins and fluoroquinolones should be considered only as alternatives when other recommended agents cannot be used, but not as the first choice for treatment of AUC. Amoxicillin or ampicillin should not be prescribed for empirical treatment because of high prevalence of antimicrobial resistance to these agents worldwide. In principle, the prescribing physician should always try to distinguish between the coccus- and coli-form of the uropathogen causing AUC based on microscopic findings.

Table 1 shows the recommended antimicrobial agents and duration of treatment for AUC. For reference, Table 2 shows antimicrobials presently available for treatment of AUC in Asian countries.

Table 1. Recommended antimicrobial therapy for acute uncomplicated cystitis in otherwise healthy, premenopausal, and non-pregnant women

Antimicrobials	Daily dose	Duration
First choice[1)]		
Fosfomycin trometamol	3g qd	1 day
Fosfomycin calcium	1g tid	2 days
Nitrofurantoin macrocrystal	100mg bid	5 to 7 days
Trimethoprim-sulphamethoxazole	1600/800mg bid	3 days
Cefaclor	250mg bid	7 days
Cephalexin	250mg qid	7 days
Amoxicillin clavulanate[2)]	500/125mg bid	7 days
Alternatives[2)]		
Cefdinir[3)]	100 mg tid	5 to 7 days
Cefcapene pivoxil[3)]	100 mg tid	5 to 7 days
Cefpodoxime proxetil[3)]	100 mg bid	5 to 7 days
Ciprofloxacin[4)]	500 mg bid	3 days
Levofloxacin[4)]	500 mg qd	3 days

1) According to availability for AUC in each country
2) If the pathogen has been shown to have a coccus form
3) If other recommended antimicrobials cannot be used
4) If the pathogen has been shown *S. saprophyticus*

Table 2. Antimicrobial availability for AUC in selected Asian countries

	China	Japan	Korea	Russia	Singapore	Taiwan
Nitrofurantoin	○			○	○	
Trimethoprim-sulphamethoxazole	○	○	○	○	○	○
Fosfomycin trometamol	○		○	○	○	○
Fosfomycin calcium		○				
Amoxicillin-clavulanate	○	○	○	○	○	○
Cephalexin[1)]	○	○	○		○	○
Cefaclor[2)]	○	○	○		○	○
Cefdinir[3)]	○	○	○			
Cefcapene pivoxil[3)]		○	○			
Cefpodoxime proxetil[3)]		○	○			
Levofloxacin	○	○	○	○	○	○
Ciprofloxacin		○	○	○	○	○

1) 1st generation cephalosporin
2) 2nd generation cephalosporin
3) 3rd generation cephalosporin

Antimicrobilas for treatment of AUC

Fosfomycin trometamol (3 g, single dose)[25](LE: 1a, GR: A) is an appropriate choice for therapy due to minimal resistance and propensity for collateral damage[26](LE: 2b). However, it is less effective than TMP/SMX or fluoroquinolones, and not reliably effective against *S. saprophyticus*[13][27](LE: 3). Fosfomycin trometamol is not available in some countries, though fosfomycin calcium may be available. A previous study reported that a regimen of fosfomycin calcium (1 g three times daily for 2 days) showed excellent microbiological eradication rates as well as clinical efficacy rates at 5-9 days and 4-6 weeks after drug administration in patients with AUC[28](LE: 2a, GR: B).

Nitrofurantoin macrocrystals at 100 mg twice daily for 5 days has efficacy comparable to 3 days of TMP/SMX[29](LE: 1a, GR: A). Although nitrofurantoin is considerably less active than TMP/SMX or fluoroquinolones toward aerobic Gram-negative rods other than *E. coli*, it may assume a more important role if fluoroquinolone-resistance continues to spread or if short-term nitrofurantoin therapy is efficacious[18](LE: 4, GR: B). Nitrofurantoin is the standard, though not available in some countries.

The Infectious Diseases Society of America (IDSA) guidelines recommend TMP/SMX at 160/800 mg twice daily for 3 days as the first choice for empirical treatment when the resistance rate among uropathogens that cause AUC is <20% in the community[30](LE: 1a, GR: A). However, the emergence of TMP/SMX-resistant uropathogens has led to a shift in the prescribing pattern of fluoroquinolones[31](LE: 2a, GR: B). Several studies have shown that TMP/SMX resistance has indeed increased in many countries[32](LE: 2a, GR: B).

Beta-lactams, including cephalexin, cefaclor, and amoxicillin/clavulanate are appropriate choices for therapy when other recommended agents cannot be used[30](LE: 1a, GR: A). Single-dose therapy with β-lactams was found to be significantly less effective than longer duration therapy in terms of the eradication rate[27]. On the other hand, 3-day therapy with β-lactams may show excellent eradication rates, similar to those obtained with 3-day therapy with TMP/SMX or fluoroquinolones, though most studies have shown that β-lactams are inferior to TMP/SMX and fluoroquinolones in terms of the bacterial recurrence rate[30][33](LE: 1a, GR: A). For these reasons, prolonged (7-day) therapy using β-lactams is recommended for empirical therapy[32](LE: 2a, GR: B).

Aminopenicillins in combination with a β-lactamase inhibitor such as amoxicillin/clavulanate is not highly effective as short-term therapy as compared to fluoroquinolones, though may be used in selected cases[34](LE: 1b, GR: A). If Gram-positive cocci are present amoxicillin/clavulanate could be recommended, because the drug is active against *enterococci* and *staphylococci* (LE: 1a, GR: A). Furthermore, aminopenicillins (amoxicillin or ampicillin) are no more useful for empirical treatment, because of the high prevalence ofE. coli resistance against these antimicrobial agents worldwide[3][13][12][32](LE: 2a, GR: B).

Fluoroquinolones are currently accepted as the standard agents for short-term (3 days) therapy[30] [33][35][36][37](LE: 1b, GR: A). Current opinion is that low-dose fluoroquinolones should no longer be used because of the potential for emergence of resistance[32][38](LE: 2a, GR: B).In this regard, 500-mg levofloxacin tablets are recommended as a once-daily administration for treatment of infections[39](LE: 2a, GR: B). Although a high-dose fluoroquinolone regimen may still be effective for treatment of AUC caused by a resistant pathogen and despite fluoroquinolones are presently recommended in several guidelines and reviews for treatment of AUC as the most

popular alternative antimicrobials [30][40][41], it should be noted, that the rates of fluoroquinolone-resistant E. coli are much higher in some Asian than in European countries[42][43][44][45][46]. Thus it is important to consider strategies for better use of fluoroquinolones in Asia. Fluoroquinolones have a propensity for collateral damage and should be reserved for more important infections than AUC, and should be considered only as alternatives but not as the first choice for treatment of AUC[30](LE: 1a, GR: A).

S. saprophyticusis uniquely associated with uncomplicated UTIs in humans. A UTI caused by *S. saprophyticusis* associated with recent sexual intercourse, and occurs more often during the late summer and fall[47]. According to the detection rate of pathogens by menopausal status, AUC caused by *S. saprophyticusis* significantly more common in premenopausal women[13](LE: 3). In addition, *S. saprophyticus* strains were found have a high susceptibility to fluoroquinolones as compared to other β-lactams and FOM[13](LE: 3). Thus, fluoroquinolones are an alternative choice in young sexually active women with *S. saprophyticus* as 2nd most frequent pathogen[13](LE: 3, GR: B).

Third generation oral cephalosporins, including cefdinir, cefcapene-pivoxil, and cefpodoxime-proxetil,given as 5-7-day regimens are alternative choices for therapy when other recommended agents cannot be used[30](LE: 1a, GR: A), but should not be prescribed if cocci are present. It has been reported that cefpodoxime-proxetil may beuseful as short-term therapy in selected cases[48] (LE: 1b, GR: A)

Consideration of antimicrobial resistance

The global increase in antibiotic resistance and regionally different antibiogram results make it difficult to choose the most appropriate antimicrobial agent for empirical treatment of a UTI. In addition, adverse effects including negative ecological effects and selection of resistance must be carefully considered. Recent reports have indicated increased isolation of fluoroquinolone-resistant or ESBL-producing Gram-negative bacilli in patients with AUC in Asian countries[13][49][50](LE: 3). Striking evidence has also been presented in regard to the increase in *E. coli* strains resistant to fluoroquinolones, which may reflect overuse of quinolones[46](LE: 3) and prior exposure to them[51](LE: 3) for treatment of community-acquired UTIs. Production of ESBL byE. coli largely contributes toresistance to third- and fourth-generation cephalosporins. Abuse of several different classes of antibiotics in the same patient may cause the resultant mutants to be resistant to structurally and functionally diverse antimicrobials[52]. It should be noted that in many Asian countries the resistance of *E. coli* against TMP/SMX, β-lactams, and fluoroquinolones might be above 20%, a recommended threshold for empiric therapy[42][43][44][49](LE: 3).

Pregnant women with asymptomatic bacteriuria / AUC (unusual andspecial cases)

Risk/ Epidemiology/ Etiology

Asymptomatic bacteriuria occurs in 2-10% of pregnancies and 30% of women with asymptomatic bacteriuria develop pyelonephritis during pregnancy[53]. Early detection of asymptomatic bacteriuria in pregnant patients is important, as bacteriuria is an established risk factor for serious complications including acute pyelonephritis, preterm delivery, and low birth weight. Antibiotic treatment is effective for reducing the risk of pyelonephritis during pregnancy[53](LE: 1a, GR: A).

Organisms causing bacteriuria are similar in both pregnant and non-pregnant women, with E. coli being the most common pathogen associated with both symptomatic and asymptomatic bacteriuria, representing 70-80% of isolates.

Selection of antimicrobilas for treatment of asymptomatic bacteriuria / AUC during pregnancy

Acute cystitis should be effectively treated and asymptomatic bacteriuria detected during pregnancy should also be eradicated with antimicrobial therapy[53](LE: 1a, GR: A). According to the available susceptibility patterns of uropathogens in AUC, fosfomycin trometamol, nitrofurantoin macrocrystals, and β-lactams including cephalexin and amoxicillin/clavulanate are considered to be the drugs of first choice[54][55](Table 3). The safety of fosfomycin calcium taken during pregnancy has not been established, while fluoroquinolones, tetracycline, and TMP/SMX should be avoided because of their associated toxicity in newborns[55](LE: 1b, GR: A).

Table 3. Recommended antimicrobial therapy for asymptomatic bacteriuria or acute uncomplicated cystitis in pregnant women

Antimicrobials	Daily dose	Duration
First choice[1)]		
Fosfomycin trometamol	3g qd	1 day
Nitrofurantoin macrocrystal	100mg bid	5 to 7 days
Cephalexin	250mg qid	5 to 7 days
Amoxicillin clavulanate	500/125mg bid	7 days
Alternatives[2)]		
Cefdinir	100mg tid	5 to 7 days
Cefcapene pivoxil	100mg tid	5 to 7 days
Cefpodoxime proxetil	100mg bid	5 to 7 days

1) According to availability for AUC in each country
2) If other recommended antibiotics cannot be used

Duration of therapy / AUC during pregnancy

There is no clear consensus in presented reports regarding antimicrobial choice or duration of therapy for uncomplicated UTIs and asymptomatic bacteriuria during pregnancy. A single dose regimen for asymptomatic bacteriuria or AUC in pregnant women was been reported to result in a lower incidence of adverse effects,as well as newborn and maternal adverse outcomes as compared to longer periods of antimicrobial therapy[56][57]. However, a single-dose regimen with nitrofurantoin or β-lactams was found to be less efficient than a 7-day regimen. Therefore, nitrofurantoin or β-lactams should be administeredfor 5 or more days[56]. On the other hand,a comparison of single-dose fosfomycin trometamol with 7-day amoxicillin clavulanate treatment for asymptomatic bacteriuria during pregnancy showed no differences between the two treatments regarding cure and recurrence[58](LE: 1b, GR: A). Pregnant women with asymptomatic bacteriuria should be treated using the standard regimen of antimicrobials until more data

become available testing 7-day compared with three- or five-day regimens[57](LE: 1b, GR: A). Consequently, it is recommended that those patients with AUC or asymptomatic bacteriuria should be treated by a single dose of fosfomycin trometamol, or a 5- to 7-day treatment of nitrofurantoin or β-lactams.

Treatment algorithm

Figure 2 presents an algorithm for clinical management of AUC.

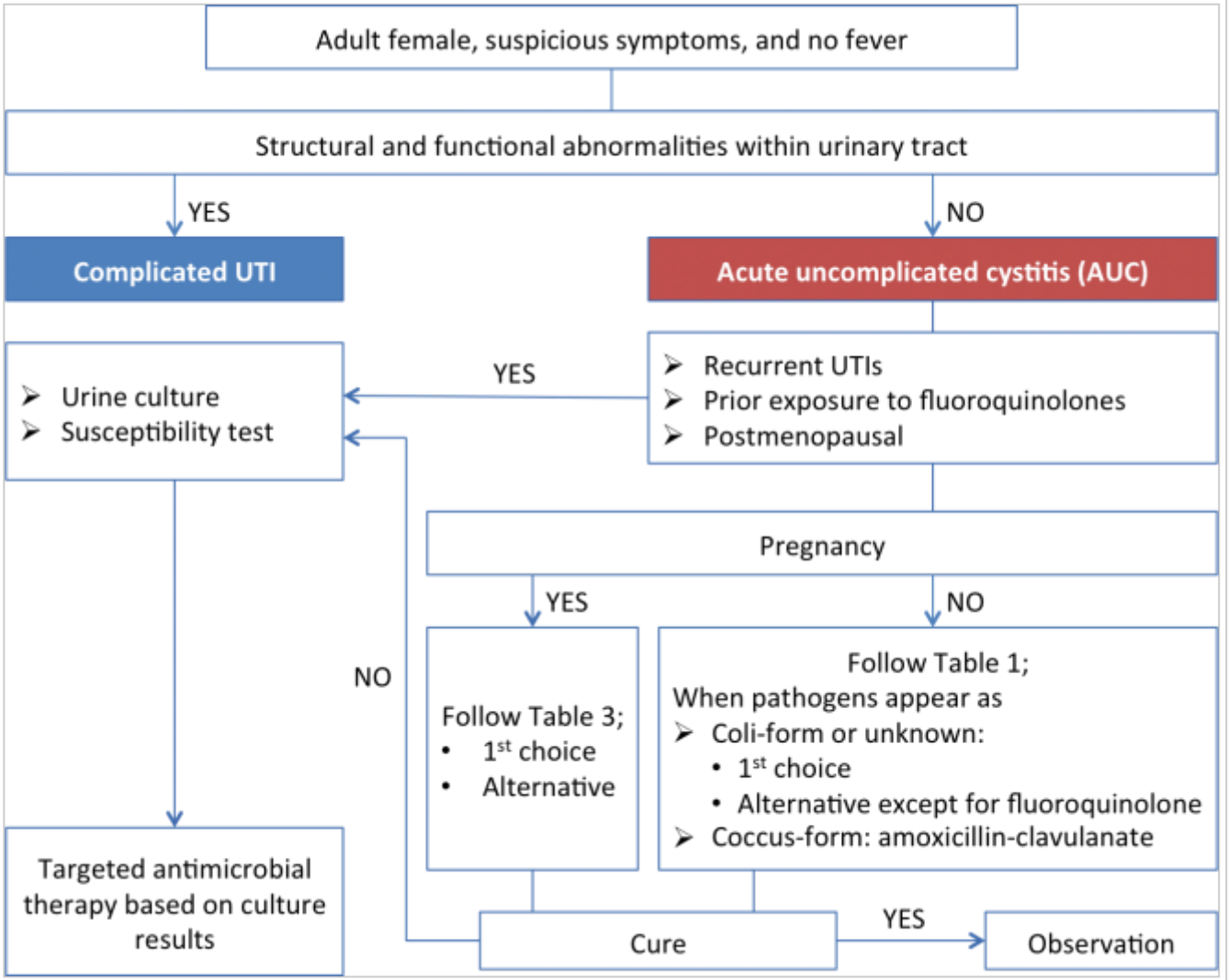

Figure 2. Algorithm for clinical management of acute uncomplicated cystitis

Abbreviations

AUC: acute uncomplicated cystitis, CFU: colony-forming units, EAU: European Association of Urology, ESBL: extended-spectrum β-lactamase, IDSA:Infectious Diseases Society of America, RCT:randomized controlled trial, TMP/SMX: trimethoprim-sulfamethoxazole, UTI: urinary tract infection

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Acute uncomplicated pyelonephritis

From AAUS

Contents

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Executive summary

Epidemiology and pathogenesis

1. Classification and characteristics of the disease: Pyelonephritis is the inflammation of the renal parenchyma and renal pelvis by ascending infection on the urinary tract. Renal tissue destruction spreads to the parenchyma and it is easy to induce sepsis or bloodstream infection (LE:3). It is classified as acute uncomplicated UTI and complicated UTI with the underlying disease.

2. The spectrum and frequency of causative organisms: The spectrum of etiological bacteria is similar in uncomplicated upper and lower UTIs from the infectious mechanism, with Escherichia coli the causative pathogen in about 80% of cases (LE: 2a).

Treatment

1. Principles of antimicrobial therapy: The renal excretion typed antibiotics, such as β- lactams and quinolones are recommended (LE:1a, GR:A).

2. De-escalation: We must determine the effect of empirical therapy to guide the three days after the start of treatment. Then, in accordance with bacterial culture results, it is necessary to switch to definitive therapy (LE:2a, GR:A).

3. Switch therapy: We recommend switching to oral medications from parenteral antimicrobial agents by around 24 hours after symptom remission, such as antipyretic. The total duration of administration is for 14 days (LE:1a, GR:A).

4. Add on therapy: Oral agent is selected for the first line chemotherapy to the outpatients, who are mild or moderate cases of acute uncomplicated pyelonephritis.However, the combination of a single injection of the drug during the first visit is also recommended (LE:1a, GR:A).

5. Severe condition: When we find special conditions such as hydronephrosis, abscess formation and gas production, we must diagnose accurately and quickly and perform urological procedure to hold the renal function (LE:2a, GR:A).

6. Combination therapy: We recommend combination therapy to more severe cases in pyelonephritis patients with urosepsis, severe sepsis, and septic shock (LE:2a, GR:A).

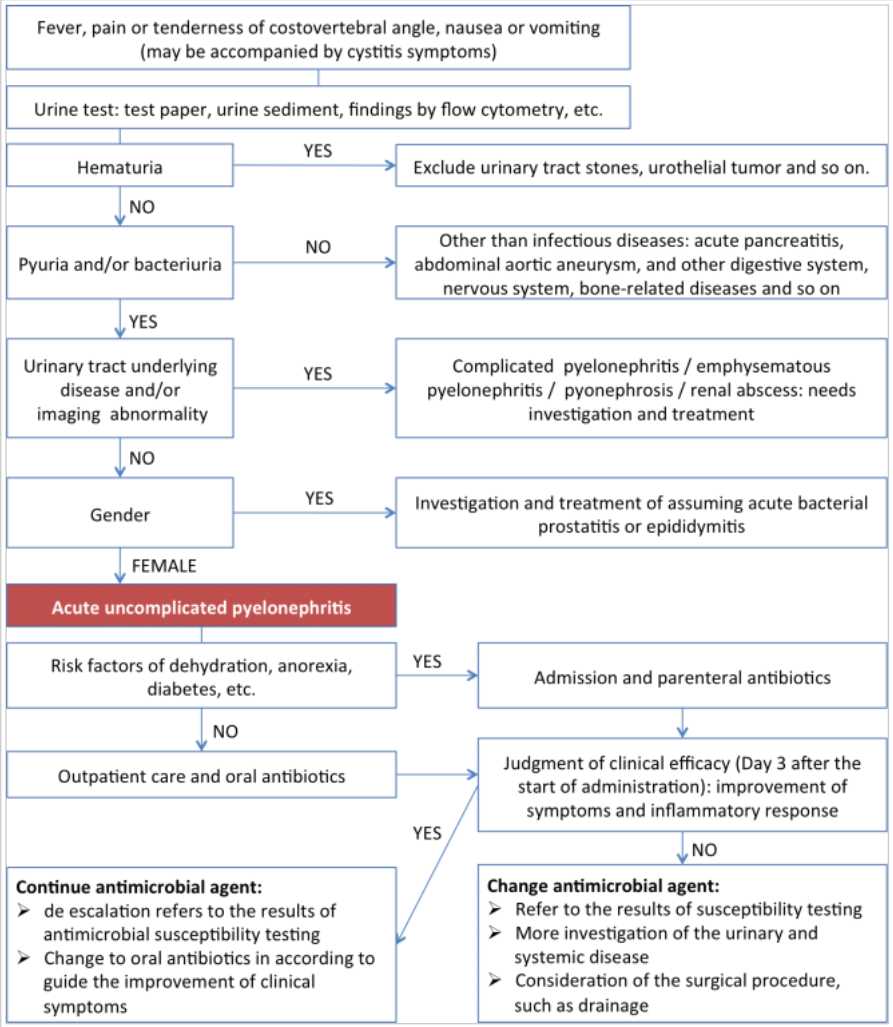

Figure 1. Algorithm of the diagnosis and treatment for acute pyelonephritis

Criteria that can be expected healing by outpati
① Not a shock vital
② Not enough to meet the diagnostic criteria of
③ No gastrointestinal symptoms such as nause
④ No sign of dehydration
⑤ No underlying disease that reduces the immu cancers, diabetes, and AIDS)
⑥ No sign of very serious infections (such as lo confusion)
⑦ Can deal with the pain in the only oral medici

Introduction

Recently the present state of microbial resistance development is alarming[1]. The use of antibiotics in different Asian countries mirrors the global increase in resistant strains[2][3]. Especially the presence of ESBL producing bacteria showing resistance to most antibiotics is steadily increasing in the population[4].

It is essential to consider the local microbial environment and resistance pattern as well as risk factors for harboring resistant microbes in individual patients.There is a direct correlation between the use of antibiotics and resistance development. There is an urgent need for combating resistance development by a prudent use of available antibiotics.

The current guidelines aim to provide both urologists and physicians from other medical specialties with evidence-based guidance regarding the treatment of UTI. High quality clinical research using strict internationally recognized definitions and classifications as presented in this section are encouraged.

Definition of the disease

Overview

Acute uncomplicated pyelonephritis remains one of the most common indications for prescribing of antimicrobials to otherwise healthy community-dwelling women. Despite published guidelines for the optimal selection of an antimicrobial agent and duration of therapy, studies demonstrate a wide variation in prescribing practices[5][6][7][8][9].

The focus of this guideline is treatment of women with acute uncomplicated pyelonephritis, diagnoses limited in these guidelines to premenopausal, non-pregnant women with no known urological abnormalities or comorbidities. It should be noted that women who are postmenopausal or have well-controlled diabetes without urological sequelae may be considered by some experts to have uncomplicated UTI, but a discussion of specific management of these groups is outside the scope of this guideline.

The issues of in vitro resistance prevalence and the potential for collateral damage were considered as important factors in making optimal treatment choices and thus are reflected in the rankings of recommendations.

Epidemiology

Acute uncomplicated pyelonephritis is with a predilection for sexually active women. All male patients are treated as complicated pyelonephritis. The spectrum of etiological agents is similar in uncomplicated upper and lower UTIs, with *Escherichia coli* the causative pathogen in 70-95% of cases[10] and *Staphylococcus saprophyticus*in 5-10%. Occasionally, other *Enterobacteriaceae*, such as *Proteus mirabilis* and *Klebsiella* spp., are

isolated[11](LE: 2a).

As a result of the lack of suitable surveillance studies, the spectrum and susceptibility patterns of uropathogens that cause uncomplicated cystitis can be used as a guide for empirical therapy[12](LE: 4, GR: B). However, *S. saprophyticus* is less frequent in acute pyelonephritis as compared to acute cystitis (LE: 4, GR: B).

Classifications

Traditionally, UTI is classified based on clinical symptoms, laboratory data, and microbiological findings. Practically, UTI has been divided in uncomplicated and complicated case, which is with the underlying diseases. When we decide the policy of therapy, grade of severity of infection is so important. EAU guideline[5] set on a scale of 1-6 that is related to the risk of fatal outcome. Grade 2 indicates mild or moderate case and grade 3 means severe cases. Mild and moderate cases are indicated as the patients not requiring hospitalization and severe cases are indicated as women with pyelonephritis requiring hospitalization[13].

Diagnostic criteria

Clinical symptoms

Acute pyelonephritis is suggested by flank pain, nausea and vomiting, fever (> 38°C) and general malaise, and it can occur in the absence of symptoms of cystitis[14].

Physical examination

Costovertebral angletenderness of the affected side is often appeared.

Laboratory investigation

Urinalysis, including the assessment of white and red blood cells and nitrites, is recommended for routine diagnosis[15](LE: 4, GR: C). Colony counts > 10^4cfu/mL of uropathogens are considered to be indicative of clinically relevant bacteriuria[16](LE: 2b, GR: C).Urine culture test is essential in order to examine the drug susceptibility and the proof of the causative bacteria. In blood examination, inflammatory findings which are leukocytosis, left-shifted nuclear, CRP[17][18][19]and procalcitonin[19] rise, and elevated sedimentation rate can be seen.

Suspecting the presence of bacteremia, it is necessary to blood culture test in situations of sepsis with systemic inflammatory response syndrome[18][20]. There may be accompanied by a state of shock, it should distribute attention to hemodynamics[13].

Radiological investigation

Evaluation of the upper urinary tract with ultrasound should be performed to rule out urinary obstruction or renal stone disease (LE: 4, GR: C).

Additional investigations, such as an non-enhanced helical CT, excretory urography, or DMSA scanning, should be considered if the patients remain febrile after 72 h of treatment (LE: 4, GR: C).

Abdominal CT is also useful in the differential diagnosis of emphysematous pyelonephritis, pyonephrosis, renal abscess, and acute uncomplicated pyelonephritis[21].

Treatment

Medication

In patients suspected of having pyelonephritis, a urineculture and susceptibility test should always be performed, andinitial empirical therapy should be tailored appropriately onthe basis of the infecting uropathogen (LE:3, GR:A).

Mild and moderate cases are indicated as the patients not requiring hospitalization and severe cases are indicated as women with pyelonephritis requiring hospitalization[13].

For the treatment of acute pyelonephritis, the renal excretion typed antibiotics, such as β- lactams[22] or quinolones[23][24] , is recommended (LE;1, GR:A). Safety margin of aminoglycosidesis so narrow that patients on renal dysfunctionmust require attentions (LE:4, GR:B). If necessary, it is recommended TDM.

In the Gram-positive bacteria, susceptibility to the first and second-line drugs is often seemed to be poor. So we need to require attention to the selection of antibiotics in the treatment (LE:3, GR:B).

Mild and moderate cases of acute uncomplicated pyelonephritis

In mild and moderate cases of acute uncomplicated pyelonephritis, oral therapy of 10-14 days is usually sufficient (LE: 1b, GR: B). A fluoroquinolone for 7-10 days can be recommended as first-line therapy if the resistance rate of *E. coli* is still < 10% [25] (LE: 1b, GR: A). If the fluoroquinolone dose is increased, the treatment can probably be reduced to 5 days[26][27](LE: 1b, GR: B). New typed fluroquinolone, such as sitafloxacin and moxifloxacin can be also expected clinical effect against fluoroquinolone-low susceptible strains[28](LE: 4, GR: C). However, increasing numbers of fluoroquinolone-resistant *E. coli* in the community have already been found in some parts of the Asian countries, thus restricting the empirical use of fluoroquinolones[3].

Oral ciprofloxacin (500 mg twice daily) for 7-10 days, with or without an initial 400 mg dose of intravenous ciprofloxacin, is an appropriate choice for therapy in patients not requiring hospitalization where the prevalence of resistance of community uropathogens to fluoroquinolones is not known to exceed 10% (LE: 1, GR: A). If an initial one-time intravenous agent is used, a long acting antimicrobial, such as 1 g of ceftriaxone or a consolidated 24 hours dose of an aminoglycoside, could be used in lieu of an intravenous fluoroquinolone (LE: 3, GR: B). If the prevalence of

fluoroquinolone resistance is thought to exceed 10%, 1g of ceftriaxone or aminoglycoside is recommended an initial one-time intravenous agent (LE:3, GR:B). (i. Data are insufficient to make a recommendation about what fluoroquinolone resistance level requires an alternativeagent in conjunction with or to replace a fluoroquinolonefor treatment of pyelonephritis.)

A third-generation oral cephalosporin, such as cefpodoxime proxetil, ceftibuten, cefditoren pivoxil, or cefcapene pivoxil could be an alternative [29] [30](LE: 1b, GR: B). However, available studies have demonstrated only equivalent clinical, but not microbiological, efficacy compared with ciprofloxacin.

Oral β-lactam agents are less effective than other available agents for treatment of pyelonephritis (LE: 3, GR: B). If an oral β-lactam agent is used, an initial intravenous long-acting antimicrobial agent (LE: 2, GR: B) or a consolidated aminoglycoside, is recommended (LE: 3, GR: B). (i. Data are insufficient to modify the previous guideline recommendation for a duration of therapy of 10–14 days for treatment of pyelonephritis with a β-lactam agent.)

Oral trimethoprim-sulfamethoxazole (160/800 mg [1 double-strength tablet] twice-daily for 14 days) is an appropriate choice for therapy if the uropathogen is known to be susceptible (LE: 1, GR: A). If trimethoprim-sulfamethoxazole is used when the susceptibility is not known, an initial intravenous long-acting antimicrobial agent (LE: 2, GR: B) or a consolidated aminoglycoside, is recommended (LE: 3, GR: B).

In communities with high rates of fluoroquinolone-resistant and ESBL-producing *E. coli* (> 10%), initial empirical therapy with an aminoglycoside[31] or carbapenem has to be considered until susceptibility testing demonstrates that oral drugs can also be used (LE: 4, GR: B).

Table 1. Oral therapy in mild and moderate cases

Antibiotics	Daily dose	Duration	References
Ciprofloxacin[1)]	500mg bid or 1000mg qd	7-10 days	23, 24, 31
Levofloxacin[1)]	500-750mg qd	7-10 days	25, 26, 33
Sitafloxacin	100mg qd	7-10 days	9
Moxifloxacin	400mg qd	5-7 days	8
Alternatives (clinical but not microbiological equivalent efficacy compared with fluoroquinolones)			
Cefpodoxime proxetil	200mg bid	10-14 days	28
Ceftibuten	400mg qd	10 days	26
Ceftitoren pivoxil	200mg tid	14 days	9
Cefcapen pivoxil	100-150 mg tid	14 days	9
Only if the pathogen is known to be susceptible (not for initial empirical therapy)			
Trimethoprim-sulfamethoxazole	160/800mg tid	14 days	15
Co-amoxiclav[2), 3)]	0.5/0.125g tid	14 days	5
Amoxicillin/Clavulanic acid	0.875-2/0.125g bid	14 days	9

1) lower dose studied, but higher dose recommended by experts.
2) not studied as monotherapy for acute uncomplicated pyelonephritis.
3) mainly for Gram-positive pathogens

Severe cases of acute uncomplicated pyelonephritis

Patients with severe pyelonephritis, who cannot take oral medication because of systemic symptoms such as nausea and vomiting, have to be treated initially with one of the following parenteral antibiotics:

Table 2. Initial parenteral therapy in severe cases

Antibiotics	Daily dose	References
Ciprofloxacin	400mg bid	24
Levofloxacin[1)]	500-750mg qd	22, 33
Pazufloxacin	500-1000mg bid	9
Alternatives		
Cefotaxime[2)]	2g tid	9
Ceftriaxone[1), 4)]	1-2g qd	33
Ceftazidime[2)]	1-2g tid	34
Cefepime[1), 4)]	1-2g bid	35
Co-amoxiclav[2), 3)]	1.5g tid	5
Ampicillin/sulbactam		8
Piperacillin/tazobactam	4.5g tid	36
Ticarcillin/clavulanate		8
Ertapenem[4)]	1g qd	33
Imipenem/cilastatin[4)]	0.5/0.5g tid	36
Meropenem[4)]	1g tid	34
Doripenem[4)]	0.5g tid	37
Gentamicin[2)]	5mg/kg qd	30
Amikacin[2)]	15mg/kg qd	9

1) Lower dose studied, but higher dose recommended by experts.
2) Not studied as monotherapy in acute uncomplicated pyelonephritis.
3) Mainly for Gram-positive pathogens.
4) Same protocol for acute uncomplicated pyelonephritis and complicated UTI (stratification not always possible).

Women with pyelonephritis requiring hospitalization should be initially treated with an intravenous antimicrobial regimen, such as a fluoroquinolone; an aminoglycoside[31], with or without ampicillin; an extended-spectrum cephalosporinor extended-spectrum penicillin, with or without anaminoglycoside; or a carbapenem. The choice between these agents should be based on local resistance data, and theregimen should be tailored on the basis of susceptibility results(LE: 3, GR: B).

Hospital admission should be considered if complicating factors cannot be ruled out by available diagnostic procedures and/or the patient has clinical signs and symptoms of sepsis (LE: 4, GR: B).

After improvement, the patient can be switched to an oral regimen using one of the above-mentioned antibacterials, if active against the infecting organism, to complete the 1-2 week course of therapy (LE: 1b, GR: B).

Follow up

Routine post-treatment urinalysis and urine cultures in an asymptomatic patient might not be indicated (LE: 4, GR: C). In women whose pyelonephritis symptoms do not improve within 3 days, or resolve and then recur within 2 weeks, repeated urine culture and antimicrobial susceptibility tests and an appropriate investigation,such as renal ultrasound, CT or renal scintigraphy, should be performed (LE: 4, GR: B).

In patients with no urological abnormality, it should be assumed that the infecting organism is not susceptible to the agent originally used, and an alternative tailored treatment should be considered based on culture results (LE: 4, GR: B). For patients who relapse with the same pathogen, the diagnosis of uncomplicated pyelonephritis should be reconsidered. Appropriate diagnostic steps are necessary to rule out any complicating factors (LE: 4, GR: C).

Abbreviations

ESBL: extended-spectrum β-lactamase, UTI: urinary tract infection, CRP: C-reactive protein, TDM: therapeutic drug monitoring, CT: computed tomography, DMSA: dimercaptosuccinic acid

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Complicated UTIs with the neurogenic bladder

From AAUS

Contents

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Executive summary

Epidemiology and pathogenesis

1. Urinary tract infection (UTI) in patients with neurogenic bladder causes significant morbidity and mortality.

Diagnosis

1. UTI in neurogenic bladder causes atypical symptomatology. Urine tests are pivotal in confirming or excluding UTI, and in guiding appropriate antibiotic treatment.

Treatment

1. Symptomatic UTI warrants appropriate antibiotic treatment with reference to culture results and local antibiotic resistance patterns. Asymptomatic bacteriuria should not be treated, and antibiotic prophylaxis is generally not recommended.

2. Adequate bladder drainage is essential in reducing the occurrence of urinary tract infections.

3. Recurrent UTI in neurogenic bladder may necessitate the treatment of neurogenic detrusor overactivity and the restoration of low bladder pressure during bladder storage and voiding by drugs or surgery.

Introduction

Urinary tract infection in patients with neurogenic bladder causes high morbidity, impaired quality of life, and still significant mortality[1].

Diagnosis

UTI in patients with neurogenic bladder is characterized by clinical symptoms and laboratory findings of leukocyturia, bacteriuria, and positive urine culture[2][3][4].

Signs and symptoms of UTI in neurogenic bladder are different from those in non-neurogenic bladder. They include cloudy urine, foul smelling urine, fever, malaise and lethargy, new or increased urine leakage, increased spasticity, autonomic dysreflexia, loin pain, suprapubic pain, and dysuria [2][5](LE: 2a). One has to beware that catheter-associated UTI can be asymptomatic[6] (LE: 2b).

Urine specimen may be obtained by clean-catch midstream technique, from a newly inserted catheter or bladder puncture[2][4][7]. Microscopic analysis of urine, particularly for bacteria and white cells, is very helpful in evaluating presence of bacteriuria and quantitatively the degree of pyuria. Leukocyturia is deemed significant when there are 10 or more white cells per high-power microscopic field (400x) in centrifuged urine sediment, or 10 or more white cells per uL in unspun urine using counting chamber[3][7](LE: 2b). Pyuria however has low specificity as diagnostic test for UTI. Yet lack of pyuria generally indicates absence of UTI [6][8](LE: 2b).

Quantitative criteria of significant bacteriuria as defined by urine culture are clean-void urine with $>10^4$ cfu/ml, urine from intermittent catheterization with $>10^2$ cfu/ml, and any detectable concentration in suprapubic aspirate or urine specimen from indwelling catheter[3](LE: 4).

The usefulness of urine dipstick test alone to diagnose UTI is still not proven. Yet urine dipstick test is useful to exclude UTI, if results of both nitrites and leukocyte esterase are negative[2][9](LE: 1a).

Treatment

Spectrum of pathogens causing UTI in patients with neurogenic bladder differs from that in patients with normal bladder function and is much broader. Majority of UTIs and bacteriuria are caused by Gram-negative bacilli and enterococci, which are commensal organisms of bowel and perineum, and exogenous bacteria from hospital environment. UTIs are often polymicrobial. Urine culture and sensitivity testing must be performed before initiating antibiotic therapy[8].

Symptomatic UTI warrants antibiotic treatment. Optimal duration of therapy has not been established[8]. It ranges generally from five to maximum fourteen days depending on severity. Seven days of therapy is most commonly used[3][8][10](LE: 3, GR: B). There is no definite superiority of one agent or class of antimicrobials, and regional differences in antibiotic resistance patterns need to be taken into consideration[11](LE: 3, GR: B).

Lack of pyuria reasonably predicts absence of UTI in neurogenic bladder[6][8](LE: 2b, GR: B). Asymptomatic bacteriuria should not be treated[8], even in cases of intermittent catheterization[3], because it has not been shown to be beneficial and it increases the risk of developing antimicrobial resistance[12](LE: 1a, GR: A).

Also, antibiotic prophylaxis is generally not recommended, because its benefit is unproven, and it is associated with development of antimicrobial resistance[8][12](LE: 1a, GR: A).

Prevention of recurrent UTI

Patients with neurogenic bladder dysfunction have increased risk of developing urinary tract infections[13]. Adequate bladder drainage is an important prophylactic measure against recurrent urinary tract infections[14][15](LE: 2b, GR: B).

Initial bladder management during the period of spinal or cerebral shock in acute neurological lesions thus consists of proper bladder drainage. Bladder emptying in acute phase can be achieved by aseptic intermittent catheterization, or by indwelling suprapubic or urethral catheters[16][17][18](LE: 3, GR: B).

In the long-term management of neurogenic bladder dysfunction, the most important issue is the method of bladder emptying. This can be achieved by long-term indwelling catheters or by intermittent catheterization[19]. Chronic indwelling catheters can either be suprapubic catheter cystostomy or urethral catheter. Intermittent catheterization can either be clean intermittent catheterization (CIC) by carer, or clean intermittent self-catheterization (CISC)[20][21].

Suprapubic catheterization may have comparable risk of UTI to intermittent catheterization, but has significant long-term morbidity from suprapubic tube complications[22][23]. Intermittent catheterization has lower UTI rate and less complications than indwelling urethral catheterization; CIC or CISC are the best voiding methods for reducing bacteriuria and urinary tract infections in neurogenic bladders[24][25][26][27][28]. CIC and CISC are generally deemed effective, safe, practical and cost-effective methods of bladder emptying. Clean intermittent catheterization - whenever possible self catheterization - should be used as a standard routine treatment for patients who are unable to empty their bladders (LE: 2b, GR: B). There are suggestions that hydrophilic coated catheters[29][30][31], pre-lubricated catheters[32], or catheters with closed system[33] may have additional advantages, and re-used catheters could be safe[34](LE: 1b, GR: C).

There is no convincing clinical evidence to date that cranberry[35](LE: 1a, GR: A), lactobacillus or other probiotics can prevent UTI, particularly in patients with neurogenic bladder.

Spinal cord lesion causes concomitant neurological bowel dysfunction, resulting in constipation and faecal incontinence. Bowel management aiming at regular emptying of bowel relieves constipation and faecal soiling, and reduces the risk of urinary tract infection[36][37](LE: 2a, GR: B).

Neuro-urological management

Prime objective in preventing recurrent UTI in neurogenic bladder is to treat neurogenic detrusor overactivity and to restore low bladder pressure during bladder storage and voiding[38].

Oral anticholinergic medications are widely used as first-line treatment for patients with neurogenic detrusor overactivity. However they need to be taken long-term, are ineffective in some patients, or can cause troublesome side-effects such as dry mouth, constipation, drowsiness and blurred vision[38][39].

Injection of botulinum neurotoxin (Botox) into bladder wall is effective in treating neurogenic detrusor overactivity, and is indicated in patients refractory to or experiencing side effects from anticholinergics[39][40][41][42](LE: 1a, GR: A). Botox injection is effective in achieving continence, reducing incontinence episodes, improving urodynamic parameters and health-related quality of life. Significant adverse effects of Botox injection are asymptomatic urinary infection, urinary retention, and de novo intermittent catheterization.

Neurogenic bladder with low compliance may eventually necessitate surgical intervention to convert the high-pressure bladder into a low-pressure storage reservoir. Bladder augmentation in itself (LE: 3, GR: B), or when combined with simultaneous procedures (like surgery on bladder outlet, and/or construction of a continent abdominal stoma by applying the Mitrofanoff principle), can produce sustainable improvements in bladder capacity, continence, urinary infection rate and preserve renal function in the long term.

Abbreviations

UTI: urinary tract infection, CIC: clean intermittent catheterization, CISC: clean intermittent self-catheterization

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Complicated UTIs with BPH

From AAUS

Contents

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Executive summary

Epidemiology and pathogenesis

1. There is no clear evidence showing that the occurrence of UTI in the aging male population is associated with either PVR or BOO, therefore antibiotic prophylaxis is not indicated in such patients (GR: B).

2. In men with lower urinary tractsymptoms (LUTS) due to benignprostatic hyperplasia (BPH) the riskof UTI islow, therefore antibioticprophylaxis is not indicated (GR: A).

Diagnosis

1. In patients with early recurrent or persistent UTI, imaging and urological investigations should be performed to identify underlying abnormalities that may be surgically correctable (GR: A).

2. An assessment for the presence of bacteriuria should be obtained, so results will be available to direct antimicrobial therapy prior to the procedure (GR: A).

Treatment

1. Medical therapy for BPH, i.e. alpha blocker and/or finasteride, cannot reduce the incidence of UTI (GR: A).

2. Recurrent or persistent UTI in men with BOO and BPH is an indication for prostatectomy (GR: A).

3. The presence of infection in patients with BPH should prompt appropriate evaluation and therapybefore treatment of BPH (GR: A).

4. Screening for and treatment of asymptomatic bacteriuria before transurethral resection of the prostate is recommended (GR: A).

5. Antimicrobial therapy should be initiated shortly before the procedure (GR: A).

6. Antimicrobial therapy should not be continued beyond the procedure, unless an indwelling catheter remains in place(GR: B).

Introduction

UTI with urinary tract obstruction is a kind of complicated UTI. The presence of structural or functional obstruction and urinary stasis is an underlying condition that interferes with host defence mechanisms, which increase the risks of acquiring infection or of failing therapy. Benign prostatic hyperplasia (BPH) is the most frequent reason causing lower urinary tract obstruction. This chapter covers the association between urinary tract infections (UTIs) and BPH.

Methodology

An electronic literature search was performed on PubMed from 2004 through 2014, limited to studies in the English language, using the key words "benign prostatic hyperplasia" OR "BPH" AND "urinary tract infection". Abstracts were reviewed, relevant articles were studied in full-length version, and further references were obtained from these articles.In total, 74 abstracts were reviewed, 67 articles were studied in detail, and 31 of them were included as references in this part.

Definition

Complicated urinary tract infection which may involve either the bladder or kidneys, is a symptomatic urinary infection in individuals with functional or structural abnormalities of the genitourinary tract[1].

Asymptomatic bacteriuria: or asymptomatic urinary infection, is isolation of a specified quantitative count of bacteriain an appropriately collected urine specimen obtained from aperson without symptoms or signs referable to urinary infection[2].

Characterization (etiology/epidemiology)

BPH is the major predisposition to UTIs in men (LE: 3)[3]. The incidence of UTIs in the placebo-treated patients was 0.1/100 patient-years (LE: 1b)[4]. A history of BPH was also associated with urinary-source bacteremia among hospitalized male patients(Level 3)[5].

Urinary tract abnormalities may predispose to infection with organisms other than *E. coli*, and long-term antibiotic therapy often leads to bacterial resistance or fungal super infection with *Candida albicans* (LE: 3)[6]. The reported prevalence rates of bacteria isolated from serious UTI are: *E. coli* 21–54%, *Enterococci* species 6–23%, *miscellaneous* Gram-negatives 4–20%, *Pseudomonas aeruginosa* 2–19%, *Providencia* species 18%, *Klebsiella pneumoniae* 2–17%, *Enterobacter* species 2–10%, *Proteus mirabilis* 1–10%, *Citrobacter* species 5–6%, coagulase negative *Staphylococci* 1–4%, group B *Streptococci* 1–4%, *Staphylococcus aureus* 1–2% (LE: 3)[7][8].

Classifications/ Characterizations

Symptomatic UTI: The sudden aggravation of LUTS, micturition pain, dysuria, urinary frequency, sometimes associated with low or high fever is a typical symptoms in man suffered from UTI with BPH.

Asymptomatic bacteriuria: Bacteriuria prior to prostatectomy in men with BPH has been reported in 28% to 54% of cases. The incidence is higher in those catheterized before operation (44% to 57%) than in those not catheterized. (LE: 3)[9][10][11][12].

Clinical features

Unlike other manifestations of BPH, the UTI is not disease or gender specific. One must be cautious in assuming a causal relationship to BPH. The presence of a large post void residual (PVR) would allow more time for bacterial adherence and multiplication which may lead to severe UTI that is difficult to eradicate, but there is little evidence showing that the occurrence of UTI in the aging male population is associated with either PVR or bladder outflow obstruction (BOO) (LE: 3)[13].

Diagnosis

Physical examination of the external genitalia is indicated to exclude meatal stenosis or a palpable urethral mass and an abdominal examination is necessary to exclude urinary retention.Weather there is CVA pain. Digital rectal examination (DRE) should be performed to rule out acute bacterial prostatitis.

Urinalysis to the patients of BPH, a urinalysis is recommended to be sure that the patient'ssymptoms are not related to infection. Urinalysis is performed to rule out a urinary tract infection; and, if an infection is suspected, a urine specimen should be sent for culture and sensitivity.

Urine culture to the patients of BPH with UTI symptoms, significant bacteriuria is defined by counts of > 10^4 cfu/mL, in the midstream urine (MSU) or straight catheter urine sample (LE: 1a)[14][15]. To the patients of BPH without UTI symptoms, the diagnosis of asymptomatic bacteriuria should be based on results of culture of a urine specimen collectedin a manner that minimizes contamination. Diagnosis criteria are listed in Table 1.

Table 1. Diagnosis criteria of asymptomatic bacteriuria in man with BPH

	Reference	LE	GR
For men, a count of $>10^3$ cfu/mL of a microorganism in a voided urine specimen is diagnostic of bacteriuria.	15	2a	B
For men with specimens collected using an external condom catheter, $>10^5$ cfu/mL is an appropriate quantitative diagnostic criterion.	16	2a	B
For patients with indwelling urethral catheters, a count of $>10^5$ cfu/mL is diagnostic of bacteriuria.	17	2b	B
For a urine specimen collected by in and out catheter, a count of >100 cfu/mL is consistent with bacteriuria.	17	2a	B

Upper tract imaging should be performed to the patients of BPH with a history of urinary infection. Ultrasound with abdominal radiography is equivalent to intravenous urography (IVU) as screening study in patients with complicated UTI, and is the imaging study of first choice, while computerised tomography (CT) is indicated if more detailed information is required.

Treatment

The treatment of UTI in the presence of urinary tract obstruction requires effective antibiotic therapy as well as appropriate Urological intervention to remove predisposing factors and to restore as far as possible the normal anatomy and function of the urinary tract in order to prevent septicemia and recurrent UTI (LE: 3)[16].

BPH treatment

Medication/drug therapy

Because the incidence of UTI is relatively uncommon and non–disease specific events in the aging male population, it would be extremely difficult to design a prospective study to determine whether any BPH treatment prevents this event in an unselected cohort of men. There is no evidence to show that the doxazosin, finasteride or combination therapy can reduce the incidence of UTI in the patients with BPH (LE: 1b)[17]. Even not the Phytotherapy (LE: 3)[18].

Interventions

Recurrent UTI caused by bladder outlet obstruction is one of the indications for trans urethral resection of prostate (TURP) (LE: 1a)[19]. In older surgical series, UTI was the indication for surgical intervention in about 12% of men with BPH (LE: 3)[20][21]. In a study of men with BPH treated at hospitals in Japan, UTI was the reason for presentation in 4% (LE: 3)[22].

Treatment of symptomatic UTI

The presence of infection in patients with BPH should prompt appropriate evaluation and therapy before treatment of BPH (LE: 3)[16]. In patients with mild to moderate UTI (no nausea or vomiting) the recommended empirical treatment is an oral fluoroquinolone used on an outpatient. A 7-day course of therapy is recommended (LE: 3)[16].

Severely ill patients with possible urosepsis should be hospitalized and empirical therapy should usually include an intravenous anti-pseudomonal agent. Targeted therapy should be initiated once susceptibility data are known. Agents commonly prescribed include aminoglycosides, beta-lactamase inhibitor combinations, imipenem, advanced-generation cephalosporins and fluoroquinolones. For patients with fever or more severe systemic infection, therapy for 10 to 14 days is recommended. Urine cultures should be performed during antibiotic treatment and 7–14 days after cessation of therapy to determine whether treatment has been effective (LE: 3)[3][16][23][24].

Screening and treatment of asymptomatic bacteriuria

Bacteremia occurs in up to 60% of bacteriuric patients who undergo TURP, and there is clinical evidence of sepsis in 6%–10% of these persons (LE: 3) [25]. The effectiveness of antimicrobial treatment in prevent in these complications in bacteriuric men undergoing TURP has been supported (LE: 1b)[26][27][28][29][30]. The appropriate timing for initiation of antimicrobial therapyis not well defined. Initiationof therapy the night before or immediately before the procedure is effective (LE: 1b)[31][30]. In the absence of an indwelling catheter, antimicrobial therapy can likely be discontinued immediately after the procedure (LE: 1b)[31][29][30]. When an indwelling catheter remains in place after TURP, it has been recommended that antimicrobial therapy be continued until the catheter is removed (LE: 1b)[25][26].

Abbreviations

UTI: Urinary Tract Infection, PVR: Postvoid Residual, BOO: Bladder Outflow Obstruction, LUTS: Lower Urinary Tract Symptoms, BPH: Benign Prostatic Hyperplasia, CVA: Costovertebral Angle, DRE: DigitalRectal Examination, MSU: MidstreamUrine, IVU: IntravenousUrography, CT: Computerised Tomography, TURP: Trans Urethral Resection of Prostate

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Complicated UTIs with urolithiasis

From AAUS

Contents

Author

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Executive summary

Diagnosis

1. Although it is not sufficient toexclude the presence of urinary tractinfection (UTI) midstream urine (MSU) culture should be obtained before any treatment is planned.(GR: A)

2. Incase of an UTI with systemic symptoms (fever, but also chills and low temperature) blood culture must be performed. (GR: A)

3. Image studies including US and CT must be highly recommended for diagnosis and evaluation of cUTI associated with urolithiasis.(GR: A)

Treatment

1. For sepsis with obstructing stones, the collecting system should be urgently decompressed, using percutaneous drainage or ureteral stenting.(GR: A)

2. Definitive treatment of the stone should be delayed until sepsis is resolved. (GR: A)

3. Collect urine for antibiogram test following decompression.(GR: A)

4. Start antibiotics immediately thereafter (+ intensive care if necessary). (GR: A)

5. Re-evaluate antibiotic regimen following antibiogram findings.(GR: A)

6. Recommendations for therapeutic measures of infection stones

7. Surgical removal of the stone material as complete as possible (GR: A)

8. Short-term antibiotic course (GR: B)

9. Long-term antibiotic course (GR: B)

10. Urinary acidification: ammonium chloride, 1 g, 2 or 3 times daily (GR: B)

11. Urinary acidification: methionine, 200-500 mg, 1-3 times daily (GR: B)

12. Urease inhibition (GR: A)

Introduction

Urolithiasis may be a cause as well as a result of UTI. Stone obstruction leads to urinary stasis, which enables bacteria to adhere to the urothelium and multiply,thus causing UTI. Primary UTI caused byurea-splitting organisms may lead to struvite stone formation, causing obstruction,stasis and further infection. This is the clinical consequences of the "vicious cycle": stones → obstruction → stasis → infection → stones. Obstructive pyelonephritis is also one of the life-threatening cUTI, and prompt diagnosis and treatment including medical as well as surgical interventions to rescue the patients. Complicated UTIs with urolithiasis are discussed in the chapter.

Methodology

An electronic literature search was performed on PubMed from 2004 through 2014, limited to studies in the English language, using the key words "Urolithiasis" OR "urinary calculi" AND "urinary tract infection". Abstracts were reviewed, relevant articles were studied in full-length version, and further references were obtained from these articles. In total, 103 abstracts were reviewed, 86 articles were studied in detail, and 47 were included as references in this part.

Definition

Stones with infection: stones complicated by UTIs, which are metabolic stones that passively trap bacteria from coexistent UTIs and may consist of calcium or non-calcium.

Infection stones: stones that occur following UTIs caused by urease-producing gram-negative organisms, which pathogenesis play a key role in stone formation. Infection stones contain the following minerals: struvite and/or carbonate apatite and/or ammonium urate.

Staghorn calculi are those stones that fill the major part of therenal collecting system. Typically, they occupy the renal pelvis andbranch into most of the calyces, mimicking the horns of a deer orstag.

Epidemiology

The incidence of infected urolithiasis has increased in recent years.The rates of associated sepsis increased from 6.9% to 8.5%, and severe sepsis increased from 1.7% to 3.2%; mortality rates at 0.25–0.20%. The rising prevalence has been linked to increasing rates of obesity, diabetes, and metabolic syndrome. Women were twice likely to have infected urolithiasis (LE: 3)[1]. To the complete kidney staghorn calculi, 56% of them weremetabolic and 44% were infection stones (LE: 3)[2]. Staghorn calculi or high stone burden, infection, and ureteral obstruction are the top three causes of loss for function in one kidney (LE: 1a)[3]. Urinary tract obstruction due to urolithiasis is also the main cause of emphysematous pyelonephritis (LE: 3)[4] and xanthogranulomatous pyelonephritis (LE: 3)[5].

Classification

Stones with infection

There are about 8%- 24%of patients presenting with acute nephrolithiasis having UTI in the emergency department (LE: 3)[6][7]and 12.5%of patients emergency drainage because of the SIRS from urosepsis.The risk factors for emergency drainage arepatient's performance status, ageand sex (LE: 3). For these patients, Escherichia coliis the most frequenturopathogen, others including Proteus mirabilis, Klebsiella, and Enterococcus. Some of them aremultiple uropathogens infection. Candida albicans can also be isolated from urine of these patients (LE: 3,1b)[8][9].

Infection stones

The occurrence of infection stones has decreased over the past 20 years as a result of the significantly improved diagnosis and treatment of UTIs. (LE: 3)[10]The incidence varies according to geographical location, gender, and age of the patient.In industrialized countries, the relative proportion of occurrence in women ranged from 3.2 to 10.1%. (LE: 3)[11] In developing countries, major differences in the incidence of infection stones were observed according to continent and region, from 42.9% in Sub-Saharan Africa to 13% in South America and 2.7% in Asia Minor. (LE: 3)[12]

Infection stones are not associated with metabolic abnormalities intrinsic to the patient, but are a result from bacterial metabolism(LE: 1a)[13]. Formation of infection stones depends on urea-hydrolization in the presence of urease by urease-producing bacteria. (Table 1) (LE: 1a)[14][15][16][17]

Table 1. Urease producing uropathogens

Permanently	Partially	Rarely/Never
Proteus spp.	*Enterobacter gergoviae*	*Escherichia coli*
Providencia rettgeri	*Klebsiella spp.*	*Entercoccus spp*
Morganella morganii	*Providencia stuartii*	*Pseudomonas aeruginosa*
Corynebacterium urealyticum	*Serratia marcescens*	
Ureaplasma urealyticum	*Staphylococcus spp.*	

Clinical features

Clinical presentation of infected urolithiasis can vary from the dysuria, urgency, frequency, flank pain, costovertebral angle tenderness, suprapubic pain and fever to severe obstructive acute pyelonephritis with imminent urosepsis. Nearly an half of patients with flank pain are caused by a ureteral stone (LE: 3)[18].

Risk factors for development of infection stones are urinary tract obstructions, catheter, neurogenic bladder voiding disruptions, pouches, as well as distal renal tubular acidosis and medullary sponge kidney (LE: 1a)[19][20].

Diagnostic criteria (testing procedures)

Symptoms (physical examination):

Fever,heart rate, respiratory rate, blood pressure, CVA pain, any abnormal situation of urinary system.

Laboratory tests (radiological investigation, others)

Blood analysis for leucocyte, Serum creatinine, CRP, PCT.

Urinalysis:

Pyuria has only a moderate accuracy in identifying UTI. Fever, a greater degree of pyuria and female sex increases the likelihood of infection. (LE: 3)[6].

Urine pH measurements: Infection stones contain struvite and/or carbonate apatite and/or ammonium urate typically providing evidence for urease-producing bacteria, which increase ammonia ions and develop alkaline urine. Carbonate apatite starts to crystallise at a urine pH Level of 6.8. Struvite only precipitates at pH > 7.2 (LE: 1a)[15][16][17][19].

Urine culture is needed. Significant bacteriuria is defined by counts of > 10^4 cfu/mL, in the mid stream urine (MSU) or straight catheter urine sample (LE: 1a)[21][22]. Positive bladder urine culture does not always correlate with stone and renalpelvic cultures, including in patients with sterile positive bladder urine culture.To the patients with obstructing ureteral stone or infected stones,midstream urine culture and sensitivity test is a poor predictor of infection (LE: 3)[23].

Blood culture: Incase of an UTI with systemic symptoms (fever, but also chills and low temperature), blood culture must be performed. Two sets allow for the differentiation between true bacteremia and contamination.

A single physical examination or laboratory finding cannot predict UTI in urolithiasis patients with complete reliability. The presence of pyruria, fever, and leukocytosis significantly increase the odds of a positive urine culture (LE: 3)[24].

Imaging might be considered in men, diabetic persons and patients with history of relapsing UTI , urolithiasis structural and urological abnormality, patients with symptoms of urolithiasis the, febrile UTI, urine pH≥7.0, and/or renal insufficiency (estimated glomerular filtration rate, ≤40 mL/min/1.73 m^3)[25][26][27](LE: 1a) (LE: 3) (LE: 3). Ultrasound, plain abdominal film, urographyand abdominal and pelvic CT scans are the most common imaging tools. MR urography is an attractiv ealternative to CT urography because ionizing radiation is not used.However, the sensitivities for detecting urolithiasis and small urothelial carcinoma(largely due to the inferior spatial resolution relative to CT) are presumably lower for MR urography (LE: 1a)[28].

Treatment

Stones with infection

Decompression Infection in the obstructed urinary tract caused by urolithiasis poses an imminent threat to the patient and may induce significant morbidity including sepsis, pyonephrosis (suppurative destruction of renal parenchyma), and even death (LE: 3)[29]. The treatment of infected and obstructive urolithiasis involves prompt decompression of the renal collecting system.For decompression of the renal collecting system, retrograde ureteral catheterization (RUC) and percutaneous nephrostomy (PCN) are equally effective (LE: 1b)[30]. Neither modality demonstrated superiority in promoting a more rapid recovery after drainage. The decision of which mode of drainage to use may be based on logistical factors, surgeon preference and stone characteristics (LE: 3)[9]. RUC has certain failure rate (LE: 1b)[31]. PCN avoids general anesthesia, aswell as instrumentation of the infected urinary tract, and it is classically considered as a safer method of drainage in critically ill patients (LE: 3)[32]. Training background, favorable physician reimbursement, the timing of the intervention and patient-specific factors such as prostatic enlargement or altered lower urinary tract anatomy are the significant drivers in this decision-making process (LE: 3,4)[33][34]

Antibiotic treatment

The antimicrobial treatment options for empirical therapy of stones with infection are listed in Table 2[35].

Table 2. Antimicrobial treatment options for empirical therapy (modified from EAU guidelines 2014)[35]

Antibiotics recommended for initial empirical treatment
Fluoroquinolones
Aminopenicillin plus a BLI
Cephalosporin (Groups 2 or 3a)
Aminoglycoside
Antibiotics recommended for empirical treatment in case of initial failure, or for severe cases
Fluoroquinolone (if not used for initial therapy)
Ureidopenicillin (piperacillin) plus BLI
Cephalosporin (Group 3b)
Carbapenem
Combination therapy: - Aminoglycoside + BLI - Aminoglycoside + fluoroquinolone
BLI = β-lactam inhibitor

The most common gram positive UTI pathogen in most countries of Asia is *Enterococcus* spp. Effective antibiotic options are listed in Table 3.[36]

Table 3. Effective antimicrobial treatment options for *Enterococcus* spp.
Ampicillin or amoxicillin
Ampicillin-sulbactam or amoxicillin-clavulanate ± aminoglycosides
Vancomycin or teicoplanin
Tigecycline (for multidrug-resistant Enterobacteriaceae and *Acinetobacter baumannii* and vancomycin-resistant enterococci)

Infection Stones

There are three points of treatment to achieve possible therapy (LE: 1a)[16].

1) Removal of all stones and stone analysis are the first step of infection stone treatment with endoscopic equipment and shockwave lithotripsy.

2) Antibiotic therapy Antibiotic therapy is advised in patients affected by infection stones prior to and/or after treatment. Antibiotic therapy significantly reduces the bacterial load, decreasing the risk of sepsis, antibiotics prevent recurrence or re-growth of stones after treatment. Urine specimens for bacteriological cultures should be routinely collected at each follow-up visit. In case of recurring UTI antibiotic therapy based on results of sensitivity testing should be carried out[19]. Different schedules of targeted antibiotic therapy are shown in Table 4 [37][38][39][40](LE: 3).

Table 4. Different schedules of targeted antibiotic therapy
1 to 2 weeks target antibiotics before PCNL+ ESWL + broad-spectrum IV therapy intra- and post-operatively + Low dose prophylactic or suppressive antibiotics for the first 1 to 2 years of follow up.[37] (LE 3)
A minimum 7-day course of target oral antibiotics until the day of PCNL.[38] (LE 3)
1–2 days of antibiotic prophylaxis PCNL surgery.[39] (LE 3)
2-weeks full course of target antibiotics before PCNL.[40] (LE 3)

3) Prevention of recurrence

All infection-stone formers are deemed at high risk of recurrence.Some methods can be used to prevent the recurrence of infection stone:

Lifestyle or dietary modification :

Increase fluid intake: at least 2 L per day. Chronic low fluid intake/low urine output is associated with the occurrence of UTI, and ensuring a high urine output with increased fluid intake has been shown to prevent recurrent urolithiasis (LE: 2a)[41].

Urease inhibitors

Aceto-hydroxamic acid (AHA) causes a complete non-reversible and non-competitive inhibition of the enzyme urease (LE: 1b)[42].

Dissolution therapy

Chemolysis with hemiacidrin may be a secondary treatment for infection stones and the success rates in stone dissolution is 68-80%,which are described in the literatures (LE: 3)[43][44].

Urinary acidification

Methionine, 200-500 mg, 1-3 times daily or ammonium chloride, 1 g, 2 or 3 times daily can be used (LE: 3)[45][46].

Urinary alkalinization

Oral intake of citrate can be used in order to prevent struvite crystal formation and aggregation by increasing urinary citrate Levels, although there has been a reluctance in relation to the potential increase in urinary pH (LE: 1b)[47].

Abbreviations

UTI: Urinary Tract Infection, MSU: Midstream Urine, SIRS: Systemic Inflammatory Response Syndrome, CVA: Costovertebral Angle, CRP: C-Reactive Protein, PCT: Procalcitonin, CT: Computer Tomography, MR: Magnetic Resonance, RUC: Retrograde Ureteral Catheterization, PCN: Percutaneous Nephrostomy, PCNL: Percutaneous Nephrolithotomy, ESWL: Extracorporeal Shock Wave Lithotripsy , AHA: Aceto-Hydroxamic Acid

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Complicated UTIs with diabetes mellitus

From AAUS

Contents

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Executive Summary

Diagnosis

1. In emphysematous pyelonephritis, computed tomography (CT) is the imaging procedure of choice to confirm the presence and extent of parenchymal gas. (LE: 3b, GR: B)

Treatmet

1. The treatment of UTI in patients with DM does not differ from the treatment in those without the disease in terms of antimicrobial choice or duration of therapy. (LE: 4, GR: C)

2. With asymptomatic bacteriuria, antibiotic treatment is not recommended in non-pregnant women of any age. (LE: 1b, GR: A)

3. In emphysematous pyelonephritis, nephrectomy is limited to selected groups who are fit for surgery and fulfill one or more of the following criteria: possession of a non-functioning kidney or presentation of gross renal parenchymal destruction. (LE: 4, GR: C)

4. In emphysematous cystitis, systemic antimicrobials and relief of any complicating bladder outlet obstruction, if present, are adequate therapy. (LE: 4, GR: C)

5. In a patient with a UTI with a persistent fever after 3-4 days of antibiotics, consider papillary necrosis, renal abscess or EPN. (LE: 4, GR: C)

Introduction

Diabetes mellitus has a number of long-term effects on the genito-urinar ysystem. Urinary tract infection is a significant problem in patients with diabetes mellitus because of the multiple effects of this disease on the urinary tract and the host immune system. Diabetes mellitus is frequently associated with the more severe manifestations of urinary tract infection. Patients with diabetes mellitus are more likely to be hospitalized for the treatment of pyelonephritis, more likely to have a bacteremic infection, and more frequently have bilateral renal infection compared with populations without diabetes mellitus. Bacteriuria is more common in diabetic women than in non-diabetic women due to a combination of host and local risk factors. Upper urinary tract infection complications are also more common in this group.

Diabetic patients are at higher risk for intra- or peri-renal abscesses. A number of uncommon complicated urinary tract infection complications occur more frequently in diabetics, such as emphysematous pyelonephritis.Because of the frequency and severity of urinary tract infections in diabetic patients, prompt diagnosis and early therapy is warranted.

In addition, the current issues surrounding anti-diabetic medicine, sodium-glucose transport proteins (SGLT2) inhibitors and urinary tract infection is worthy of discussion.

General medical treatment principles in UTI with diabetes mellitus

The empiric antibiotic therapy of diabetic patients with complicated urinary tract infections is similar to that of patients with acute pyelonephritis because the causative pathogens are usually the same. Enteric gram-negative bacilli, such as *E. coli*, *Proteus sp, Klebsiella sp, and Enterobacter,* are the usual bacterial causes. For these serious infections, *Pseudomonas aeruginosa* and *Enterococcus* spp. may also need to be considered as possible causes, particularly in patients who have recurrent infections, a history of previous urinary infections caused by these pathogens, or have previously been on broad spectrum antimicrobials. As with pyelonephritis, the timely initiation of appropriate therapy with parenteral agents and intravenous hydration is critical in the diabetic patient for both recovery and for the avoidance of potential complications. Oral outpatient therapy is not recommended in the initial therapy of diabetic patients with complicated urinary tract infections. Due to the severity of the illness and the potential for high morbidity and mortality with complicated upper urinary tract disease in the diabetic patient, hospitalization and initial parenteral antibiotic therapy is recommended. Surgical drainage and debridement or CT-guided drainage may also be required for some complications as discussed under the individual entities.[1] The uncommon but serious complicationsof emphysematous cystitis, pyelonephritis,and papillary necrosis, virtually only occur in patients with diabetes mellitus. Despite these observations, the treatment of UTI in patients with DM does not differ

from treatment in those without the disease in terms of the antimicrobial agent or the duration of therapy.[2](LE: 4, GR: C) With asymptomatic bacteriuria, antibiotic treatment is not recommended in non-pregnant women of any age. (LE: 1b, GR: A)

Epidemiology / Etiology

Epidemiology of UTI with DM

Diabetes mellitus increases the risk of acute pyelonephritis from infection by *Enterobacteriaceae* that originate in the lower urogenital tract. Persons with type 2 diabetes have an increased risk of UTI, in particular when they are treated by oral medication or insulin.[3][4][5] They also have increased risk of complications from UTIs. For example, patients with diabetes have a five to ten-fold higher risk of acute pyelonephritis.[6] Additionally, UTIs in patients with diabetes are difficult to treat and recur often.[7]Patients with diabetes have a 40% increased risk of recurrent cystitis.[5]

The complications of symptomatic UTI are also increased in patients with DM, and women with type-1 DM are ata greater risk of developing pyelonephritis and subsequent impaired renal function. Other clinical manifestations that are unique or strongly associated with DM include renal abscess formation and papillary necrosis. Furthermore, diabetic patients are commonly infected with species other than *E. coli,* in particular *Klebsiella* and other Gram negative rods, *enterococci* and group B *streptococci*.[8][9]

There does not appear to be an increased prevalence of urinary tract infections in men with diabetes mellitus. However, women with DM are at a greater risk of both symptomatic and asymptomatic UTI. While there is little available information in male patients or those with type-1 DM, postmenopausal women with type-2 DM have double the risk of developing a symptomatic UTI. The risk is further increased three- to four-fold in those taking oral hypoglycemics or those with insulin-controlled DM, indicating a possible association between an increased incidence of UTI and the severity of DM.[10]

Pathogenesis of UTI with DM

It has previously been recognized that diabetic patients are particularly susceptible to rapid progression of renal parenchymal infection and the ensuing complications. The chronic effects of diabetes mellitus on the genitourinary system include diabetic cystopathy, diabetic nephropathy, renal papillary necrosis, renal arterystenosis, and vas deferens calcification.[11]

Women with type 1 diabetes are particularly at risk if they have had diabetes for a significant amount of time or complications have developed, particularly peripheral neuropathy and proteinuria. The most important predisposing factor may be bladder dysfunction as a result of diabetic neuropathy and cystopathy. Generalized vascular disease as a result of long-standing diabetes mellitus may also be important. Finally, although the degree of glycosuria has not been directly implicated in clinical studies, high levels of urinary glucose have been shown to impair phagocytic leukocyte function. Glycosuria inhibits phagocytosis, may inhibit cellular immunity, and encourages bacterial adherence.

Bacteriology

The bacteria isolated from diabetic patients with aUTI are similar to those found in nondiabetic patients with a complicated UTI.[2] As in uncomplicated UTIs, *E. coli* causes the majority of infections. However, other strains are relatively more frequently cultured in these patients. For

example, one study reported *E. coli* to be the causative uropathogen in 47% of the UTIs in diabetic patients and in 68% of the UTIs in nondiabetic patients.[12] Non-*E. coli* uropathogens found inpatients with DM include *Klebsiella* spp., *Enterobacter* spp., *Proteus* spp., Group B *Streptococci* and *Enterococcus faecalis*.[13][14][15]

Classifications / Characterizations

Urinary tract infections associated withdiabetes includethe following:

1. Asymptomatic bacteriuria
2. Emphysematous pyelonephritis and emphysematous cystitis
3. Renal papillary necrosis
4. The issue of UTI in the pooled analyses of the SGLT2 clinical trials

Clinical features / Diagnosis / Treatment

Asymptomatic bacteriuria

Bacteriuria and urinary tract infections are more common in diabetic women compared to non-diabetic women. Urinary tract infections in women with diabetes mellitus is related to the duration of diabetes mellitus and the presence of long term complications but not metabolic control.[16] The prevalence of asymptomatic bacteriuria is 3 times greater in women with diabetes mellitus than in women without diabetes mellitus.[13] In a prospective study of non-pregnant women with diabetes mellitus, 26% had significant bacteriuria (> 10^5cfu/mL) compared with only 6% of controls. The most common bacterial cause of urinary tract infection in patients with diabetes is still E coli; other enteric coliforms, such as Klebsiella pneumoniae and Proteus mirabilis, are also common. Klebsiella pneumoniae, in particular, is more common in diabetic patients compared to non-diabetics in both community-acquired and nosocomial infections.[12] Recently, the importance of asymptomatic bacteriuria in patients with DM has been questioned. There was no consensus on the questions of pre-emptive screening, treatment and prophylaxis of asymptomatic bacteriuria. However, these issues have been addressed in a placebo-controlled, double-blind randomized trial,[17] (LE: 1b) which concluded that treatment does not reduce complications and the diabetes should not therefore be regarded as an indication for the screening or treatment of asymptomatic bacteriuria. The findings from this trial have been subsequently recognized in the guidelines published by the Infectious Diseases Society of America (IDSA) on the diagnosis and treatment of asymptomatic bacteriuria in general.[18] Conversely, antibiotic treatment of asymptomatic bacteriuria significantly increases the risk of adverse events without a significant clinical benefit and also increases resistance.[17] The clearance of asymptomatic bacteriuria should not be attempted if the intention is to prevent complications, notably acute pyelonephritis (GR: A).

Emphysematous UTIs

Emphysematous pyelonephritis

EPN is a severe, necrotizing form of acute multifocal bacterial nephritis that results in the presence of gas within the renal parenchyma. Often, the infection, and consequently the gas, extends through the renal capsule and involves the kidney and the perinephric space as well.More than 200 cases have been reported in literature to date.[19]Underlying poorly controlled diabetes mellitus ispresent in up to 90% of the affected patients.[20]

The most common offending organisms are *E. coli* and *Klebsiella*, followed by *Proteus*.[20] The diagnosis of EPN is often delayed because the clinical manifestations are nonspecific and are no different than the classic upper UTI triad (fever, flank pain and pyuria). Therefore, in a patient with UTI, if the fever does not subside after 3-4 days of antibiotics,consider papillary necrosis, renal abscess or EPN.(LE: 4, GR: C)

A common clinical triad of predisposing factors is diabetes mellitus, remote or recent kidney infection, and obstruction. EPN is more common in women than in men (2:1). The presenting symptoms are similar to patients with acute pyelonephritis or renal abscess and consist of fever, chills, and frequently nausea and vomiting. The localization of the gas as intrarenal, perinephric, or confined to the collecting system is crucial in determining the therapy and prognosis, and CT is the study of choice.[21]

A necrotizing infection of the renal parenchyma and its surrounding areas causes gas accumulation in the renal parenchyma, collecting system or the perinephric tissue. Between 85% and 100% of the patients with this condition are diabetics, approximately 40% have an obstruction that most commonly an obstruction of the calculus, and it is a bilateral obstruction in 10% of cases.[22]

Poor prognostic indicators

Poor prognostic indicators ofthe affected patients are acute renal failure, shock, thrombocytopenia, altered sensorium, and severe proteinuria.

Diagnosis(CT abdomen is diagnostic)

EPN requires a radiological diagnosis. Conventional radiography may demonstrate gas bubbles overlying the renal fossa. Ultrasonography (US) characteristically shows an enlarged kidney containing high-amplitude echoes within the renal parenchyma.[23] Computed tomography (CT) is the imaging procedure of choice to confirm the presence and extent of parenchymal gas.[20] (LE: 3b, GR: B)

A radiologic classification system has been proposed to help with appropriate management planning.[24] The classification isbased on the location of the gas in the kidney as follows:

- Class 1: Gas confined to the collecting system
- Class 2: Gas confined to the renal parenchyma
- Class 3a: Perinephric extension of gas or abscess
- Class 3b: Extension of gas beyond the Gerota fascia
- Class 4: EPN in bilateral or solitary kidney

Management

Treatment of EPN involves broad-spectrum antimicrobial therapy, hyperglycemic control, and adequate urinary drainage with correction of any outlet obstruction.Patients with necrotizing infections will require a more aggressive treatment that includes surgery.[25] The initial management of a patient with EPN is resuscitation; a three-pronged approach should be applied to address the fluid/hemodynamic status, diabetic control and an antibiotic regimen. A decision must then be made as to whether medical therapy alone, percutaneous drainage or nephrectomy is required.[21] Earlier series have stressed the need for urgent nephrectomy. With the advent of CT scanning, more powerful antibiotics,and better access to life support, an alternative conservative approach has emerged, which is based on appropriate antibiotics and percutaneous drainage.[26] (GR: C)

Surgical interventions

It is of the utmost importance to decide the appropriate time of surgical interventions. The urologist and the endocrinologist have to be in constant collaboration to monitor the day-to-day progress of a conservatively managed patient so that the urologist can intervene when appropriate.

- Class 1 and 2 can be managed conservatively and may require percutaneous drainage (PCD) in some cases.
- Class 3a and b requires PCD, and if poor prognostic factors exist, the, nephrectomy is appropriate.
- Class 4 bilateral requires PCD, and if it is not controlled,consider nephrectomy.

Nephrectomy is now limited to a select group of patientswith EPN who are fit for surgery and fulfill one or moreof the following criteria: possession of a nonfunctioningkidney orpresentation of gross renal parenchymaldestruction. (LE: 4, GR: C)

Patients with two or more risk factors (altered consciousness, thrombocytopenia, shock, and acute renal failure) require aggressive treatment. There have been trials using parental antibiotics and percutaneous drainage in classes 3A, 3B, and 4 in the absence of risk factors.[21][24] For glycemic control, intravenous insulin is ideal, and at times rates of up to 20 to 30 units of regular insulin hourly may be required for patients in sepsis.[27] (GR: C)

Emphysematous cystitis

Emphysematous cystitis results from a primary infection of the bladder. Emphysematous cystitis is rare and is characterized by pockets of gas in and around the bladder wall produced by bacterial or fungal fermentation. More than 50% of patients with have diabetes mellitus. *E. coli* is the most common causative organism.[28]

Approximately 50% to 80% of the patients reported with emphysematous cystitis are diabetics.[28][29][30][31] The condition may result in a "cobble stone" appearance with a translucent line of air outlining the bladder wall. The radiographic findings provide the first and the only diagnostic clue. Nevertheless, CT is considered to be the preferred method of diagnosis because of its high sensitivity and specificity in the detection of abnormal gas and its anatomical extension.[32]

In general, systemic antimicrobials and relief of any complicating bladder outlet obstruction, if present, are the adequate therapies.1 (GR: B)

Papillary necrosis

Renal papillary necrosis has a variable clinical course that ranges from achronic, protracted, and relapsing form to an acute, rapidly progressive form. Papillary necrosis is common in diabetics, particularly in association with acute pyelonephritis. It is associated with permanent renal parenchymal scarring, although it is difficult to exclude obstruction by the sloughed papillae as the cause of the nephropathy. Perfusion compromise as a consequence of vasculitis in diabetes mellitus, tuberculosis, or the curtailment of flow observed in hemoglobinopathy,analgesic nephropathy, or acute urinary obstruction, also sets the stage for ischemic changes in the medullary pyramid.[33]

Urinary tract infection is virtually always a concurrent complication when renal papillary necrosis is documented in a patient with diabetes.[34]Renal insufficiencyor acute renal failure is a common complication. Renal papillary necrosisshould be considered in the diabetic patient presenting with symptoms ofpyelonephritis who does not respond well to antibiotic therapy or in whomrenal insufficiency develops.[35][36] The acute progressive form is particularly rare but can result in death from septicemia and renal failure. Patients with the more common chronic form may remain asymptomatic or symptomatic. The most common presenting symptoms in symptomatic patients include fever and chills, flank and/or abdominal pain, and hematuria. This condition should be suspected in diabetic patients who develop recurrent episodes of UTI, renal colic, hematuria, obstructive uropathy, or unexplained renal failure.[37][38]

Renal papillary necrosis is a radiologic diagnosis that is confirmed by histology of the voided medullary tissue. Intravenous urography is the most sensitive investigative approach,but it is rarely used today because of the adverse effect of contrast media on renal function in diabetic patients. Inpatients with poor renal function, CT may demonstrate necrotic papillae allowing for the diagnosis to be made.[39]

Treatment of renal papillary necrosis includes aggressive antibiotic therapy when infection is demonstrated. Relief of the obstruction may also be required. The prognosis for this condition is not well defined. Antibiotic prophylaxis for the treatment of asymptomatic bacteriuria is likely required (GR: C).

The issue of UTI in the pooled analysis of the SGLT2 clinical trials

The kidney plays an important role in glucose homeostasis not only in gluconeogenesis but also in reabsorbing filtered glucose via transporters called sodium-glucose transport proteins (SGLTs). SGLT2 has become the focus of significant interest in the field of type 2 diabetes.[13] SGLT2 inhibitors block the reabsorption of filtered glucose, leading to glucosuria and improvements in glycemic control. SGLT2 inhibitors are also associated with caloric loss, which has the potential for weight loss.[12]

Dapagliflozin is the selective, orally active, once-daily SGLT2 inhibitor for which there is the most clinical data published in the literature.

Glucose in the urine may encourage bacteria in the urinary tract to flourish and can result in infection.Some studies have shown an increased incidence of events suggestive of urinary tract infections (UTIs) in patients taking SGLT-2 inhibitors.

Urinary tract infections

The incidence of lower urinary tract infections was higher in the dapagliflozin groups compared to those on the placebo and on the other oral hypoglycemics used in the various studies[14][15] [33] but was reported to be the same in one study.[39] The reported urinary tract infection rates

were 1%–12.9% in the dapagliflozin groups versus 0%–6.2% in the control groups. Most urinary tract infections were single events, were mild to moderate in intensity, and responded to routine management.[15][39]

Genital infections

There was an increase in genital infections in the dapagliflozin groups compared to controls in almost all of the studies with the incidence increasing with higher doses of dapagliflozin. The reported incidence varied from 3% to 13% versus 0% to 5% in the placebo group.[14][15][33][39]

In a Japanese study on dapagliflozin, four patients across all groups reported events suggestive of genital infection and four reported events suggestive of urinary tract infection. No events suggestive of pyelonephritis were reported.[40]

Conclusion

Treatment with SGLT2 inhibitors, including dapagliflozin, may be associated with a slight increased risk of development of UTI or UTI symptoms. However, the study lacked a correlation analysis of glycosuria and UTI development. This issue requires additional detailed investigations.

Abbreviations

UTI: Urinary tract infection, DM: diabetes mellitus, EPN: emphysematous pyelonephritis

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Catheter-associated UTIs

From AAUS

Contents

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Executive summary

Epidemiology and pathogenesis

1. CAUTIs are the commonest nosocomial infections. Definitions remain controversial, but the NHSN definitions have been widely accepted.

2. Higher rates of CAUTIs and antibiotic resistant organisms have been reported in parts of Asia. Hence, antimicrobial treatment choice should be guided by local antibiograms and culture results (LE: 4).

Treatment

1. CAASB should not be routinely treated with antibiotics (LE: 1b). Routine surveillance cultures are not warranted and should not be done.

2. Reducing the duration of urethral catheterization remains key to the prevention of CAUTIs (LE: 2b), for which various reminder systems have been shown to be effective (LE: 1a).

3. Urinary catheter care bundles have also been shown to reduce CAUTI rates (LE: 2a).

Introduction

This guideline is an update of recently published guidelines from Asia[1] and beyond[2][3] on the management and prevention of CAUTIs.

Definition

CAUTI refers to UTIs associated with indwelling urinary catheters, which are defined as drainage tubes inserted into the urinary bladder through the urethra, left in place, and connected to a collection system[3].

The definition of CAUTI remains controversial, with all guidelines agreeing that symptoms alone are not reliable for the diagnosis of CAUTI[1][2][3][4][5][6][7][8]. For surveillance purposes, the US CDC's NHSN definitions have commonly been accepted and used in most published reports[9], despite these definitions being difficult to apply in practice[10]. The NHSN definitions are described below in the diagnosis section.

Alternative urinary drainage methods are available, such as clean intermittent ("in-and-out") urinary catheterization, external catheters that fit over or adhere to the genitalia ("condom" catheters), suprapubic catheters and nephrostomy tubes. Although UTIs associated with these methods may be considered device-associated, NHSN CAUTI definitions typically refer only to UTIs associated with indwelling urethral catheters. Hence, CAUTI will be taken to refer only to indwelling urethral catheters throughout this guideline.

Epidemiology

UTIs remain the commonest nosocomial infections worldwide, and have been estimated to cause approximately 30% of HCAIs in the acute care setting in the United States[11]. Of these, approximately 75% are associated with an indwelling urinary catheter.

The impact of CAUTI is likely to be even greater in Asia[12]. A surveillance study was conducted over 6 years by the International Nosocomial Infection Control Consortium in 422 ICUs of 36 countries in Latin America, Asia, Africa, and Europe, of which 57% were in Asia. The study found developing countries to have a rate of 6.3 CAUTIs per 1,000 urinary catheter-days, compared to 3.3 per 1,000 catheter-days in comparable US ICUs[13]. CAUTIs in developing countries were also associated with higher rates of antibiotic resistance on microbiological surveillance.

The sheer frequency of urinary catheter usage in most healthcare settings highlights the impact and significance of CAUTI in the healthcare system globally and in Asia[3][12][14][15][16][17][18]

Pathogenesis and risk factors

The presence of a urethral catheter will bypass or inhibit natural host defenses, predisposing patients to CAUTIs[19]. This is further exacerbated by the development of biofilm on the urinary catheters, which provides a favorable environment for bacterial proliferation & invasion[1][20]. Bacteria may be introduced into the urinary tract via several routes, such as:

1. Inoculation at the time of catheter insertion, especially in patients who have had inadequate disinfection of the perineum prior to catheterization.

2. Via intraluminal ascent in the urinary catheter lumen after contamination of the closed urinary catheter system (such as via breaks in aseptic practice during the emptying of the urinary drainage bag, or temporary disconnection of catheters from urinary bags).

3. Via extraluminal route of ascent along the external surface of the urinary catheter into the urethra.

The most common uropathogen isolated from the catheterized urinary tract is Escherichia coli. Other common organisms isolated in patients who had short-term catheterisation include Pseudomonas, Klebsiella, Proteus, Enterococcius and Candida species. Proteus mirabilis bacteriuria is often associated with catheter obstruction, and polymicrobial bacteriuria is commonly found in patients with long-term catheters[21]. Risk factors for CAUTI which have been identified in prospective observational studies include[19][22][23][24]

- Duration of catheterization
- Female gender
- Anatomical or functional abnormalities of the urinary tract
- Insertion of the catheter outside the operating room
- Diabetes mellitus
- Poor catheter care or breaks in aseptic technique

Diagnosis

Symptoms (physical examination)

Among patients without catheters with microbiology confirmed bacteriuria, the presence of symptoms attributable to an infection of the urinary tract has classically differentiated patients with asymptomatic bacteriuria from those with symptomatic UTI. These symptoms include fever, urgency, dysuria, hematuria, suprapubic pain and costovertebral angle tenderness[25][26][27].

However, this distinction may be difficult in some patients with chronic indwelling catheters, such as in patients with spinal cord injury, and patients who are unable to communicate due to illness, comorbidities or extremes of age[2][22][26][28][29] In particular, symptoms referable to the urinary tract have been found to be uncommon in patients with CAUTI for whom the catheter alone may be a source of symptoms, and have poor predictive value for differentiating CAUTIs from CAASBs4.

Criteria and classification

The criteria and classifications of CAUTI and CAASB, as adapted from the US NHSN3, are as detailed below in Table 1. There are other more complex classification criteria which have been developed8 for research purposes, but the NHSN criteria are most practical in the setting of surveillance and clinical decision making. Criteria for the categories of presence of indwelling urinary catheter, symptoms and positive microbiology must all be met to qualify for the diagnosis of CAUTI. Culture of indwelling urinary catheter is not recommended.

Table 1. Criteria and classification of CAUTI and CAASB

	Indwelling urinary catheter criteria	Symptoms criteria	Microbiological criteria
CAUTI	In place for >2 days, and the catheter was in place on the date of development of CAUTI	At least 1 of the following: • Fever >38°C • Suprapubic pain or tenderness • Flank pain or costovertebral angle tenderness	Positive urine culture of ≥10^5 CFU/ml, with no more than 2 species of microorganisms. OR Positive urine culture of ≥10^3 and <10^5 CFU/ml, with no more than 2 species of microorganisms, AND one of the following: • Positive urine dipstick for leukocyte esterase and/or nitrite • Pyuria (≥10 WBC/mm^3 of unspun urine or >5 WBC/high power field of spun urine • Microorganism seen on Gram's stain of unspun urine
	In place for >2 days, but removed on the day of, or the day before the development of CAUTI	At least 1 of the following: • Urgency, frequency or dysuria with no other cause • Fever >38°C • Suprapubic pain or tenderness • Flank pain or costovertebral angle tenderness	Positive urine culture of ≥10^5 CFU/ml, with no more than 2 species of microorganisms. OR Positive urine culture of ≥10^3 and <10^5 CFU/ml, with no more than 2 species of microorganisms, AND one of the following: • Positive urine dipstick for leukocyte esterase and/or nitrite • Pyuria (≥10 WBC/mm^3 of unspun urine or >5 WBC/high power field of spun urine • Microorganism seen on Gram's stain of unspun urine
CAASB	In place for >2 days, and either in place on the date of assessment, OR removed on the day of or the day before assessment	No symptoms of UTI, including: • Urgency, frequency or dysuria • Fever • Suprapubic pain or tenderness • Flank pain or costovertebral angle tenderness	Positive urine culture of ≥10^5 CFU/ml.

• Routine urine cultures in asymptomatic catheterized patients are not recommended.

Treatment

The treatment, management and prevention of CAUTIs are as follows:

Medication / Drug Therapy

Significantly higher rates of antibiotic resistance have been found in Asia as compared to Europe and North America[30]. In addition, clinical prescribing practices and availability of antibiotics differ between countries and healthcare facilities. Hence, no single set of recommendation for empiric antibiotics can be

made for the treatment of CAUTIs in Asia. Recommendations with regards to selection of antibiotics are detailed in Table 2. There is considerable controversy regarding the duration of treatment, the need to treat bacteriuria once catheters are removed[31], and the role of periodic treatment in spinal cord injured patients[32]. No general recommendation can be made for these situations.[33][34][35]

Table 2. Principles to guide selection of antibiotics

Recommendation	LE/GR
1. Monitoring of local antibiotic resistance patterns in uropathogens.	4/C
2. Urine cultures, preferably before initiation of antibiotic therapy, to guide choice of definitive antibiotic therapy.	4/C
3. Empiric antimicrobial therapy could be guided by recent prior urine culture results, where possible.[33]	2b/C
4. Early de-escalation of antibiotic therapy, as guided by urine culture results, to the narrowest spectrum antibiotic available.	4/C
5. Shorter 5 day course of antibiotics with catheter exchange may be considered in the treatment of CAUTI in patients with spinal cord injury.[34]	1b/B
6. CAASB should not be routinely treated with antibiotics.[2][35]	1b/B

Procedures and interventions

Asepsis of the urinary catheter system is vital for the prevention of CAUTI. Interventions towards this end have been recently been focused on the use of modified catheters, as well as aseptic insertion and maintenance of urinary catheters. Recommendations regarding the use of catheters are detailed in Table 3.
[36][37][38][39][40][41][42][43][44][45][46]

Table 3. Recommendations on the use of urinary catheters

Recommendation	LE/GR
1. Evidence for antibiotic or antiseptic impregnated or coated urinary catheters are as follows:[19][36][37][38][39] • Use of hydrophilic-coated catheters was associated with a lower incidence of CAUTIs.[37][38] • Antibiotic-impregnated catheters lowered rates of asymptomatic bacteriuria in the short term (less than 1 week), but this effect was not significant at longer durations.[19][36][39][40][41] • Silver alloy catheters significantly reduced incidence of asymptomatic bacteriuria, and may be considered. However, clinical impact on reduction of symptomatic CAUTI has not been determined, and increased costs of these catheters must be considered. Conversely, silver oxide catheters have not been found to decrease incidence of bacteriuria.[36][39][40][41] • Chlorhexidine coated urinary catheters have shown efficacy in preventing biofilm formation in in vitro and animal studies, but evidence for clinical efficacy are still lacking.[42][43]	1b/C
2. Alternative methods of bladder drainage with external and suprapubic catheters may be considered, but evidence of efficacy in preventing CAUTI remains limited.[44][45]	1b/C
3. Consider changing long-term indwelling urinary catheters prior to initiating antimicrobial therapy.[46]	1b/B

Prophylaxis, prevention and monitoring

Principles for prevention of CAUTI may be broadly classified under the following categories:

• Avoiding unnecessary urinary catheterization and minimizing duration of catheterization via close surveillance and reminder systems.

• Preserving aseptic condition and closed drainage of urinary catheter system during insertion and maintenance.

• Implementation of urinary catheter care bundles and infection control programs.

Specific recommendations are detailed in Table 4.[47][48][49][50][51][52][53][54][55][56][57][58][59][60][61][62][63][64][65][66][67][68][69][70][71][72][73][74][75][76][77][78][79][80][81][82][83][84]

Table 4. Recommendations for the prevention of CAUTIs

Recommendation	LE/GR
1. Early removal of indwelling urinary catheters reduces the risks of subsequent CAUTI[47] and other complications.[48]	2b/B
2. Heath care workers are often unaware about the presence of an indwelling catheter in patients.[49] This should be addressed, so as to minimize inappropriate use of indwelling catheters and reduce duration of catheterization.	3/B
3. Nurse generated or electronic-based reminder and stop-order systems for the removal of urinary catheters reduce utilization of indwelling catheters and rates of CAUTIs[50-68]	1a/B
4. Urinary catheter care bundles and infection control programs reduce rates of CAUTI.[2][9][69–79] These bundles and programs may include the following components: • Educational and training interventions on catheter indications,[80][81] insertion techniques, care and management. • Avoidance of indwelling catheter use, and the use of alternatives to indwelling urinary catheters where appropriate. • Aseptic catheter insertion technique by trained personnel, with all necessary supplies needed being made conveniently available. Records and indications for catheter insertion should be maintained. • Attention to hand hygiene practices • Surveillance and performance feedback systems.	2a/B
5. Secure and maintain integrity of closed urinary catheter systems, and prevent flow obstruction.[2]	3/B
6. No recommendation can be made for the routine use of antibiotic prophylaxis for the prevention of CAUTI: • The use of antibiotic prophylaxis during short-term urinary catheterization of up to 14 days in adult patients was reviewed in several randomized controlled trials. Meta-analysis showed only limited evidence in reduction of rates of bacteriuria, pyuria and febrile morbidity in surgical patients post-operatively, and reduction of symptomatic UTIs with antibiotic prophylaxis at the time of catheter removal.[32][82][83] • Meta-analysis on the use of antibiotic prophylaxis in patients requiring long-term intermittent or indwelling urinary catheterization showed inconsistent and limited evidence of efficacy.[84] • The decision to use antibiotic prophylaxis must consider local microbial prevalence and antibiotic resistance patterns, as well as risk-benefit ratio and cost considerations of the antibiotic. In Asia, it is unlikely that prophylaxis will be effective in view of high rates of antimicrobial resistance, and it might have the unintended consequence of selecting for even more resistant pathogens.	1a/D

Algorithm

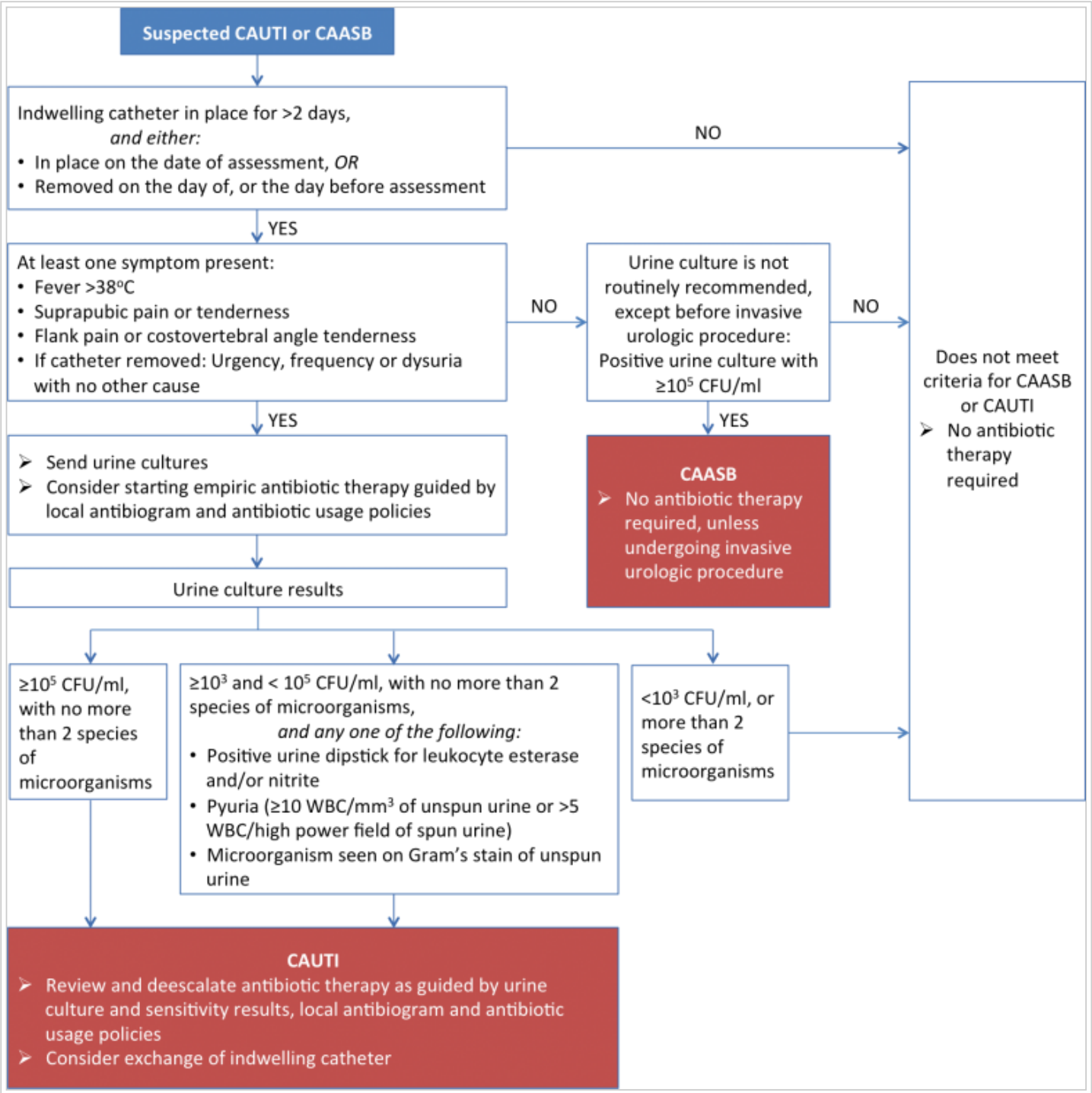

Figure 1. Algorithm for diagnosis, classification and management of CAUTI and CAASB

Abbreviations

CAASB: catheter-associated asymptomatic bacteriuria, CAUTI: catheter-associated urinary tract infection, CDC: Centers for Disease Control and Prevention, CFU: colony-forming unit, HAI/HCAI: healthcare-associated infections, ICU: intensive care unit, NHSN: National Healthcare Safety Network, US: United States, UTI: urinary tract infection, WBC: white blood cell

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Urogenital tuberculosis

From AAUS

Contents

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Executive summary

Epidemiology and Pathogenesis

1. Urogenital tuberculosis (UGTB) is a second-third frequent form of tuberculosis (TB), but a large proportion of patients is underdiagnosed (LE: 2).

2. UGTB includes urinary tract TB and male and female genital TB; exact wording is necessary for correct estimation of the epidemic situation (LE: 1).

3. UGTB is often (about 40%) associated with pulmonary TB (PTB) and/or other localizations of TB (actual or cured) (LE: 1).

4. Male genital tuberculosis (MGTB) is usually (over 50%) associated with PTB and/or renal TB (actual or cured), but isolated forms are also possible. More often the epididymis and prostate are involved (LE: 1).

5. The main route of infection is via hematogenous and lymphatic spread, but direct extension from infected urine and ejaculate spread is also possible (LE: 1).

Diagnosis

1. All patients with genital TB should be screened for chest and upper urinary tract involvement and human immunodeficiency virus (HIV) infection (GR: A).

2. At least three, but preferably five serial microbiologic studies with urine (including post-ejaculate and post-massage urine), ejaculate and prostate secretion including smears, cultures, including automated system Bactec (GR: A) and polymerase chain reaction (PCR), including geneXpert (GR: B) should be performed to make the diagnosis of UGTB.

3. In isolated external genital TB without renal and prostate involvement, diagnosis of MGBT is often only possible by histo-pathomorphology (GR: B).

4. In difficult cases a provocative subcutaneous tuberculin test is recommended (GR: B).

5. Radiologic studies are not useful for diagnosis of UGTB on early stages, before development of the tissue destruction (LE: 2).

6. For cavernous prostate tuberculosis retrograde urethrography is crucial (GR: A)

7. Fine needle aspiration cytology (FNAC) is an accurate and rapid diagnostic tool for scrotal TB, but may be complicated by TB generalization (GR: C).

8. If there is no evidence of *M. tuberculosis* (Mtb) diagnosis of UGTB may be made on the basis of skin-test, histological picture, caverns revealed by urography, sterile pyuria etc (GR: B).

9. Diagnosis of the iatrogenic (Bacillus Calmette–Guérin (BCG) - induced) bladder TB (complication of the BCG-therapy for bladder cancer) may be made by clinical features - significant dysuria and decrease of the bladder volume; confirmation only by histology, not by bacteriology (GR: C).

Treatment

1. Short term treatment for six to nine months is suitable in uncomplicated cases in regions with low incidence of TB (GR: B).

2. In complicated cases (relapse, immunosuppression, drug-resistance) and in epidemic regions anti-TB therapy should be longer, up to 12-14 months with four to five drugs (GR: B).

3. Multi-drug resistant tuberculosis (MDR-TB) should be treated with at least 5 anti-TB drugs for at least 18 months (GR: B).

4. BCG-induced bladder TB should be treated with 2 -3 anti-TB drugs for 2-4 months, if the volume is normal; if microcystis developed – cystectomy and following enteroplastic reconstructions are indicated with the same anti-TB therapy (GR: B).

Introduction

According to World Health Organization (WHO) reports, reviewed March 2014, about one-third of the world's population has latent TB, which means people have been infected by Mtb but are not (yet) ill with disease and cannot transmit the disease. People infected with Mtb have a lifetime risk of falling ill with TB of 10%. However persons with compromised immune systems, such as people living with human immunodeficiency virus (HIV), malnutrition or diabetes, or people who use tobacco, have a much higher risk of falling ill[1].

TB is second only to HIV/AIDS as the greatest killer worldwide due to a single infectious agent. In 2012, 8.6 million people fell ill with TB and 1.3 million died from TB. TB is a leading killer of people living with HIV causing one fifth of all deaths[1].

In 2012, the largest number of new TB cases occurred in Asia, accounting for 60% of new cases globally. UGTB is frequent form of TB, but it is a mostly overlooked disease. Despite major efforts to increase case detection, an estimated one third of new TB cases are still being missed each year, and the unavailability of a rapid, low-cost, accurate diagnostic assay that can be used at the point of care is a major hindrance. There are a very few multicenter randomized studies on UGTB because of absence of unique approach to definition, diagnosis, therapy and management of this disease.

Terms and definitions

The first note of UGTB was made by Porter in 1894[2]; in 1937 Wildbolz[3] suggested the term genitourinary TB. However, the term UGTB is more correct, because kidney TB (KTB), which is usually primary, is diagnosed more often than genital TB.

Urogenital tuberculosis (UGTB) - infectious inflammation of any urogenital organ - isolated or in combination (kidney and/or male or female genitals), - caused by Mtb or *M. bovis*.

Genital tuberculosis (GTB) – infectious inflammation of the female or male genitals – accordingly female genital tuberculosis (FGTB) or male genital tuberculosis (MGTB) caused by Mtb or *M. bovis*.

Kidney tuberculosis (KTB) - infectious inflammation of kidney parenchyma, caused by Mtb or *M. bovis*.

Urinary tract tuberculosis (UTTB) – infectious-allergic inflammation of calyx, pelvic and upper and lower urinary tract caused by Mtb or M. bovis, always secondary to kidney TB and should be considered as a complication of kidney TB.

Generalized urogenital tuberculosis (gUGTB) – generalized tuberculosis of the kidney and the male or female genitals, respectively.

Etiology of UGTB

There is a big family of *Mycobacterium* – but not all members of this family are pathogenic for human. *Mycobacterium tuberculosis* and *M. bovis* are combined in mycobacterial complex; they are obligatory pathogens for human organizm. In 80–95% UGTB is caused by Mtb, but *M. bovis* is also an etiological agent of TB[4][5][6], because tuberculosis is an anthropozoonotic infection. Bacillus Calmette–Guérin (BCG), which are in fact attenuated M. bovis, are widely used for the therapy of superficial bladder cancer. In some conditions BCG-therapy may be complicated by iatrogenic BCG-induced UGTB - mainly bladder or prostate TB, but in rare cases also BCG sepsis is possible[7][8][9][10].

Epidemiology of UGTB

Before anti-TB drugs were available, UGTB was an extremely frequent disease: every fifth patient treated in urological department had kidney TB (KTB), more than one third of all pyonephrosis were by TB etiology[11]. Now UGTB is the second most common form of TB in countries with a severe epidemic situation and the third most common form in regions with low incidence of TB; the share of UGTB among extrapulmonary TB accounts for 33.7–45.5%. In developed countries 2–10% pulmonary TB (PTB) patients have also UGTB[12][13]. In 20% PTB patients UGTB will develop later, after recovery from the first disease[14]. In Russia TB of bone and joints and UGTB has about the same frequency now[15].

Classifications of UGTB

UGTB includes many forms of TB with its own clinical features requiring specific therapy and management. Therefore correct clinical classification and staging are important for optimal management and therapy[16]. UGTB can be subclassified into the following entities: kidney tuberculosis and genital tuberculosis.

Kidney tuberculosis

There are four stages to be considered for Kidney tuberculosis:

Stage 1: TB of kidney parenchyma (non-destructive form, KTB-1).

Stage 2: TB papillitis (small-destructive form, KTB-2).

Stage 3: Cavernous kidney TB (destructive form, KTB-3).

Stage 4: Polycavernous kidney TB (widespread-destructive form, KTB-4).

Complications of kidney TB are chronic renal failure, fistula, high blood pressure.

Urinary tract TB includes

1) TB of ureter.

2) TB of the bladder is divided into 4 stages[16]:

Stage 1: tubercle-infiltrative;

Stage 2: erosive-ulcerous;

Stage 3: spastic cystitis, which in fact means overactive bladder;

Stage 4: contracted bladder up to full obliteration.

There is one more form of bladder TB, the iatrogenic BCG-induced bladder TB, which develops as a complication of BCG therapy for bladder cancer.

3) TB of urethra.

Male genital tuberculosis (MGTB) is subdivided into 4 categories

1) TB epididymitis (uni- or bilateral).

2) TB orchiepididymitis (uni- or bilateral).

3) TB of the prostate (infiltrative or cavernous forms).

4) TB of seminal vesicles.

5) TB of the penis.

Complications of MGTB are strictures, fistula, infertility, sexual dysfunction.

Female genital tuberculosis (FGTB) (is not included in this Chapter).

Generalized urogenital tuberculosis (gUGTB): simultaneous lesion of the kidney and the genital organs; gUGTB is always considered as a complicated TB.

Clinical features

Clinical features of UGTB have no specific signs, are instable and depend on many factors; this is one of the reasons for late diagnosis.

Clinical features of kidney TB

As whole KTB patients complain of flank pain (up to 80%) and/or dysuria (up to 54%). If the urinary tract is involved, then renal colic (24%) and gross-hematuria (up to 20%) are possible. Prostate TB manifests by perineal pain and dysuria, and in half of the cases by hemospermia. TB orchiepididymitis always starts from epididymitis, isolated TB orchitis does not exist. Oedema and swelling of the scrotal organs and pain are most often the first symptoms. In 68% there is an acute debut of the disease. Nevertheless, in 32-40% the disease has a chronic or asymptomatic course[15][16][17][18].

1) KTB-1 has minimal lesion without destruction, full recovery is possible by anti-TB drugs. Intravenous urography (IVU) is normal. Urinalysis in children is often normal, but in adults low level leucocyturia may be found. Usually patients have no complaints and are diagnosed by chance. KTB-1 is complicated very rarely. Prognosis is good, usually outcome is full recovery. With inappropriate therapy KTB-1 may progress to destructive form. KTB-1 should be confirmed by bacteriology in any case. Usually Mtb in KTB-1 patients are sensitive to anti-Tb drugs. Mtb detection in urine is always necessary for diagnosing kidney TB stage 1, but may not always be revealed in other forms of UGTB.

2) KTB-2 is subject to conservative therapy, but if KTB-2 is complicated by urinary tract TB, than reconstructive surgery is indicated. Prognosis is good; usual outcome is recovery with fibrous deformation and post-tuberculous pyelonephritis. With inappropriate therapy KTB-2 may progress to the next stage. Mtb is not detected in all cases and may be resistant.

3) KTB-3 has two ways of pathogenesis, from TB of parenchyma or from papillitis. The first way means development of a sub-cortical cavern without connection to the collecting system. The clinical manifestation of a sub-cortical cavern is similar to a renal carbuncle, thus the diagnosis is usually made after the operation. The second way is the destruction of the papilla until a cavern is developed. Complications develop in more than half of the patients. Full recovery by anti-TB drugs is impossible, surgery is generally indicated. The best outcome is the formation of a sterile cyst; a negative outcome is further destruction upto polycavernous TB.

4) KTB-4 means several caverns in the kidney; nevertheless overall renal function may be sufficient. KTB-4 may result in fistulas due to pyonephrosis. Self-recovery is also possible, when a stricture of the ureter locks the kidney and caseation in the caverns is impregnated by calcium, the so-called auto-amputation of the kidney. KTB-4 is almost always complicated; very often the contralateral kidney is involved. Recovery with anti-TB drugs only is impossible; surgery is necessary, basically nephrectomy.

Urinary tract TB

Urinary tract TB is a specific complication of KTB and so is always secondary to KTB. Urinary tract TB with any localization first appears as an oedema; the next stages are infiltration, ulceration and fibrosis.

1) TB of ureter usually develops in the lower third, but multiple lesions are possible, too. Incorrect therapy may lead to development of a ureteral stricture which may result in loss of the kidney, even if TB is finally cured.

2) TB of the bladder. The main symptom is frequency, then urgency, hematuria. The first two stages should be treated by standard anti-TB drugs; the 3-rd stage with standard anti-TB drugs and trospium chloride, and the 4-th stage is indicated for cystectomy with following enteroplasty.

3) TB of urethra. TB of the urethra is nowadays not a frequent complication; usually it is diagnosed at the stage of a stricture.

Male genital tuberculosis (MGTB)

1) TB epididymitis may be mono- bilateral; bilateral TB epididymitis is always secondary to prostate TB. Isolated TB epididymitis was found in 22% as accidental surgical finding[16][19].

2) TB of the testis is always secondary to infection of the epididymis, which in most cases is blood-borne because of the extensive blood supply of the epididymis, particularly the lobus minor. In 62% of patients with orchiepididymitis KTB is diagnosed as well. Every third patient has bilateral lesions. In about 12% the disease is complicated by fistulas[16][19]

3) TB of the prostate is an often under-diagnosed disease. Three quarters of men died from all forms of TB, had prostate TB, mostly overlooked alive[20]. Prostate TB is important due to the following:

- It may also be a sexually transmitted disease. Up to 50% of prostate TB patients have Mtb in their ejaculate if they are co-morbid with hepatitis and syphilis[21].
- It leads to infertility.
- It causes chronic pelvic pain like any other prostatitis, reducing significantly the quality of life[22].

- It decreases the sexual function, also reducing the quality of life[19]. In 79% prostate TB was accompanied by KTB, in 31% by TB orchiepididymitis, and in 5% isolated prostate TB was diagnosed[16].

4) TB of seminal vesicles is secondary to prostate TB and leads to infertility. As drainage of caseous ejaculate is difficult, TB of seminal vesicles exhibits a tendency to calcification[23].

5) TB of the penis is very rare, but can occur after sexual intercourse with infected females[24] or via a direct infection through a penile wound during ritual circumcision. Penile lesions present as ulcers on the glans or penile skin. Currently it is mainly a complication of BCG-therapy[25][26][27].

Risk factors for UGTB

UGTB has several risk and suspicious factors:

• contact with TB infection,

• TB of any other localization, whether active or cured, especially in disseminated forms,

• urinary tract infection (UTI) with frequent recurrences and resistant to standard therapy,

• UTI with persistent dysuria, leading to decreasing bladder volume,

• sterile pyuria,

• pyuria in all portions of 3-glass test in patient with epididymitis / orchiepididymitis,

• pyospermia and/or hemospermia,

• scrotal, perineal and lumbar fistulas.

Diagnosis

History

Risk factors for UGTB should be evaluated carefully.

Physical examination

A special attention should be paid to any fistula. In acute course of TB epididymitis hard painful enlarged epididymis intimate welded with testis is palpated. In chronic course epididymis is hard, enlarged, and painless with clear border from the testis; in 35–40% the lesion is bilateral. Digital rectal examination of the patient with prostate TB shows moderate enlarged tuberous prostate gland with weak pain. Again – scrotal and perineal fistulae are highly suspicious for TB[28].

Laboratory tests

1) Urinalysis. Leucocyturia was found in 90–100% of patients with KTB, and hematuria in 50–60% [16].

2) Bacteriology. In "before-antibacterial era" sterile pyuria was specific for KTB, but now up to 75% patients have non-specific pyelonephritis alongside with KTB and therefore common microflora and Mtb may be found in urine together[29][30][31]. To diagnose common UTI a bacterial growth of at least 103 CFU/ml is needed, but even one single Mtb is evidentiary of UGTB[16][32]. The diagnosis of UGTB is absolutely confirmed when Mtb is revealed, but in recent years only in half of TB patients Mtb could be found. Therefore in patients suspected of UGTB, but without documented evidence of Mtb, the clinical diagnosis of UGTB has to be made on the basis of other clinical features, such as skin-test, histological picture, caverns revealed by urography, sterile pyuria etc[16]. The spectrum of the methods for identification of Mtb is shown in the table 1.

Table 1. Spectrum of bacteriological investigations for UGTB diagnosis

Recommendation	LE	GR
Direct smear microscopy (Ziehl–Neelsen stain)	2	B
Luminescent microscopy	2	B
Solid culture methods (Lowenstein-Jensen, Finn-II medium)	2	B
Liquid culture methods (medium Middlbrook 7H9; commercial broth-based culture systems detect TB bacteria) Bactec MGIT	2	B
Polymerase chain reaction (PCR)	2	B
Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance (GeneXpert MTB/RIF)	2	B
Immune-ferment analysis ELISPOT	3	C
Interferon-gamma release assay (IGRA)	3	C
Isothermal microcalorimetry	3	C

3) Histology. Histological investigation may reveal epithelioid granuloma, caseous necrosis, but they are fast replaced with fibrous tissue especially due to non-optimal previous therapy. If the patient was treated with fluoroquinolones and amikacin for common UTI, which in fact masks UGTB, specific histological changes transform into fibrosis, and pathomorphological confirmation of the disease becomes impossible.

4) Ultrasound investigation. Renal ultrasound may give indirect evidence of UGTB only. As prostate TB in 79% is accompanied by KTB[19], pathological findings detected by renal ultrasound in patients with "chronic prostatitis" are very suspicious for UGTB. TB epididymitis and orchitis present as diffusely enlarged lesions, which may be homogeneous or heterogeneous and can also occur as nodular enlarged heterogeneously hypoechoic lesions[33]. Transrectal ultrasound may reveal hypo- and hyperechoic lesions of the prostate, predominately in the peripheral zone, but also as prostatolithiasis which in fact may be calcified zones of TB inflammation[34].

5) Radiological investigations is indicated for patients suspected of UGTB: plain X-ray films of the urinary tract may detect calcification in the renal areas and in the lower urogenital tract; IVU is indicated for patients with leucocyturia and/or abnormality on ultrasound investigations. Retrograde urethrography should be performed in all patients with genital TB to exclude caverns of the prostate. X-ray examination is very useful to detect cavernous forms of UGTB, both in KTB intravenous urogram (IVU) and prostate TB (urethrography), but multi-sliced computer

tomography is significantly more informative. In contrast-enhanced CT scan TB of the prostate or seminal vesicles can be seen as low density or cavitation lesions due to necrosis and caseation with or without calcification. Without calcification, the findings may be similar to pyogenic prostatic abscesses[35][36]. UGTB in early stages, however, has no specific radiological image.

6) Instrumental interventions for UGTB diagnostics are of limited value, especially nowadays.

6.1) Cystoscopy is indicated for all UGTB patients with dysuria. Persistent dysuria in KTB patient is suspicious of bladder TB, even without histological confirmation, which may be obtained in 12% of the patients with bladder TB stage 4 only[37]. Any mucosal pathology should be biopsied and investigated both by histology and bacteriology, although the absence of specific findings do not exclude the diagnosis of TB as was shown above.

6.2) Ureteropyeloscopy may accidentally reveal TB ulcers, especially when the procedure is performed to the patients with renal colic because of roentgen-negative stone.

6.3) Prostate biopsy should be performed only after urethrography in order to exclude caverns. Tissue of the prostate gland should be investigated by histology and bacteriology, at least by PCR[38][39].

6.4) Biopsy of scrotal organs. Fine needle aspiration cytology (FNAC) may be useful to diagnose TB of the external male genitals[40]. However, scrotal violation should be considered if the mass is malignant. Fatal complications due to fulminant generalization of TB have occurred after biopsies performed in non-treated patients with active UGTB.

7) Provocative tests. The Mantoux test is positive in more than 90% of TB patients, but it has no value in regions with a severe epidemic situation (e.g. China, Russia, India, and Pakistan), where almost all adults are infected with Mtb and thus all have positive skin tuberculin test. New Diaskintest has high specificity, but low sensitivity, and is not recommended for diagnosis of UGTB. Subcutaneous tuberculin provocative test is recommended[41].

8) Therapy ex juvantibus If the patient is suspected on UGTB, but there are no evidence of Mtb or typical histological findings, and data of tuberculin provocative test as well as X-ray imaging are unconvincing, the clinical diagnosis of UGTB has to be made on the basis of therapy ex juvantibus, which is sub-classified on two types. Therapy ex juvantibus 1st type is indicated to the patient with low suspicion for UGTB. Antibiotic which does not inhibit Mtb (fosfomycin, cefalosporins, and nitrofurantoin) is prescribed; a positive result allows excluding the diagnosis UGTB. If there remains doubt about the etiology of UTI, therapy ex juvantibus 2nd type is indicated. Therapy ex juvantibus 2nd type includes 2-4 antibiotics which inhibit only Mtb (isoniazid, PAS, protionamid, etionamid, ethambutol, pyrazinamide); positive result in two months allows establishing UGTB[41]. Detailed diagnostic algorithm is exhibited in the table 2.

Table 2. Recommendation for examination of the patients suspicious for UGTB

Recommendation	LE	GR
Key points of the epidemic history: contact with TB infection, TB in history, especially in childhood, living in the region with high prevalence of TB – now or earlier.	2	B
Key points of the medical anamnesis: torpid course of UTI, often recurrences, persistent dysuria, renal colic without stone, decreasing of bladder volume, hematuria, hemospermia, pyospermia, sterile pyuria.	2	B
Key point of physical examination – lumbar, scrotal or perineal fistula	2	B
Empiric therapy of the UTI in the region with high prevalence of TB should avoid antibiotics, which inhibit Mtb, masks UGTB, delayed diagnosis and makes worse results of bacteriological and histological investigations	2	B
Pathological material for bacteriological investigations includes: middle portion of morning urine stream (sediment), menstrual blood, expressed prostatic secretion, ejaculate, post-massage urine (sediment), post-ejaculate urine (sediment), tissue specimens after biopsy or surgery, pus from fistula	2	B
Ultrasound renal investigation	2	B
Transrectal ultrasound investigation	2	B
Kidney biopsy	3	C
Biopsy of scrotal organs	3	C
Biopsy of bladder wall	2	B
Prostate biopsy	2	B
Complex radiological investigation	2	B
Provocative subcutaneous tuberculin test	3	C
Therapy ex juvantibus 1-2 type	3	C

If there is no evidence of Mtb diagnosis UGTB in patient with high risk of the development of the disease may be made on the basis of results of skin-test, histological picture, caverns revealed by urography, sterile pyuria etc[16].

Therapy

The main principles of anti-TB chemotherapy are: continuity, controllability, succession of the treatment. The patient has to take minimum 4 anti-TB drugs simultaneously during a minimum of 4 months, depending on the form UGTB. Neglecting of these principles leads to development of drug-resistance of Mtb and relapse of TB. The classification of the anti-TB drugs is given in Table 3.

Table 3. The classification of the anti-TB drugs

First line anti-TB drugs (basic)	Second line anti-TB drugs (reserve)	Third line drugs for special clinical situation
Isoniazid (H)	Protionamyd (Pt) /Etionamyd (Et)	Amoxicillin-clavulanate
Rifampicin (R)	Kanamycin (K)	Meropenem
Pyrazinamide (Z)	Amikacin (A)	Imipenem
Streptomycin (S)	Capreomycin (Cap)	Clarithromycin
Ethambutol (E)	Cycloserin (Cs)	Linezolid
	Rifabutin (Rb)	
	Para-aminosalicylic acid (PAS)	
	Fluorquinolons (Fq)	
	Bedaquilin (Bq)	
	Perhlozone (Pz)	
	Terizidon (Tz)	

Etiotropic therapy

The therapy for UGTB differs from the therapy of PTB. Thus, streptomycin and kanamycin are not recommended for UGTB; among fluoroquinolones ofloxacin or levofloxacin only are suitable for UGTB therapy. Moxifloxacin and sparfloxacin are respiratory fluoroquinolones, so they are good for PTB, but not optimal for UGTB.

PAS is highly recommended for UGTB with involvement of pelvic organs, amoxicillin/clavulanate should be prescribed together with meropenem or imipenem, as they potentiate anti-TB effect. Cycloserin is highly recommended, if the patient has comorbidity of UGTB and non-specific UTI. Patient with comorbidity of UGTB and HIV and receiving anti-retrovirus therapy should be treated with rifabutin instead of rifampicin. Rifampicin and streptomycin are contraindicated for patients after organ transplantation. Amikacin as well as streptomycin and kanamycin are contraindicated for UTTB patients.

Depending on the form of UGTB 5 regimes of chemotherapy are defined:

Regime I is applied in new-revealed treatment-naive patients with drug-susceptible (or if there was no growth of Mtb) non-complicated KTB 1-2 stages, isolated TB epididymitis, patients who were diagnosed by histology after organ-removed surgery performed in general urology, if there is no other TB focus.

Regime II is applied in new-revealed treatment-naive patients with drug-susceptible (or if there was no growth of Mtb) non-complicated KTB 3-4 stages.

Regime III is applied in new-revealed treatment-naive patients with drug-susceptible (or if there was no growth of Mtb) KTB 4 stage, KTB any stage complicated by UTTB, prostate TB, gUGTB.

Regime IV is applied in patients with relapse of UGTB, with high risk of MDR, independent on stage and form.

Regime V is applied in patients with MDR-UGTB, independent on the stage and form.

Every regime includes the phase of intensive therapy followed by the continuation phase (see Table 4).

Table 4. Standard schemes of a chemotherapy for UGTB

Regime	Phase	
	Intensive	**Continuation**
I	2 H R Z E / Am	4 H R / 6 H_3 R_3
II	1 H Z R Ofl/Lef Cs/Am +2 H Z R Cs/Am	5 H Z R / 6 H_3 R_3 E_3
III	2 H Z R Ofl/Lef Cs/PAS +2 H Z R Cs/PAS	4 H Z R / 5 H_3 R_3 E_3
IV	4 Cap Z Ofl/Lef Cs /PAS /Pt(Et) + 2 Cap Z Cs /PAS /Pt(Et)	6 E Z PAS/ Pt(Et)
V	Accordingly to sensitivity of Mtb Not less than 5 drugs 6-8 Cap Z Ofl/Lef Cs /PAS /Pt(Et)/ E /Rb/ /Cs [Amx Imp Clr Mp]	Not less than 4 drugs E Pt Ofl/Lef Rb Cs PAS[Amx Imp Clr Mp] Length not less than 18 months

- Abbreviations: see Table 3.

Abbreviations see Table 3

The dosage depends on the weight; recommended ones are given in Table 5.

Table 5. Recommended daily dosage of antituberculous drugs for adults (mg)

Drug	Patient's weight		
	33-50 kg	51-70 kg	More than 70 kg (max.)
Isoniazid	300	300-600	600
Rifampicin	450	450-600	600
Pyrazinamide	1000-1500	1500-2000	2500
Amikacin	500-750	1000	1000
Ethambutol	800-1200	1200-1600	1600-2000
Levofloxacin	500	500-750	750-1000
Ofloxacin	400-800	800	800-1000
Protionamid/ etionamid	500	750	750-1000
Capreomycin	500-750	750-1000	1000
PAS	3000 -5000	5000-8000	8000-12000
Cycloserin	500	500-750	750-1000

Anti-TB drugs may be prescribed per os, but parenteral administration (optimal intravenous infusion) is preferable, as it provides better control and minimizes side effects.

Pathogenetic therapy

Some pathogenetic medications are used as additional treatment: tocopferol, canephron; trospium chloride for bladder TB 3 stage, afala and prostanorm for prostate TB etc[16][42].

Surgery for UGTB

UGTB like any other UTI may and should be cured conservatively (if it is diagnosed in-time). Surgical intervention is indicated for KTB 3-4 stages, for correction of complications (UTTB).

Table 6. Surgical treatment for UGTB

Indication	Surgery	GR
1. Kidney TB:		
KTB-3, resistant to standard therapy (notably cavern with pyogenic layer remains, Mtb in urine, pyuria) for 2-4 months	Cavernectomy (partial nephrectomy), optimal – laparoscopically.	A
KTB-4	Nephrectomy, optimal – laparoscopically	A
2. Urinary tract tuberculosis:		
Stricture of ureter, urethra	Standard plastic operation	A
Bladder TB 4 stage	Cystectomy (in male patients – cystprostatectomy) with following enteroplastic by standard technique	A
3. TB epididymo-orchitis:		
Fluctuation, abscess	Incision of abscess and drainage	A
Torpid course with low efficiency of conservative treatment for 1-2 months	Orchidectomy	A
4. Prostate TB: *(Normally, prostate TB is not indicated for surgery.)*		
Development of abscess	Drainage of abscess	A

All surgical interventions should be performed on the background of anti-TB therapy, the exact time point will be estimated after histological investigation of the removed tissue[37][39][40].

BCG-induced UGTB

The intravesical bacillus Calmette-Guerin (BCG) after transurethral resection in Ta and T1 bladder cancer provides a significantly better prophylaxis of tumor recurrence than TUR alone, and superiority of BCG over mitomycin C for prevention of tumor recurrences has been shown as well. Instillation of BCG causes specific inflammation of the bladder mucosa that kills cancer cells – but it should be controlled local temporary inflammation. The loss of the control results in the spread of infection. Systemic dissemination of bacilli may lead to development of generalized BCG-induced TB, when all organs, including meninges are involved in TB inflammation. Among urogenital complications of BCG-therapy bladder TB is most common, TB orchiepididymitis and TB of penis and rare. Frequency of BCG induced granulomatous prostatitis differs from 3 to 75%. In the majority of the cases the patients are asymptomatic and only rarely (0.9–1.3%) are there clinical complaints, slight induration of the prostate or elevated PSA level[43]. Mycobacterial prostatitis does not require anti-TB therapy as it is clinically insignificant, but rather close monitoring[44][45].

Diagnostic criteria for BCG-induced bladder TB are: dysuria and pyuria in 3 weeks after the instillation of BCG, decreasing of the bladder volume. Patho-histological confirmation is crucial, but in about 50% only fibrosis and inflammation may be found in the biopsies. Microbiology is not helpful. Involvement of the detrusor and development of a shrinked bladder represent the clinical background or the so-called iatrogenic BCG-induced bladder TB.

Iatrogenic BCG-induced bladder TB should be treated with rifampicin 0.6 and isoniazid 0.6 for 2 months; if there is also growth of non-specific microflora in urine – in addition levofloxacin 0.5 daily should be prescribed. If in 8 weeks patients became well – without dysuria and normal urinalysis – anti-TB therapy is finished. If in 8 weeks the dynamic is good, but patient isn't still recovery – anti-TB therapy should be continued for more two months. If in 8 weeks of the therapy with rifampicin and isoniazid result is poor and bladder volume is 100 ml and less – cystectomy (in male patients – cystprostatectomy) is indicated with following enteroplastic; after surgery therapy with rifampicin, isoniazid and levofloxacin should me continued for at least 2 months – till full recovery (normal urinalysis, sufficient bladder volume).

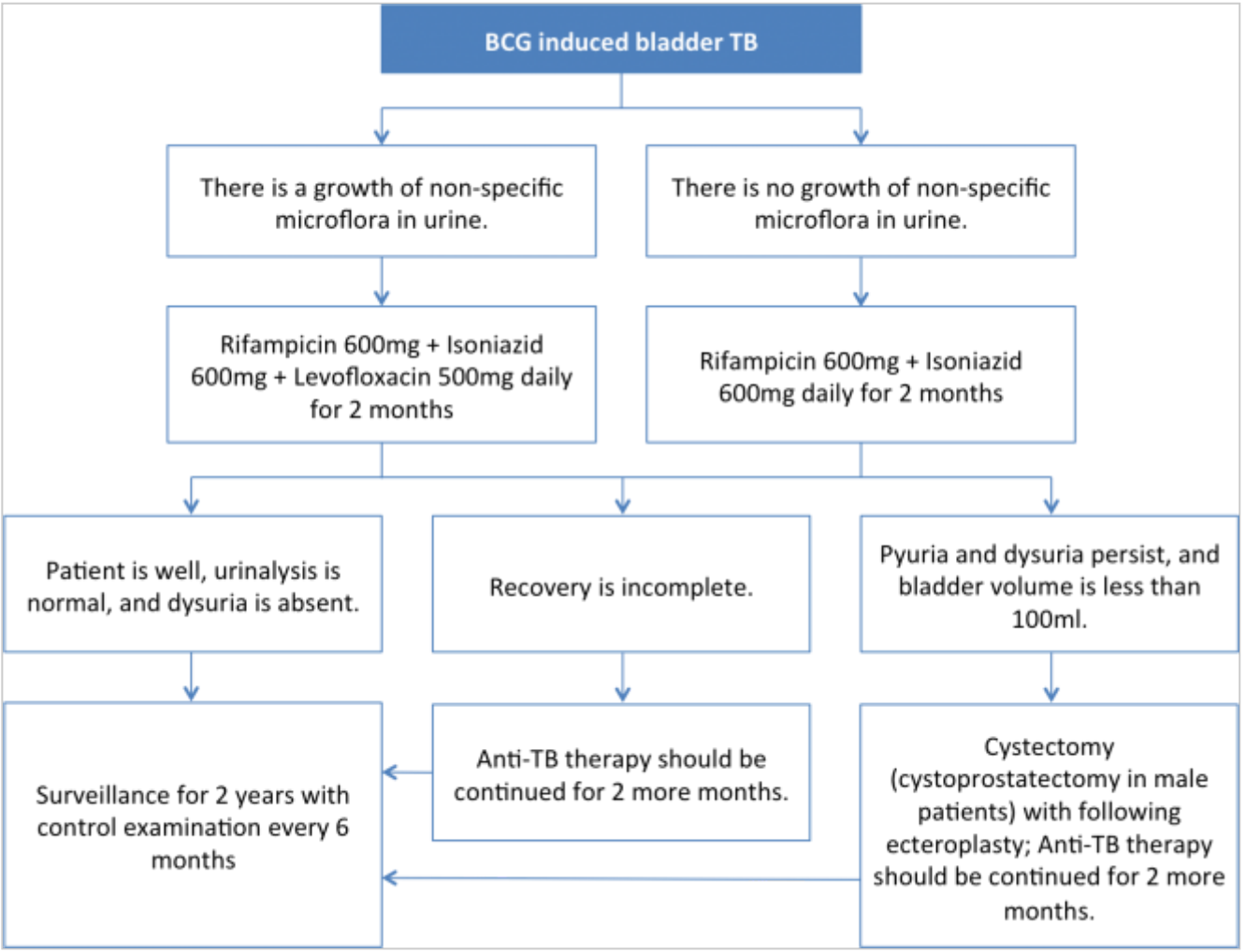

Figure 1. Algorithm of the management of BCG-induced UGTB patient

To prevent this complication vaccine shouldn't be introduced in time of cystitis. If a patient has dysuria and leucocyturia – BCG-instillation is contra-indicated, and therapy with non-steroid anti-inflammatory drugs and nitrofurantoin or fosfomycin for 3-5 days should be prescribed. BCG-therapy may be continued only when symptoms of cystitis improved. The scheduled BCG regimen shouldn't be resumed after recovering of BCG-induced TB.

Patients with BCG-induced orchiepididymitis should be treated with rifampicin 0.6 + isoniazid 0.6 + levofloxacin 0.5 daily for 2 months, in case of abscess formation orchiectomy is indicated. Patients with symptomatic BCG-induced prostatitis should be treated with rifampicin 0.6 + isoniazid 0.6 + levofloxacin 0.5 daily for 4 -6 months up to dissolving symptoms, with following surveillance for 2 years with control examination each 6 months.

Follow-up and prevention

Patients with UGTB should be followed-up for control of eradication or if symptoms persist or recur after completion of the therapy every 6 months for 1-3 years, depending on form and stage of the disease.

To prevent a relapse repeated short-course (for 2 months) therapy with isoniazid and rifampicin is recommended for patients with complicated UGTB; in MDR-UGTB preventive therapy is prescribed accordingly to the sensitivity of Mtb.

Specific prophylaxis from UGTB is absent now.

Abbreviations

BCG: Bacillus Calmette–Guérin, FGTB: female genital tuberculosis, FNAC: Fine needle aspiration cytology, gUGTB: Generalized urogenital tuberculosis, HIV: human immunodeficiency virus, IVU: Intravenous urography, KTB: Kidney tuberculosis, MGTB: male genital tuberculosis, MDR: multi-drug resistant, Mtb: Mycobacterium tuberculosis, PCR: polymerase chain reaction, PTB: pulmonary tuberculosis, TB: tuberculosis, UGTB: Urogenital tuberculosis, UTI: urogenital tract infection, UTTB: urinary tract tuberculosis, WHO: World Health Organization

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UTIs in children

From AAUS

Contents

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Executive summary

Epidemiology and pathogenesis

1. Classification according to the sites of infection (lower tract versus upper tract), the number of episode (first versus recurrent), the severity (simple versus severe), or the existence of complicating factor (uncomplicated versus complicated) is useful to differentiate children with UTI whether they are at risk of renal damage or not (LE: 2, GR: B).

2. The presence of UTI should be considered on the basis of clinical presentation, the age of the child, and the severity of the disease. However, clinical symptoms/signs are not sufficiently accurate to definitively diagnose UTI (LE: 1a, GR: A).

Diagnosis

1. Diagnosis of UTI requires both urinalysis that suggests infection and positive urine culture (LE: 3, GR B). For pre-toilet trained children, urine specimen for culture should be collected by urethral catheterization or suprapubic aspiration. For toilet trained children, midstream clean

catch urine is reliable (LE: 3, GR: A). Urine culture is considered positive if it demonstrates growth of a single bacterium with the following colony counts: (1) any growth by suprapubic aspiration, (2) $>5 \times 10^4$ CFU/ml by urethral catheterization, or (3) $>10^5$ CFU/ml by midstream clean catch (LE: 3, GR: B).

2. The goals of imaging studies are to localize the infection (lower or upper tract UTIs), to demonstrate anatomical or functional abnormalities, to detect significant VUR, and to detect congenital or acquired renal scarring (LE: 2, GR: B).

3. For children with febrile UTI, renal and bladder ultrasonography (RBUS) should be routinely performed as soon as possible (LE: 3, GR: C). RBUS should be followed up 6 months later in children with acute pyelonephritis and/or VUR (LE: 3, GR: C).

4. Acute DMSA scan can be performed when severe acute pyelonephritis or congenital hypodysplasia is noted on RBUS or when the diagnosis of UTI is in doubt by the clinical presentation (LE: 3, GR: C). Late DMSA scan (> 6 months after the febrile UTI) can be performed in children with severe acute pyelonephritis, high-grade VUR, recurrent febrile UTIs, or abnormal renal parenchyma on the follow-up RBUS (LE: 3, GR: C).

5. Top-down or bottom-up approach for febrile UTI is suggested for the diagnosis of VUR. For top-down approach, VCUG should not be performed routinely for children after the first febrile UTI. VCUG is indicated when abnormalities are apparent on either RBUS or DMSA scan or both (LE: 2, GR: B). VCUG is also suggested after a repeat febrile UTI (LE:2, GR: B). The bottom-up approach consists of a RBUS and a VCUG for the initial investigation for febrile UTI (LE: 2, GR: B).

Treatment

1. Appropriate antibiotic should be given immediately after urine specimen for culture has been obtained (LE:2, GR: A). Initiating therapy with oral or parenteral antibiotics is equally efficacious for children (> 3 months) with uncomplicated UTI (LE: 2: GR: A).

2. The choice of empirical antibiotic agents is guided by the expected pathogen and the local resistance patterns (LE: 2, GR: A). For children with febrile UTI, the total course of antibiotic therapy should be 7-14 days (LE: 2, GR: B).

3. The potential benefit of preventing recurrent UTI by antimicrobial prophylaxis should be weighed against the risk of antimicrobial resistance with future infections. (LE: 2, GR: B)

4. Antimicrobial prophylaxis to prevent recurrent UTI may be considered in infants and children with or without vesicoureteral reflux (VUR) after a first UTI. (LE: 1b, GR: B)

5. Circumcision may, but not definitively, reduce the risk of febrile UTI in males and breakthrough febrile UTI in males with VUR. Circumcision should be offered to uncircumcised boys with febrile UTI and VUR in countries where circumcision is accepted by the general population (LE: 3, GR: B), while in countries where childhood circumcision is rarely performed, other measures for febrile UTI/VUR should be the preferred choice (LE: 4, GR: C).

6. BBD is one of the key factors of progression of renal scarring (LE: 2). Early recognition and management of LUTD and bowel dysfunction are important in prevention of UTI recurrence (LE: 2, GR: A).

7. Despite the concerns about ionizing radiation and its invasive nature, conventional VCUG remains the gold standard to detect VUR because the test allows better determination of the grade of VUR (in a single or duplicated kidney) and better assessment of bladder and urethral configuration (LE: 2, GR: B).

8. Antibiotic prophylaxis to prevent recurrent febrile UTI is indicated in children with moderate to high grade (III-V) VUR (LE: 1b, GR: A).

9. Surgical intervention should be used to treat VUR in the setting of recurrent febrile UTI because it has been shown to decrease the incidence of recurrent pyelonephritis (LE: 2, GR: B).

Prevention

1. Bladder dysfunction increases the risk of UTI and can lead to significant delay in resolution of VUR. (LE: 2, GR: B)

2. Breast feeding may protect infants from UTI (LE: 2), and is strongly recommended for prevention of UTI in infants (LE: 3, GR: A).

3. Cranberry and related products may prevent UTI in children (LE: 3) and may be considered in the prevention of UTI in children (GR: C).

4. Probiotics may prevent UTI in children and in children (LE: 3) and may be considered in the prevention of UTI in children (GR: C).

Introduction

Urinary tract infection (UTI) is a common infection in children and infants around the world. Many existing guidelines for pediatric UTI come from Western countries. To our knowledge, only few guidelines come from Asian countries. Management of pediatric UTI should be based on scientific evidence and tailored to local cultural and social environment.

UTI represents the most common bacterial infection in children ≦2 years of age[1] (LE: 2a). The outcome of UTI is usually benign, but in early infancy, it can progress to renal scarring, especially when associated with febrile UTI. Delayed sequelae related to renal scarring include hypertension, proteinuria, renal damage and even chronic renal failure in a significant number of adults[2] (LE: 2a). The risk of UTI during the first decade of life is 1% in males and 3% in females[3]. The incidence of UTI is higher in boys than girls ≦3 months of age. The overall recurrence rate for the neonatal period has been reported to be 25% and that for toilet trained children is 30-50%[3] [4].

The common pathogens are Gram-negative, mainly enteric, bacteria. Of these, *E. coli* is responsible for more than 80% of UTI episodes[5]. The urinary tract is a sterile space with an impermeable lining. Retrograde ascent is the most common mechanism of infection. Nosocomial infection and involvement as part of a systemic infection are less common[6].

Risk factors for the development and recurrence of UTI should be explored and managed. Neurogenic and non-neurogenic lower urinary tract dysfunction may lead to elevated post-void residual urine (PVR) and secondary VUR[4]. Comprehensive approach for UTI in children without neuropathic bladder is summarized in Figure 1.

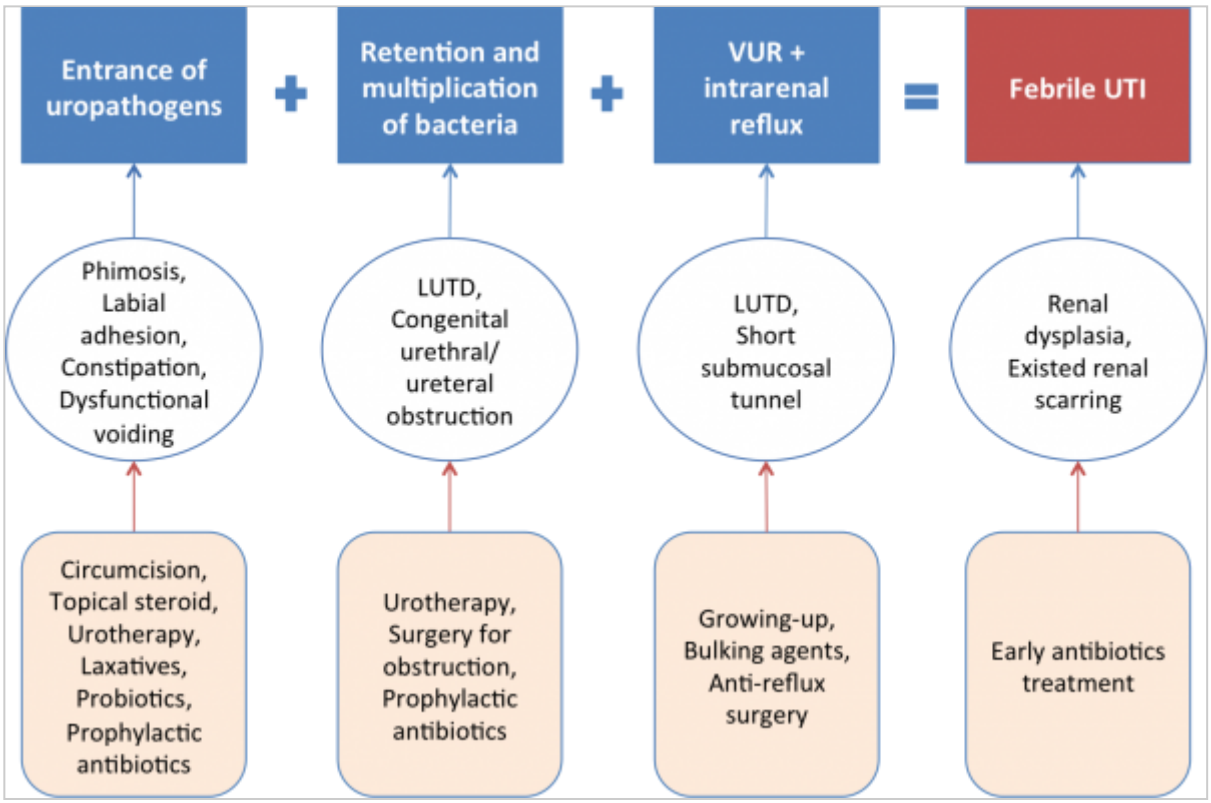

Figure 1. Comprehensive approach for risk factors and treatment for pediatric febrile UTI

Classification of Urinary Tract Infections in Children

Summary of Recommendations

Classification according to the sites of infection (lower tract versus upper tract), the number of episode (first versus recurrent), the severity (simple versus severe), or the existence of complicating factor (uncomplicated versus complicated) is useful to differentiate children with UTI whether they are at risk of renal damage or not (LE: 2, GR: B).

Introduction

Many classification systems have been introduced to identify children with UTI whose kidneys are at risk or not. UTIs can be classified by the site of infection (lower tract versus upper tract), by the number of episode (first versus recurrent), by severity (simple versus severe), by the presence of symptoms (asymptomatic versus symptomatic), or by the existence of complicating factor (uncomplicated versus complicated) (Table 1). Such classifications imply severity of infection when, in fact, this cannot be documented clinically nor may "milder" infections require less rigorous evaluation.

Table 1. Classifications of urinary tract infections in children
1. Classification according to site Lower urinary tract (cystitis) Upper urinary tract (pyelonephritis)
2. Classification according to episode (complication possibility) First infection Recurrent infection Unresolved Persistence infection Reinfection
3. Classification according to severity (complication possibility) Simple UTIs Severe UTIs
4. Classification according to symptom Asymptomatic bacteriuria Symptomatic bacteriuria
5. Classification according to complicating factor (complication possibility) Uncomplicated UTIs Complicated UTIs

Classification according to site of UTIs

Understanding and appropriately differentiating cystitis from pyelonephritis is crucial and imperative for two reasons: (a) to permit identification, treatment, and evaluation of the children who are at risk for kidney damage; and (b) to avoid unnecessary evaluation and treatment of children who are not at risk.

Classification according to the number of UTI episode

UTI can be cateGR:ized as first infection and recurrent infection. The recurrent UTIs can be sub-categorized further as unresolved bacteriuria, bacterial persistence, or reinfection[7][8][9][10].

First infection is simply the initial UTI that is diagnosed. Recurrent infection can be subgrouped as unresolved infection, bacterial persistence and reinfection. Unresolved infection indicates that initial therapy has been inadequate in eliminating bacterial growth in the urinary tract. Bacterial persistence is caused by reemergence of bacteria from a site within the urinary tract and may be due to a nidus for persistent infection that cannot be eradicated. As a result, the same pathogen is identified in recurrent infections, but episodes of sterile urine may occur during and shortly following antimicrobial treatment. Bacteria reside in an isolated portion (or anomaly) of the urinary tract where the pathogens are shielded from the current treatment, resulting in a persistent nidus of infection (e.g., infected staghorn stones, Table 2)[7].

Table 2. Surgically correctable causes of bacterial persistence in children
Infection stones
Infected nonfunctioning or poorly functioning kidneys or renal segments
Infected ureteral stumps after nephrectomy
Vesicointestinal or urethrorectal fistula
Vesicovaginal fistula
Infected necrotic papillae in papillary necrosis
Unilateral medullary sponge kidney
Infected urachal cyst
Infected urethral diverticulum or periurethral gland

Reinfection is different from bacterial persistence. In reinfection, each episode can be caused by a variety of new infecting organisms, whereas in bacterial persistence, the same infecting organism is always isolated. Reinfection most frequently occurs by the fecal-perineal-urethral route in girls and periurethral colonization in boys. Confusion in this form of pathogenesis sometimes occurs because Escherichia coli, the most common general pathogenic species which exist in many different serotypes. Thus, recurrent *Escherichia coli* UTI does not equate to infection with the same organism. With serotyping, reinfection can be established, but this is done rarely in the routine clinical setting.

Classification according to severity of UTIs

From the clinical point of view, simple and severe forms of UTIs should be differentiated because to some extent the severity of symptoms dictates the degree of urgency with which investigation and treatment are to be undertaken (Table 3).

Table 3. Clinical classification of pediatric urinary tract infections (UTIs) according to severity

Severe UTI	Simple UTI
Fever >38.5°C	Mild pyrexia
Persistent vomiting	Good fluid intake
Serious dehydration	Slight dehydration
Poor treatment compliance	Good treatment compliance

Classification according to symptom

This classification system is based on the existence of local or systemic symptoms.

Classification according to complicating factor

Useful criteria for distinguishing complicated from uncomplicated UTI are summarized in the Table 4[11].

Table 4. Clinical classification of pediatric urinary tract infections according to complicating factors

History	Complicated UTI	Uncomplicated UTI
Age	<3 months	>3 months
Systemic symptoms	+	-
Known urologic anomaly	+	-
Physical examination		
Fever	+	-
Flank pain	+	-
Abdominal or flank mass	+	-
Laboratory findings		
Unusual pathogen	+	-
Azotemia	+	-
Leukocytosis	+	-
Radiologic indication of obstruction	+	

Conclusions

For the practical purposes, four kinds of classification (lower tract versus upper tract, first versus recurrent, simple versus severe or uncomplicated or complicated) are widely used. Such classifications are based on the natural history and subsequent evaluation and management which imply possibility of complication.

Diagnosis of the initial UTI in infants and children

Summary of Recommendations

1. Clinical symptoms and signs

The presence of UTI should be considered on the basis of clinical presentation, the age of the child, and the severity of the disease. However, clinical symptoms/signs are not sufficiently accurate to definitively diagnose UTI (LE: 1a, GR: A).

2. Urinalysis and urine culture for diagnosis of UTI

Diagnosis of UTI requires both urinalysis that suggests infection and positive urine culture (LE: 3, GR B). For pre-toilet trained children, urine specimen for culture should be collected by urethral catheterization or suprapubic aspiration. For toilet trained children, midstream clean catch urine is reliable (LE: 3, GR: A). Urine culture is considered positive if it demonstrates growth of a single bacterium with the following colony counts: (1) any growth by suprapubic aspiration, (2) $>5 \times 10^4$ CFU/ml by urethral catheterization, or (3) $>10^5$ CFU/ml by midstream clean catch (LE: 3, GR: B).

UTI is a common serious bacterial infection in childhood. Accurate and timely diagnosis and treatment is important for the prevention of long-term morbidity and sequelae (e.g. hypertension, proteinuria, and chronic kidney disease). The symptoms and signs of UTI are very broad and largely depend on the age of the patients. Young children with UTI may present non-specific symptoms. Fever may be the sole presentation in young infants and is considered as an

important marker of renal parenchymal involvement. Among children 2 to 24 months of age with a fever without obvious source, prevalence of UTI is about 5% [12]. Neonates and young infants with febrile UTI are more likely to have bacteremia or sepsis than older children and should be carefully evaluated and managed[13]. UTI in infants can manifest as diverse and non-specific symptoms. Fever, sepsis, lethargy, prolonged jaundice, hematuria, poor feeding, vomiting, diarrhea, irritability, failure to thrive, cloudy or malodorous urine, and crying on passing urine are the possible presentation in newborn and young infants. Older children are able to verbalize better specific symptoms, such as dysuria, frequency, urgency, new onset urinary incontinence, abdominal or flank pain, suprapubic discomfort, and vomiting. In older children, the presence of specific urinary symptoms can be used as a criterion for further examination[14]. A critical review concluded that although individual symptom and sign were helpful in the diagnosis of UTI, no individual symptom/sign or any combination of them were sufficient enough to identify children with UTI[15].

Investigation for UTI starts by examining the urine. For pre-toilet trained children, urinalysis and urine culture can be collected from suprapubic aspiration or urethral catheterization when the child is ill and require immediate antibiotic therapy. A fresh bag urine specimen can also be used and examined as an initial screening tool. Numerous studies and meta-analyses have examined their accuracy to predict or exclude UTI in children (Table 5)[16][17]Finnell 2011). To diagnose UTI, urinalysis should focus on biochemical analyses of leukocyte esterase and nitrite through a rapid dipstick method and urine microscopic examination for pyuria and bacteriuria. Positive leukocyte esterase is comparable to pyuria (WBC≧ 5/HPF) by microscopy. False positive results may be caused by external contamination (vulvovaginitis), viral infection (roseola infantum), Kawasaki disease, acute appendicitis, or vigorous exercise. Nitrite test has a low sensitivity (about 50%) but high specificity (98%) for pediatric UTI. Therefore, negative result of nitrite test does not rule out UTI. However, when the test is positive, UTI is very likely. A recent study shows dipstick may be an adequate screening test for UTI with a negative predictive value of 98.7%. Adding microscopy increases the negative predictive value to 99.2% but results in 8 false-positive tests for every UTI missed by dipstick[18]. Enhanced urinalysis by hemocytometer (≧ 10 WBC/μL in a counting chamber or any bacteria found in 10 oil emersion fields) has greater sensitivity and specificity than standard urinalysis (Table 5) [19][20].

Table 5. Diagnostic value of dipstick and microscopy for the diagnosis of urinary tract infections

Test	Sensitivity % (95% CI)	Specificity (95% CI)
Leukocyte esterase	79 (73-84)	87 (80-92)
Nitrite	49 (41-57)	98 (96-99)
Either leukocyte esterase or nitrite positive	88 (82-91)	79 (69-87)
Both leukocyte esterase and nitrite positive	45 (30-61)	98 (96-99)
Microscopy, WBCs	74 (67-80)	86 (82-90)
Microscopy, unstained bacteria	88 (75-94)	92 (93-96)
Microscopy, Gram-stain	91 (80-96)	96 (92-98)
Enhanced urinalysis (≧10 WBC/μL or bacteria)	95(94-96)	89 (84-93)

Physical examination should include determining the presence of phimosis, labial adhesion, and any stigmata of spinal bifida. Nonspecific tests of inflammation (such as elevated peripheral white blood cell count, C-reactive protein, or sedimentation rate) can provide helpful guidance. However, they are not considered useful diagnostic tools to identify acute pyelonephritis because of a low specificity[21]. Procalcitonin is considered the best parameter to predict the presence of renal parenchymal involvement[21].

Without contamination of perineal flora, suprapubic aspiration has been considered the standard method for urine culture in young children. Urine specimen via catheterization is associated with a higher success rate and less pain than suprapubic aspiration (Finnell, 2011). Suprapubic aspiration and transurethral catheterization are strongly recommended from 2011 AAP guidelines for children aged 2-24 months[17]. For toilet trained children, urine specimen for culture can be obtained by midstream. Urine cultures collected from a bag applied to the perineum is not suggested due to unacceptably high false-positive rates (85%) (Finnell 2011).

Definitions of positive or negative culture results are related to the methods of collection. The distal urethra or perineal area is always colonized by some fecal bacteria. Although bacteria are not present in bladder urine, a low colony count may be present in a specimen collected through voiding or catheterization. As a result, a significant colony count depends on the method of urine collection and clinical symptoms. The cutoff values for positive culture results are operational and not absolute. In the 1950s, Kass in his study on adult women established the threshold of 10^5 CFUs/ml in a voided specimen to define a positive urine culture[22]. In young children, urine is usually collected by catheterization, the cutoff for defining UTI is always considered 10^4 CFUs/ml[23][24]). However, Hoberman et al. noted that a high proportion (65%) of cultures with colony counts between 10^4 and 5 x10^4 grew mixed organisms suggestive of contamination (Hoberman 1996). Different cutoff values for positive cultures obtained by bag, midstream, catheterization, and suprapubic aspiration have been defined based on contamination risk of specimens. Most guidelines suggest any bacterial growth from suprapubic specimens is clinically significant. Table 6 shows the criteria for UTI diagnosis based on the bacteria colony counts in urine specimen and urinalysis in recent UTI guidelines.

Table 6. Criteria for UTI diagnosis based on the bacterial colony count in urine culture

Guidelines	Method of collection	Criteria (CFUs/mL)
AAP, 2011	Urinalysis and Suprapubic aspiration or catheterization	Pyuria +/- bateriuria $>5 \times 10^4$
CCHMG, 2006	Suprpubic aspiration Catheterization Clean catch midstream	$>10^3$ $>10^4$ $>10^5$
Italian Society of Pediatric Nephrology, 2011	Catheterization Clean voided urine Urine bag	$>10^4$ $>10^5$ $>10^5$
Canadian Paediatric Society, 2014	Suprapubic aspiration Catheterization Midstream	Any growth $\geqq 5 \times 10^4$ $\geqq 10^5$
EAU guidelines on urological infections, 2014	Suprapubic aspiration Catheterization Midstream	Any growth $\geqq 10^3 \sim 5 \times 10^4$ $\geqq 10^4$ with symptoms or $\geqq 10^5$ without symptoms
Asian guidelines, 2015	Urinalysis and Suprapubic aspiration Catheterization Midstream	Pyuria +/- bateriuria Any growth $>5 \times 10^4$ $>10^5$

AAP: American Academy of Pediatrics
CCMHG: Cincinnati Children's Hospital Medical Center
EAU: European Association of Urology

Like the recommendations of 2011 AAP guidelines, our criteria suggest the definitive diagnosis of UTI is made on the basis of quantitative urine culture and positive results on urinalysis. It is now recognized that the presence of white blood cells is an important feature of true UTI. Pyuria is a hallmark of UTI and helps to distinguish UTI and asymptomatic bacteriuria. Asymptomatic bacteriuria will have no pyuria, despite the positive urine culture. Asymptomatic bacteriuria is caused by bacterium of low virulence that colonizes the urinary tract and does not damage the kidney. Studies showed that antibiotic treatment for children with asymptomatic bacteriuria may do more harm than good[25].

Antimicrobial Therapy

Summary of Recommendations

1. Appropriate antibiotics should be given immediately after urine specimen for culture has been obtained (LE: 2, GR: A). Prompt treatment of a febrile UTI is important to eradicate the acute infection, to prevent bacteremia, to improve the clinical condition, and possibly to reduce the likelihood of renal damage (LE: 2, GR: B). The determination of route of administration, antibiotic of choice, and duration of treatment depends on the location of infection, age of patients,

severity of presentation, and the antibiotic resistance pattern in community (LE: 2, GR: A). Initiating therapy with oral or parenteral antibiotics is equally efficacious for children (> 3 months) with uncomplicated UTI (LE:2, GR: A).

2.The choice of empirical antibiotic agents is guided by the expected pathogen and the local resistance patterns (LE: 2, GR: A). Final antibiotic of choice should be adjusted to the narrowest spectrum antibiotic when susceptibility result is available (LE: 2, GR: B). For children with febrile UTI, the total course of antibiotic therapy should be 7-14 days (LE:2, GR: B).

In a child with suggestive clinical symptoms and positive urinalysis findings, empiric antibiotics should be initiated after appropriate urine specimen for culture has been obtained. Timely and appropriate diagnosis and prompt treatment of a febrile UTI is important to eradicate the acute infection, to prevent bacteremia (in particular, young infants less than 3 months of age), to improve the clinical condition, and possibly to reduce the likelihood of renal damage, although it was not confirmed in all studies[26][27].

Treatment of UTI depends on location of infection (upper or lower tract infection), age of patients, severity of presentation, and the antibiotic resistance pattern in community. For afebrile bacterial cystitis in children, orally administered antibiotics for 2-4 days are generally adequate and are as effective as those given for 7-14 days[28]. For uncomplicated febrile UTI, the results of the oral versus intravenous route do not differ regardless of the duration of fever, recurrence of UTI and incidence of subsequent kidney damage (renal scarring) after infection (GR: A)[29][30][31]. Meta-analysis for treatment of acute pyelonephritis in children concludes that oral therapy is appropriate when tolerated, and suggests treatment duration of 7-14 days (Hodson, 2007; Roberts, 2011). When initiating treatment, the choice of oral or parenteral antibiotics is based on age, clinical suspicion of bacteremia, toxic presentation, refusal of fluid or medication (vomiting or diarrhea), non-compliance, or complicated UTI. In general, oral antibiotics can be used effectively on an outpatient basis to treat uncomplicated UTI in children > 3 months who are clinically stable (GR: A). For young infants < 3 month of age, data on oral therapy is limited. Considering the increased incidence of urosepsis and severe infection (10%)[26], we recommended initial hospitalization and parenteral antibiotic therapy after complete septic workup for infants at this age (GR: C). Therefore, indications for hospitalization in children with febrile UTI include infants < 3 months, severely ill children, laboratory evidence of severe infection, immunocompromised children, intolerance to oral intake, concern of noncompliance, previous history of urinary tract anomalies, or failure to respond to oral antibiotics (GR: C).

Common uropathogens include Escherichia coli (accounting for more than 80% organisms causing UTIs in children), Klebsiella, Proteus, Enterobacter, Enterococcus, Citrobacter, and Staphylococcus saprophyticus (adolescent girls)[32][33]. It is reported that UTIs caused by enterococcus is associated with more underlying urinary tract anomalies than gram-negative UTI and more inappropriate antibiotic therapy, which need adequate imaging and antibiotic therapy[34]. Less common organisms such as Pseudomonas, Staphylococcus aureus, or Staphylococcus epidermidis are seen with increased frequency in children with anatomic anomalies, following genitourinary surgery or bladder catheterization, and following repeated courses of antibiotic treatments. Antibiotic resistance is a growing problem, especially for children receiving prophylactic antibiotics for VUR. Evidence suggests that age less than 1 year and recurrent UTIs appear to be independent risk factors for UTI caused by bacteria that produce extended-spectrum beta-lactamase (ESBL)[35]. They are more likely to have ESBL UTI when prophylactic cephalosporine is used[36]. The selection of empirical antibiotics is guided by local antimicrobial sensitivity patterns, but coverage for Escherichia coli as the leading pathogen should be considered. Some experts suggest using oral or parenteral third-generation cephalosporines as the initial treatment. But these cephalosporines are broad-spectrum agents. Injudicious use of these broad-spectrum antibiotics may increase the resistance rates of

uropathogens. When antibiotic susceptibility results from urine culture are available, therapy should be adjusted to the narrowest spectrum antibiotic. Oral quinolone antibiotics (ciprofloxacin), which are not licensed for use in prepubertal children, are highly efficient against most uropathogens. Its use should remain a choice for mutidrug-resistant pathogens (GR: C).

Traditional first-line antibiotic for childhood UTI, such as cotrimoxazole, with resistance rates of more than 50% in Taiwan, has been rendered inadequate[37]. The usual choices for oral antibiotics include a first-generation cephalosporine or amoxicillin-clavulanic acid. Agents do not achieve therapeutic concentrations in the bloodstream, such as nalidixic acid or nitrofurantoin, should not be used to treat young children with febrile UTI, because their serum and parenchymal concentrations may be insufficient to treat sepsis or pyelonephritis (Roberts, 2011). When intravenous treatment is required, initial combination treatment with ampicillin and an aminoglycoside (e.g. gentamicin) or cephalosporine achieves excellent therapeutic results (aminoglycosides or cephalosporine against most common gram-negative uropathogens and amipicillin against enterococcus). About 90% of febrile young children with UTIs will be afebrile within 48 hours of initiating appropriate parenteral treatment [38]. Repeat urine culture seems not to be needed in children with good clinical response (Roberts, 2011). Antibiotics can be administered parenterally for 2-4 days, followed by oral antibiotic course. Prolonged fever occurs in older children or children with lobar nephronia, renal abscess, pyonephrosis, immunodeficiency, inadequately treated infection caused by multi-resistant bacteria[38]. The total course of antibiotic therapy should be 7-14 days, whether the initial route of administration of antibiotics is oral or parenteral (then change to oral) (GR: B) (Roberts, 2011). Data comparing the efficacy of 7 days, 10 days and 14 days are not available.

More severe parenchyma infections, such as acute lobar nephronia or renal abscess, require longer antibiotic course of >14 days[39]. Preliminary study shows adjunctive oral methylprednisolone may reduce renal scarring after acute pyelonephritis[40]. However, the evidence is still limited due to the small number of study children.

Continuous Antimicrobial Prophylaxis

Summary of Recommendation

1. The potential benefit of preventing recurrent UTI by antimicrobial prophylaxis should be weighed against the risk of antimicrobial resistance with future infections. (LE: 2, GR: B)

2. Antimicrobial prophylaxis to prevent recurrent UTI may be considered in infants and children with or without vesicoureteral reflux (VUR) after a first UTI. (LE: 1b, GR: B)

Introduction

Recurrent UTI may develop in 30-50% of children with episode of symptomatic UTI1,2[41][42] and the recurrence rate is directly correlated with the number of preceding UTIs3[43]. The susceptibility for recurrences is highest within the first 2 to 6 months after a UTI4[44]. A long term antimicrobial prophylaxis is considered in cases of high susceptibility to UTIs and risk of acquired renal damage. These include patients with dilating high grade VUR, with recurrent pyelonephritic episodes or with significant urinary tract obstruction.

Selection of Antimicrobials

Antimicrobials selected for prophylaxis should fulfil the following demands: (1) effectiveness against the majority of uropathogens, (2) causing a minimum of serious side effects, (3) causing minimal bacterial resistance, (4) making little ecological impact on indigenous bacterial flora.

Usually, the prophylactic antimicrobials are given daily in the evening shortly before sleep with a quarter of the regular therapeutic dosage. Since many years, trimethoprim or cotrimoxazole and nitrofurantoin have been the substances mostly used for antimicrobial prophylaxis of UTI in children. Due to the fact that both substances in many countries are restricted on admission in early infancy, oral cephalosporines are preferred in this age group. Usable antimicrobials for prophylaxis are summarized in the Table 7.

Table 7. Usable substances for antibacterial prophylaxis

Substance	Prophylactic dosage (mg/kg/d)	Limitations in young infants
Trimethoprim	1	Until 6 weeks of age
Nitrofurantoin*	1	Until 3 months of age
Cephalexin	10	No age limitations
Cefaclor	10	No age limitations
Cefixim	2	Preterms and newborns
Ceftibuten	2	
Cefuroximaxetil	5	

* Not available in most Asian countries

Controversial issues in antimicrobial prophylaxis

The efficacy of antimicrobial prophylaxis per se has been questioned in several reviews5-8[45][46][47][48]. Recently, several reviews reported that there was no clear association between recurrent UTI and VUR, and renal damage, renal scarring, hypertension, and end-stage renal disease. A 2007 Cochrane review combined the results of two randomized studies (n = 142; median age = three years) comparing antibiotic use with no treatment in prevention of recurrent UTI in children9[49]. The results showed no difference in the risk of recurrent UTI (RR 0.75; 95% CI, 0.15 to 3.84) or renal damage (RR 1.70; 95% CI, 0.36 to 8.07).

In an updated Cochrane review, six studies of children from birth to 18 years old (n = 1,069) with initial or recurrent UTI compared the effectiveness of prophylactic antimicrobial treatment (ranging from 10 weeks to 12 months) with placebo or no treatment10[50]. Antimicrobial use did not reduce the risk of symptomatic UTI compared with placebo or no treatment (RR 0.75; 95% CI, 0.36 to 1.53). However, when only studies with a low risk of bias were analyzed, there was a statistically significant reduction in the risk of symptomatic UTI (RR 0.68; 95% CI, 0.48 to 0.95). The absolute risk reduction was estimated to be 8% (number needed to treat = 13). The authors also found no significant increased risk of resistance to the antimicrobials in the active treatment groups (RR 2.4; 95% CI, 0.62 to 9.26).

A multicenter RCT randomized 100 children younger than 30 months with VUR (grade II to IV) diagnosed after a first episode of acute pyelonephritis to receive trimethoprim/sulfamethoxazole or no treatment for two years11[51]. There was no reduction in the rate of recurrent pyelonephritis in the treatment group after one year (RR 1.42; 95% CI, 0.76 to 2.65) or after two years (RR 1.25; 95% CI, 0.54 to 2.90). There was no reduction in the incidence of renal damage after two years (RR 1.22; 95% CI, 0.75 to 1.98). Children in the treatment group had recurrent infections caused by multidrug-resistant bacteria: *Escherichia coli* in 37 cases, *Pseudomonas aeruginosa* in 3 cases, *Enterococcus faecalis* in 2 cases, and *Morganella morganii* in one case. In the control group, all recurrent infections were caused by *E. coli*, which was 100% sensitive to all antimicrobials tested.

Another prospective multicenter RCT compared the use of prophylactic trimethoprim/sulfamethoxazole with no treatment in 225 children from one month to three years of age with VUR (grade I to III) diagnosed after a first episode of febrile UTI12[52]. The study concluded that there was no statistically significant reduction of the overall incidence of recurrent UTI with antimicrobial prophylaxis in children with low-grade VUR (17 versus 26%; P = 0.2).

A double-blind RCT randomized 576 children with VUR (median age = 14 months; 71% had first diagnosed episode of UTI) to receive daily trimethoprim/sulfamethoxazole or placebo for 12 months13[53]. Children in the treatment group had a modest reduction in recurrent UTI; 13% of those in the treatment group developed recurrent UTI compared with 19% in the placebo group (hazard ratio 0.61; 95% CI, 0.40 to 0.93; P = 0.02; number needed to treat = 16). There was a reduction in febrile UTIs in the treatment group (hazard ratio 0.49; 95% CI, 0.28 to 0.86; P = 0.01; number needed to treat = 16). However, the study was underpowered to assess the effect of antimicrobial treatment on long-term renal damage. The incidence of UTI caused by an organism resistant to trimethoprim/sulfamethoxazole was higher in the treatment group (67 versus 25%; P < 0.001). There was no difference between groups in the rate of adverse reactions (P = 0.10) or the rate of hospitalization for UTI (P = 0.38).

Recently, RIVUR trial on antimicrobial prophylaxis for children with VUR was reported14. This multicentric, randomised, placebo-controlled study was designed to examine the effectiveness of antimicrobial prophylaxis in children with reflux who had suffered from UTI. The primary end-point was the efficacy of antimicrobial prophylaxis in preventing recurrence of febrile/symptomatic UTIs. Secondary end-points were the development of renal scars, treatment failure and antimicrobial resistance. A total of 607 children, aged two to 72 months, with grades I-IV reflux and documented first UTI were included. Recurrent UTI developed in 39 of 302 children who received prophylaxis as compared with 72 of 305 children who received placebo (RR 0.55; 95% CI, 0.38 to 0.78). Prophylaxis reduced the risk of recurrences by 50% (hazard ratio 0.50; 95% CI, 0.34 to 0.74) and was particularly effective in children who presented with febrile index UTI (hazard ratio, 0.41; 95% CI, 0.26 to 0.64) and in those with baseline bladder and bowel dysfunction (hazard ratio, 0.21; 95% CI, 0.08 to 0.58). The occurrence of renal scarring did not differ significantly between the prophylaxis and placebo groups (11.9% and 10.2%, respectively). Among 87 children with a first recurrence caused by *Escherichia coli*, the proportion of isolates that were resistant to trimethoprim–sulfamethoxazole was 63% in the prophylaxis group and 19% in the placebo group. The investigators concluded that among children with VUR after UTI, antimicrobial prophylaxis was associated with a substantially reduced risk of recurrence but not of renal scarring.

Problem of non-compliance

Patient compliance is one of the biggest problems with antimicrobial prophylaxis. Daschner and Marget tested compliance with long-term antimicrobial therapy by urine check in 93 children with recurrent UTIs. Only 32.2% of the children took the prescribed drugs at regular intervals,

19% did not take the antimicrobials at all. Similar results have been shown in children with VUR[54]. Rational and understandable information to the parents about aims and necessity of prophylaxis and its control is inevitable for its success.

Imaging studies after UTI

Summary of Recommendation

1. The goals of imaging studies are to localize the infection (lower or upper tract UTIs), to demonstrate anatomical or functional abnormalities, to detect significant VUR, and to detect congenital or acquired renal scarring (LE: 2, GR: B).

2. For children with febrile UTI, renal and bladder ultrasonography (RBUS) should be routinely performed as soon as possible (LE: 3, GR: C). RBUS should be followed up 6 months later in children with acute pyelonephritis and/or VUR (LE: 3, GR: C).

3. Acute DMSA scan can be performed when severe acute pyelonephritis or congenital hypodysplasia is noted on RBUS or when the diagnosis of UTI is in doubt by the clinical presentation (LE: 3, GR: C). Late DMSA scan (> 6 months after the febrile UTI) can be performed in children with severe acute pyelonephritis, high-grade VUR, recurrent febrile UTIs, or abnormal renal parenchyma on the follow-up RBUS (LE: 3, GR: C).

4. Top-down or bottom-up approach for febrile UTI is suggested for the diagnosis of VUR. For top-down approach, VCUG should not be performed routinely for children after the first febrile UTI. VCUG is indicated when abnormalities are apparent on either RBUS or DMSA scan or both (LE: 2, GR: B). VCUG is also suggested after a repeat febrile UTI (LE:2, GR: B). The bottom-up approach consists of a RBUS and a VCUG for the initial investigation for febrile UTI (LE: 2, GR: B).

The goals for management of childhood UTIs include early and correct diagnosis of UTI, early and appropriate treatment of UTI, recognition and management of acute complications, and assessment of potentially associated structural or functional abnormalities. The past years have brought marked changes in our understanding of the association between UTI, VUR, and renal scarring. With the advancement in evidence-based medicine, some information we used to believe has changed. Traditionally, it has been assumed that VUR is central to the pathogenesis of acute pyelonephritis and subsequent renal scarring after recurrent UTIs and should therefore routinely be screened and aggressively managed[23]. However, VUR is considered merely as one the risk factors for renal damage. Bacterial virulence and host resistance are as potentially important as VUR, if not more important factors.[55]. In addition to VUR, the other risk factors for scarring include the presence of congenital renal scarring (renal dysplasia), other underlying anatomic abnormalities, bladder bowel dysfunction, gender issues, presence of phimosis, age, delayed treatment of acute pyelonephritis, and recurrent UTIs. Gene polymorphism susceptibility to renal damage on the inflammatory response is also considered an important risk factor for renal damage[56].

With regard to the significance of VUR in UTI in children, there is no evidence that VUR predisposes to an increased risk of UTI per se. However, it is believed that when infection occurs in a child with high-grade VUR, it is more likely to involve upper rather than lower urinary tract. [57]. VUR is a risk factor for scarring only in the presence of acute pyelonephritis; VUR itself does not directly induce scarring without infection[58]. Furthermore, about 50% of children with an acute pyelonephritis do not have demonstrable VUR[59].

Improved prenatal ultrasonography has revealed that major renal damage in children with VUR is frequently related to congenital renal hypo-dysplasia. Renal scars may be congenital or acquired. High-grade VUR associated with congenital renal hypo-dysplasia (or "congenital reflux nephropathy") with/without voiding dysfunction is more common in male infants[60][61][62]. It may occur as part of congenital anomalies of kidney and urinary tract (CAKUT)[63][64]. The small, poorly functioning kidney with diffuse global photopenia on DMSA scan is clearly not the result of infection. In fact, congenital hypodysplastic kidney is a major cause of chronic renal failure in children who also have VUR[62]. Acquired segmental scarring as a result of UTI is a different entity. On DMSA scan, it is presented by focal areas of photopenia. It is seen more commonly in older girls with milder reflux. The renal damage in these children is usually minor and rarely causes a reduction in overall renal function. All of current management strategies for VUR are aimed at decreasing acquired scarring.

Therefore, the rationales for imaging studies are to identify risk factors and abnormalities of urinary tract that can be modified to decrease the likelihood of recurrent UTI and subsequent renal scarring. Its aim should be to localize the infection (lower or upper UTIs), to demonstrate anatomical or functional abnormalities (including bladder dysfunction), to detect significant VUR, and to detect congenital or acquired renal scarring.

Although pediatric UTI is a common illness and numerous investigations were reported in literature, the proper approach to imaging evaluation in children with febrile UTI remains controversial. Most practice guidelines recommend either RBUS or technetium-99m-labeled dimercaptosuccinic acid (DMSA) scan combined with voiding cystourethrography (VCUG) [Finnell, 2011; Roberts JA, 2011; Ammenti, 2012[65][66]. The noninvasive nature, lack of radiation, good anatomic demonstration of the entire urinary system, and low cost of RBUS make it an ideal tool for initial screening for anatomic abnormalities in infants with UTI. RBUS provides a general idea of the integrity of the urinary system. Ultrasound scanning is a good tool to assess obstructive uropathies, urolithiasis, ectopic kidney or ureter, posterior urethral valves, and duplication of the collecting system with or without ureterocele. Performance of RBUS during the acute infection is also helpful for detection of renal involvement, suspicion of bladder dysfunction (thickened bladder wall with residual urine), constipation (large rectal diameter) and early recognition of complicated infections such as lobar nephronia and abscess or pyonephrosis. However, acute-phase RBUS may increase the false-positive diagnosis of pelvic dilatation [Finnell, 2011]. Early diagnosis of pyonephrosis or abscess is important because percutaneous drainage should be considered to prevent complications when the response to antibiotic treatment is poor [Riccabona, 2007].

However, with the widespread application of antenatal US, the likelihood of detecting obstructive uropathies after UTI is decreased[67][68]. It is also less reliable for demonstrating APN, renal scarring, and detecting VUR, perhaps because reflux is an intermittent dynamic event. For screening high-grade VUR, in addition to dilated collecting system, other abnormal findings potentially associated with VUR (calyceal or ureteral dilatation, renal hypodysplasia, thickened bladder or pelvis wall, fluctuating renal pelvis) should be included[69][70]. Regardless of whether VUR is present, other conditions such as acute pyelonephritis, preexisting hypo-dysplasia or scarring, or other obstructive uropathies are also important risk factors for long-term sequelae and should be further followed up.

DMSA renal scan is the gold standard tool for identification of acute pyelonephritis or renal scarring. It can confirm acute pyelonephritis (a focal area of diminished isotope uptake with a preserved renal contour) at the time of acute infection and determine whether a permanent scar (an area with absence of isotope uptake) has occurred 6 months later. As sometimes the clinical symptoms are vague and urinalysis or urine culture is indeterminate (in children who had received antibiotics before urine culture was done), DMSA scan may be useful in confirming or

excluding the diagnosis of acute pyelonephritis[71]. It may also detect the presence of congenital renal hypo-dysplasia, although differentiating renal hypo-dysplasia from infection-related scar is sometimes difficult[67][72]. Congenital scarring and recurrent UTI constitute a large concern for long-term prognosis and should be followed up. As a result, DMSA scan can be used as a baseline test to compare potential pyelonephritic consequences in the future. An acute DMSA scan is preferred for infants with febrile UTI because they are more likely to suffer more significant morbidity with APN and subsequent renal scarring than are older children, and are less able to communicate their symptoms, leading to a potential delay in diagnosis[73]. Acute DMSA scan also provides prognostic value. It has been shown that a normal DMSA during an acute febrile UTI with or without reflux is associated with a 0% risk of renal scarring[74]. Therefore, no further imaging study is needed if RBUS and DMSA are all normal. On the contrary, extensive renal inflammatory involvement with reflux is associated with a high risk of developing renal scars[74]. However, the use of acute DMSA scan is criticized for higher costs, longer duration, radiation exposure, needing sedation in young children, and requirement of intravenous access and special equipment[75]. Because acute DMSA scans rarely change immediate management, it is not recommended as part of routine evaluation by AAP guidelines [Roberts KB, 2011], and is listed as an option by AUA and Canadian guidelines[73]Robinson, 2014]. The Italian guidelines recommend late DMSA (6 months after the febrile UTI) for all children with an abnormal US or in whom VUR has been shown, to obtain a morphologic and functional evaluation [Ammenti, 2012].

Two options are recommended for the diagnosis of VUR: the bottom-up or the top-down approach. The traditional bottom-up approach consists of a RBUS and a VCUG for the initial investigation[23]. A DMSA scan is recommended in a later stage only in patients with high-grade VUR or with recurrent f-UTIs[76]. It focuses on diagnosing and managing all-grade VUR. However, VCUG is an invasive procedure with radiation burden, discomfort due to the need for catheterization, and a risk of iatrogenic infection. There is a trend toward using less invasive methods to evaluate children with first febrile UTI and to perform VCUG more selectively. Recent meta-analyses of published data shows that low-grade VUR is of low clinical significance and does not need to be diagnosed and treated[77][12]. Furthermore, according to the meta-analysis of new AUA guidelines, the risk of acute pyelonephritis (APN) and scarring is considered higher in younger children with grades III–V VUR[73]. In addition, the effect of prophylactic antibiotic is still in doubt. The "top-down" approach is developed to screen high-grade VUR for children with febrile UTI and reduce the number of VCUG performed [Hansson, 2004; Preda, 2007[78][69][79][80][70]. The advocated approach begins with an acute DMSA scan with or without RBUS, and VCUG performed when the DMSA scan or RBUS is abnormal or there is subsequent recurrent UTI. The top-down approach focuses on renal involvement (congenital hyo-dysplasia or acquired APN) after f-UTI; therefore, a DMSA is obtained first and fewer VCUGs will be performed. However, the meta-analysis study shows the pooled sensitivity and specificity of DMSA scan for detection of high-grade VUR were only 79% and 53%, respectively, for the patient-based analysis[75]. The study concluded that acute DMSA scan has limited ability to identify risk of high grade VUR. However, when acute DMSA and RBUS are simultaneously evaluated, an abnormality on either examination has a sensitivity of 83.2-95.3% and a negative predictive value of 91.5-94.3%[69][79][70]. To avoid inter-observer variability in interpreting RBUS, the examination of RBUS needs standardization. In addition to hydronephrosis, the ultrasonic features have better include calcyceal or ureteral dilatation, variable dilatation of the pelvis, thickened pelvic or ureteral wall, lack of corticomedullary differentiation and cortical hyperechogenicity, small kidneys or cortical thinning with or without tiny cysts, and a thickened or trabeculated bladder wall (features of voiding dysfunction). The other indication for VCUG is recurrent febrile UTI. The risk of high-grade VUR is higher for children with recurrent UTI than for children with a first UTI[12].

VCUG can be performed as soon as possible provided the inflammation has subsided after treatment [Doganis D, 2009]. It can therefore eliminate the need for antibiotic prophylaxis and increase compliance. VCUG should be carefully interpreted. In addition to detection of VUR, the bladder contour, urethra, and postvoiding residual urine should be evaluated for excluding the possibility of bladder dysfunction, posterior urethral valves, ureterocele, utricle cyst, or neurogenic bladder.

The benefit of top-down approach includes reducing the numbers of VCUG performance and decreased detection and management of clinically insignificant VUR. The disadvantage of top-down approach is associated with higher economic cost, radiation burden, requirement of intravenous access and sedation of young or uncooperative children. A definitive answer to choose which approach method is still lacking, and the multiple determinant factors should be considered, including patient age, VUR grade, presence of renal damage, and recurrence of UTI. Additional evidence is required to validate any of the suggested approaches. The EAU guidelines recommended initial evaluation with RBUS and VCUG, and the top-down approach was also listed as an option[76].

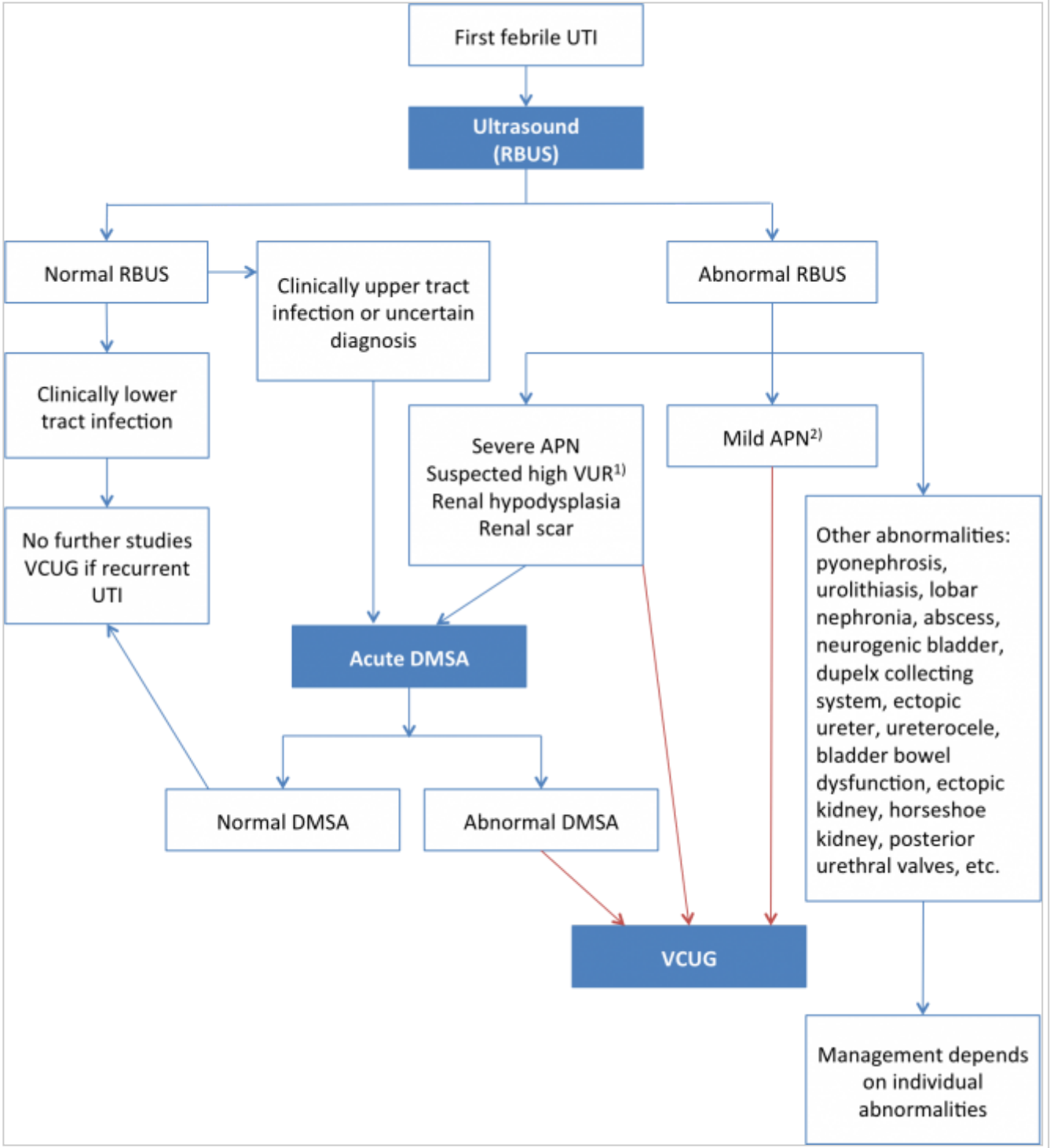

Figure 2. Top-down approach for acute imaging algorithm in children with febrile UTI

- Signs of high VUR include hydronephrosis, calyceal or ureteral dilatation, renal hypodysplasia, thickened bladder or pelvis wall, fluctuating renal pelvis
- The diagnosis of mild APN is determined by the clinical presentation and ultrasonic studies. The general condition of a child with fUTI is good, and the fever is soon controlled after adequate oral or intravenous antibiotics. The RBUS showed only mild or borderline swelling of kidney. For a child with mild APN, the risk of subsequent renal scar is low and therefore acute DMSA can be omitted.

Diagnosis and management of Risk Factors of UTI: Phimosis, Labial adhesion and vulvovaginitis

Summary of Recommendation

1. Circumcision may, but not definitively, reduce the risk of febrile UTI in males and breakthrough febrile UTI in males with VUR. Circumcision should be offered to uncircumcised boys with febrile UTI and VUR in countries where circumcision is accepted by the general population (LE: 3, GR: B), while in countries where childhood circumcision is rarely performed, other measures for febrile UTI/VUR should be the preferred choice (LE: 4, GR: C).

2. Bacterial flora exists in inner prepuce and physicians should be aware that contamination may occur in non-circumcised boys, and catheterization may be required for uncontaminated urine collection. (LE: 2, GR: C)

Circumcision and regional diversity

Febrile UTI is ascending infection of bacteria in the urinary tract, and periurethral bacterial flora has been postulated as the source of pathogenic bacteria in males. Circumcision, surgical removal of prepuce, has been performed as a ritual procedure in selected religions and ethnicities, such as Muslims and Jewish people. Many studies have been published to examine whether this ritual procedure has advantageous effect on prevention of UTI, especially in male infants with VUR. In countries like United States of America, where circumcision prevalence is between 20-80%, it can be a vital clinical question whether the circumcision should be an option for dealing with UTI. In Asian country, however, there is a sharp division in the prevalence of circumcised males, more than 80% in Islamic countries, South Korea, and Phillipines, but less than 20% in majority of the other countries, including China, India, Japan, and Taiwan [WHO 2007] Because of such radically different cultural background in Asian countries, conclusion lead from studies in one country cannot be equally applied for every Asian countries. At the same time, there are so few literatures from Asian countries on this topic. Consequently, evidences for this chapter are based on non-Asian literatures and its applicability in Asian population is discussed upon socio-cultural context.

Preputial bacterial flora and diagnosis of febrile UTI in boys

Colonization of bacteria in inner prepuce and reduction by circumcision has been documented in many studies[81][82][83][84][85][86][87]. However, there was one article reporting no difference in bacterial culture between circumcised and uncircumcised males[88], and another article documenting just a modest difference, 37% vs 28% detection of uropathogenic bacteria, between non-circumcised and circumcised patients with VUR under bacterial prophylaxis[89]. No Asian literature exists in this issue. This aspect should be primarily important upon accuracy in diagnosis of UTI upon urine specimen[90]. American Academy of Pediatrics advocates in its guideline that urine specimen should be collected by catheterization.

Evidences for circumcision in boys having febrile UTI and/or VUR

With regard to the prevalence of urinary tract infection, there is one prospective randomized study[91] demonstrating reduction in episodes of febrile UTI but was statistically not-significant. Moreover, there have been cohort studies from Canada[92], Australia [93], and the United States [94][95]Shoen et al 2000), a series of epidemiological studies from the United States[96][97][98][99], 3 meta-analyses, 2 from USA[100][99] and the other from Australia[101]. There are also 2 studies comparing incidence of febrile UTI before and after circumcision, one from Turkey[102], and the other from the United States[103]. No Asian literature exists in this issue.

There is no prospective study associating circumcision with VUR patients. One cohort study documents that, among boys with VUR detected upon prenatal hydronephrosis, higher rate of breakthrough UTI occurred in non-circumcised boys (53%) than in circumcised boys (19%)[104]. Another study documents reduced rate of breakthrough UTI after circumcision from 45.2% to 6.2%[105]. There is one report from Japan[106]on the incidence of breakthrough UTI during prophylaxis in non-circumcised population. Comparing the two reports, the incidence of breakthrough infection, which was 32.2%, was lower than what was reported in non-circumcised groups, but was higher than in circumcised groups. Another report from Korea discussed the effect of concomitant circumcision with anti-reflux surgery. The authors concluded that circumcision with anti-reflux surgery did not seem to affect the clinical course. [107] Based on these data, we conclude that circumcision may, but not definitely, reduce the risk of febrile UTI in males.

Other guidelines

Circumcision is described as a therapeutic choice against VUR in AUA guideline 2010. In United States, where circumcision rate varies among races, usually around 70-80%, this choice should be presented to parents. The guideline states that "Although there are insufficient data to evaluate the degree of this increased risk and its duration, parents need to be made aware of this association to permit informed decision-making."In Europe, the prevalence of circumcision is radically different between countries. Israel and Turkey are at one extreme with nearly 100% prevalence, but less than 20% in majority of other countries. In such context EAU guideline advocates that "Circumcision during early infancy may be considered part of the conservative approach because the procedure has been shown to be effective in reducing the risk of infection in normal children.".

Phimosis and VUR: An Asian view

In countries where neonatal circumcision is routinely performed, there may exist no clinical problem with regard to this issue. In countries where circumcision is not routinely performed in children, strong objection exists against using this procedure as a treatment of VUR. An opinion leader in eastern Asia, Kenji Shimada presents his view on this issue stating that " Instead of talking about the negative effect of the prepuce, we have to take lessons from history and reconsider its positive significance." In such view, countries where circumcision is not performed during childhood (for example China, India, Japan, Taiwan), it is difficult to conceive it as a therapeutic measure both for parents and for physicians. Moreover, the occurrence and treatment of febrile UTI among uncircumcised boys in these countries should be further studied in separate context from the countries where circumcision is highly prevalent.

On the other hand, in countries like Korea and Phillipines where circumcision is performed during childhood, but not as a routine procedure in neonates, one may adopt the conclusions similar to the United States, and may have obligation to present circumcision as a choice of treatment for male infants with febrile UTI and/or VUR. In such countries, setting an appropriate age for circumcision could be an important clinical question, since febrile UTI is more frequent during early infancy.

Labial adhesion and vulvovaginitis

Labial adhesion in its most severe form can block urinary flow and caused retention of urine in the vagina. Vulvovaginitis may be associated with UTI in girls. However, there are few literatures suggesting the involvement of this condition in febrile UTI/VUR.

Diagnosis and management of Risk Factors of UTI: Bladder Bowel Dysfunction

Summary of Recommendation

Bladder bowel dysfunction encompasses lower urinary tract dysfunction (LUTD) and bowel dysfunction is one of the key factors of progression of renal scarring (LE: 2, GR: A). LUTD can be diagnosed with 4-hours voiding observation in infants and non-invasive urodynamic studies such as uroflowmetry and PVR in toilet trained children (LE: 2, GR: B). Invasive urodynamic studies such as videourodynamic study are reserved for refractory LUTD (LE: 3, GR: C). Bowel dysfunction can be diagnosed with stool form, defecation diary, KUB, and transabdominal ultrasound for rectal distention (LE: 2, GR:B). Early recognition and management of LUTD and bowel dysfunction are important in prevention of UTI recurrence (LE: 2, GR: A).

Diagnosis of LUTD in infants and children

Diagnosis of LUTD in infants can be made with 4-hour voiding observation. Interrupted voiding is defined as re-voiding in 5 minutes. PVR >10ml or 20% bladder capacity may be regarded as elevated PVR. In toilet trained children aged 4-6 years, elevated PVR can be defined as a PVR >20ml or 10% bladder capacity, and in children aged 7-12 years as a PVR >10 ml or 6% bladder capacity. Uroflowmetry in toilet trained children is expected to be bell-shaped. Repeat abnormal uroflow pattern is suggestive of LUTD. Details on the differentiation of various type of LUTD are not covered in this paper. Recent studies suggest that infants with a PVR >10ml or 20% bladder capacity was associated with febrile UTI[108] and children with a PVR higher than the aforementioned age-specific values were at risk of recurrent febrile UTI (Yang 2014).

Significance of LUTD and UTI

LUTD with incomplete bladder emptying is deemed as an important risk factor for development and recurrence of UTI in children[109]. About 20%-50% of children with UTI and VUR have dysfunctional voiding. (Chen JJ, et al: J Urol 2004;171:1907-1910. Sjostrom S, et al. J Urol 2009; 182:2446-54.) Dysfunctional voiding predicts a lower success rate after classical anti-reflux surgery or Deflux® injection. (Higham-Kessler J, et al: J Urol. 2007;177:710-4). Sillen et al reported that infants with LUTD had higher rate of progressive renal scarring than those without LUTD. Immature voiding pattern, dyscoordination between detrusor and sphincter, is common in infants and frequently subsided after one year of age. Any surgical intervention before one year of age should be carefully considered.

Be havioral modification for LUTD

Clinically, children with UTI and poor fluid intake are encouraged to have more fluid, although relevant studies remain scarce. It is assumed that more fluid intake may result in shorter stasis time of urine in the bladder and better-wash out of bacteria in the bladder. Infrequent voiding, poor fluid intake, functional stool constipation, and dysfunctional voiding were more frequently disclosed in girls with recurrent UTI than in control girls[110][111]. When managing children with UTI, frequency/volume chart may help physicians and parents monitor the voiding frequency and fluid intake in these children. Elevated PVR has been linked to the development and recurrence of UTI[109]. Infrequent voiding may result in longer time of bacterial multiplication in the bladder and elevated PVR that was frequently observed in urinary bladder over-distension. Bladder over distension is defined as bladder capacity (voided volume + PVR) larger than 115% expected bladder capacity. At a bladder capacity reaching over-distension, more than one-third of

micturition resulted in abnormal uroflow pattern and PVR >20 ml[112]. Timed voiding schedule is advised in infrequent voiders to decrease the urinary stasis time and to avoid bladder over distension. However, optimal amount of fluid intake is not known. Furthermore, good toilet posture also play a role, which enables optimal relaxation of the pelvic floor muscle and hence reduces dysfunctional voiding and PVR. In postures with adequate bilateral foot support, the relaxation was observed in 94% recorded from the pelvic floor muscles. EMG amplitudes from the pelvic floor and adductor muscles were significantly higher in postures with unsupported legs compared with postures with supported legs[113].

Biofeedback relaxation of pelvic floor for dysfunctional voiding

Biofeedback relaxation of pelvic floor is helpful in improving voiding symptoms and urodynamic parameters in children with dysfunctional voiding [114]. In a study of girls with recurrent UTI underwent a training program including voiding and drinking schedule, pelvic floor relaxation biofeedback, instructions on toilet behavior, and biofeedback uroflowmetry, the program was effective in preventing recurrence of UTI in 35 of 42 (83%) children (De 1998). In a prospective, randomized study comparing pelvic floor exercise and biofeedback therapy in treating children with dysfunctional elimination syndrome, both groups of patients showed low rate of relapsed UTI (3.8% and 10%). Children who received biofeedback therapy had significantly reduced PVR. Children with voiding dysfunction and VUR usually have a high breakthrough infection rate of 34–43%[115]. Of 37 children with previous history of UTI, VUR and non-neurogenic LUT dysfunction who underwent biofeedback training program only 19% had breakthrough UTI during a mean follow-up of 21 months[116]. Similarly, breakthrough infection was reduced to 10% after combined conservative medical and computer game assisted pelvic floor muscle retraining program in a mean follow-up period of 24 months[117].

Diagnosis and management of functional constipation

Constipation is a common problem among children with a prevalence rate ranging from 0.7 to 29.6%[118]. Rome III criteria defined functional constipation as more than two of the following symptoms: (1) ≦2 defecation/week, (2) >1 fecal incontinence/week, (3) history of retentive posturing or stool retention, (4) painful or hard bowel movements, (5) large fecal mass in the rectum, and (6) large stool obstructing the toilet[119]. It is postulated that chronic retention of fecal mass above anal verge makes children maintain a high anal sphincter tone. The high anal tone leads to pelvic floor activity and impairs emptying function of bladder and elevated PVR which is an important factor in developing UTI[120]. This has been confirmed by a recent community investigation of 318 healthy children who had bowel movement ≦2 times/week had higher PVR (9.0 vs. 5.9 ml, P=0.01) and higher chance of elevated PVR (17.7% vs. 7.1%, P=0.01) [Chang 2012]. Another theory is that constipation may increase the uropathogenic organism in the gastrointestinal tract and then may lead to more UTI[121]. Previous studies have documented correlation between constipation and UTI. Romanczuk et al [122] evaluated 180 children suffering from recurrent UTIs and found that treatment of chronic constipation may reduce pyuria, bacteriuria, and enuresis among these children. In a study of 234 children treated for chronic constipation, relief of constipation was obtained in 52% of patients without urinary tract anomaly and resulted in disappearance of UTI[123]. Koff et al[124]evaluated 143 children with primary VUR and UTI, 66 had dysfunctional elimination syndrome in which 50% had constipation as the most prominent symptom. Of 66 with dysfunctional elimination syndrome, 82% needed surgical reimplantation of ureter, while only 18% had spontaneous resolution of reflux. Therefore, the importance of managing constipation and voiding dysfunction concurrently can not be overemphasized. Judicious history from parents is as important and well- appreciated information as the Bristol stool form scale in children. A bowel movement diary and a frequency/volume

chart should be obtained in children with recurrent UTI and constipation. This allows the physicians and/ or parents to monitor the children's condition and can supervise them as well. Treatment of constipation includes osmotic laxatives, stimulant laxatives, increasing fluids intake, biofeedback, and psychological intervention; all are effective in the management of constipation[125].

Early toilet training

Hellstrom et al.[126]had empirically suggested early initiation of toilet training in children at risk of developing UTI because children had less bladder sphincter dyssynergia and less post-void residual urine after toilet training[127][128]. A longitudinal study from Vietnam found that in the children who were potty trained very early, the dyscoordination between bladder and sphincter disappeared at age of 9 months[126]. A cross sectional study disclosed that the rate of abnormal voiding function was comparable between toilet training before and after 18 months of age[129]. Late toilet training may result in higher rates of lower urinary tract symptoms. A cohort study in the UK showed that initiating toilet training after 24 months was associated with problems attaining and maintaining bladder control[130]. However, there is a lack of prospective randomized studies to confirm the efficacy of early toilet training in reducing episode of recurrent UTIs.

Diagnosis and management of Risk Factors of UTI: VUR

Summary of Recommendation

1. At initial presentation the child with VUR should undergo a careful general medical evaluation including measurement of height, weight and blood pressure, as well as serum creatinine if bilateral renal cortical abnormalities are found (LE:2, GR: A).

2. Because VUR and UTI may affect renal structure and function, performing renal ultrasound to assess the upper urinary tract is recommended (LE: 2, GR: B).

3. DMSA renal imaging can be obtained to assess the status of the kidneys for scarring and function (LE: 1, GR: B).

4. VCUG is indicated when abnormalities are apparent on either renal/bladder ultrasound or DMSA scan or both (LE: 2, GR: B). VCUG is also suggested after a repeat febrile UTI (LE: 2, GR: B).

5. Despite the concerns about ionizing radiation and its invasive nature, conventional VCUG remains the gold standard because the test allows better determination of the grade of VUR (in a single or duplicated kidney) and better assessment of bladder and urethral configuration (LE: 2, GR: B).

6. Antibiotic prophylaxis to prevent recurrent febrile UTI is indicated in children with moderate to high grade (III-V) VUR (LE: 1b, GR: A).

7. Surgical intervention should be used to treat VUR in the setting of recurrent febrile UTI because it has been shown to decrease the incidence of recurrent pyelonephritis (LE: 1b, GR: A).

8. Bladder dysfunction increases the risk of urinary tract infections and can lead to significant delay in spontaneous resolution of VUR. Its detection by careful history and its efficient treatment therefore is mandatory in affected children (LE: 2, GR: B).

Introduction

A significant percentage of febrile UTIs are associated with VUR, especially in children evaluated before toilet training.[131] While VUR may be a benign condition with few long-term sequelae, it may also produce end stage renal disease. The rationale for prompt diagnosis and proper treatment of VUR in children with febrile UTIs are the prevention of recurrent pyelonephritis and its potential consequences, such as renal scarring. This is especially the case for younger child with "immature" kidneys that have been considered at increased risk for acquired renal scarring secondary to pyelonephritis.2 (Olbing et al, 2008) This section will focus on the diagnosis and evaluation of VUR as one of risk factors of UTI in children.

Diagnostic work-up for VUR in children with febrile urinary tract infection

In children with febrile UTI the diagnostic work-up should be focused on the evaluation of the health and development of the child, renal status, presence of VUR, and lower urinary tract function. This includes a detailed medical history (e.g. family history and screening for LUTD), a physical examination including blood pressure measurement, urinalysis (assessing for proteinuria), urine culture as indicated, and measurement of serum creatinine level in patients with bilateral renal parenchymal abnormalities. The standard imaging tests include renal and bladder ultrasonography, dimercaptosuccinic acid (DMSA) renal scan, and voiding cystourethrography (VCUG).

The standard criterion for the diagnosis of VUR is detection on VCUG. Traditionally, VCUG has been recommended in children with first proven febrile UTI. Radionuclide cystography for the detection of reflux have lower radiation exposure than conventional VCUG, but the anatomic detail depicted is inferior.4[132]Radionuclide cystography is useful for follow up. Recent studies on alternative imaging modalities for the detection of VUR have yielded good results with voiding urosonography and magnetic resonance VCUG.5-7[133][134][135]However, despite the concerns about ionizing radiation and its invasive nature, conventional VCUG remains the gold standard because the test allows better determination of the grade of VUR (in a single or duplicated kidney) and better assessment of bladder and urethral configuration. If reflux is diagnosed on VCUG, further evaluation traditionally consists of a DMSA renal scan ("bottom-up" approach). DMSA is the best nuclear agent for visualizing the cortical tissue and differential function between both kidneys. DMSA scan is used to detect and monitor renal scarring. A baseline DMSA scan at the time of diagnosis can be used for comparison with successive scans during follow-up.[136][137]

Recently an alternative "top-down" approach is more recommended. This approach carries out a DMSA scan first, close to the time of a febrile UTI, to determine the presence of pyelonephritis, which is then followed by VCUG if the DMSA scan reveals kidney involvement. A normal DMSA scan with no subsequent VCUG will fail to detect VUR in 5–27% of cases, with the cases of missed VUR being presumably less significant. In contrast, a normal DMSA scan with no VCUG will avoid unnecessary VCUG in over 50% of individuals screened.[138][139][140][141]

Video urodynamic studies are important only in patients in whom secondary reflux is suspected, such as patients with spina bifida, and in boys with a diagnosis of posterior urethral valves, for whom bladder dynamics necessitate regular follow-up.

Screening of asymptomatic siblings of reflux patients

The screening of asymptomatic siblings of reflux patients is controversial. Some authors think that early identification of children with VUR may prevent episodes of UTI and therefore renal scarring, while others think that screening asymptomatic individuals is likely to result in

significant overtreatment of clinically insignificant VUR. The estimate for renal cortical abnormalities is 19.3% (range: 11–54%), with 27.8% of patients in cohorts of symptomatic and asymptomatic children combined having renal damage. In asymptomatic siblings only, the rate of renal damage is 14.4% (range: 0–100%). Early screening appears to be more effective than late screening in preventing further renal damage by early diagnosis and treatment.[142][143][144][145] The lack of randomized clinical trials for screened patients to assess clinical health outcomes makes evidence-based guideline recommendations for VUR screening difficult.

Importance of Low Urinary Tract Dysfunction in VUR VUR, UTI and LUTD are frequently associated.[61][146][147] About half of children with VUR have bladder dysfunction.20[57]Bladder function influences the spontaneous regression rate of reflux.[124][147][148][149] These observations support the current view that bladder function is an important predictive parameter for spontaneous reflux resolution, susceptibility for pyelonephritic episodes and for renal damaging. This awareness has implications for conservative reflux therapy. It must include the treatment of pre-existing bladder dysfunction to be successful in the long run.[150]

Breast milk, cranberry products, probiotics and other means to prevent UTI

Summary of Recommendation

1. Breast feeding may protect infants from UTI (LE: 2), and is strongly recommended for prevention of UTI in infants (GR: A).

2. Cranberry and related products may prevent UTI in children (LE: 3) and may be considered in the prevention of UTI in children (GR: C).

3. Probiotics may prevent UTI in children and in children (LE: 3) and may be considered in the prevention of UTI in children (GR: C).

Breast milk

The protective role of breast milk may be attributed to the specific contents within the breast milk, including immunoglobulin A[151], anti-adhesive oligosaccharide[152], and lactoferrin[151]. The antibacterial effect and selection of low uropathogenic bacteria play the role. Marid et al. observed that shorter duration of breastfeeding was associated with higher risk of UTI in children[153]. Recently, the same group concluded that ongoing breastfeeding and a longer duration of breastfeeding resulted in a lower risk of infection after weaning, especially in girls[154]. The protective role of breastfeeding was strongest directly after birth; then, it decreased after 7 months of age. Recently, a case–control study enrolled 6198 premature infants and showed that breast milk is associated with lower risk of getting UTIs (OR = 0.314, 95% CI 0.140–0.707)[155]. In addition to UTI, breast feeding also reduced the risk of acute respiratory infections, acute otitis media, and thrush in the first 6 months of life[156]. Since breast feeding has many benefits and bears no risk, we strongly recommended breastfeeding to prevent recurrence of UTI in children with one episode of UTI.

Cranberry

From a meta-analysis by Jepson and Craig, there is some evidence supporting the use of cranberry in reduction of UTI episodes among women with recurrent UTI, while there is scarce randomized trial evaluating the effectiveness of cranberry in children[157]. The evidence of the role of cranberry in prevention of UTI in children was still inconclusive, although cranberry juice consumption provides significant anti-adherence activity against different *E. coli* uropathogenic strains in the urine compared with placebo[158]. Schlager et al conducted a double-blind, placebo-controlled, crossover study to determine the effect of cranberry juice on pyuria and symptomatic UTI in children with neurogenic bladder needing clean intermittent catheterization[159]. They found that cranberry concentrate had no effect on bacteriuria in the study population, although this may be partly due to host susceptibility to infection. Foda et al conducted a randomized single-blind cross-over study to compare cranberry juice and water, and no difference in infection of the intervention periods was observed[160]. Ferrata et al enrolled 84 girls with E. coli urinary tract infections[161]. They were randomized to receive cranberry, lactobacillus, and control group. Girls who received daily cranberry juices had less recurrence rate of UTIs. Another study showed that cranberry juice had comparable effects with cofactor in preventing UTIs in children with vesico-ureteral reflux[162]. Studies mentioned above only enrolled small number of children; more studies are required to elucidate the role of cranberry in prevention of pediatric UTI.

Probiotics

The term probiotics is defined as ''live microorganisms which when administered in adequate amounts confer a health benefit on the host'' [163]. The concept of probiotics developed from normal flora that existed in the gastrointestinal tract and genital area. The introduction of probiotics in the prevention of recurrent UTI was largely due to antibiotics failure and increased evidence of the efficacy of probiotics[163]. However, controversy exists over the efficacy of probiotics in prevention of pediatric UTI. Dani et al.[164]administered Lactobacillus GG in neonates with UTI, sepsis, and necrotizing enterocolitis; no significant effect of Lactobacillus GG in reduction of UTI was noted. Two prospective, randomized controlled studies compared the conventional antibiotics and probiotics in treating children and infants with primary VUR; the incidence of recurrent UTI was comparable in both groups of children[165][166]. Long-term effects of probiotics in children need further evaluation. Also, which strains of lactobacillus are more helpful in preventing pediatric UTI needs further elucidation. Despite the possible clinical effects of probiotics on UTI in children, 2 cases with bacteremia of lactobacilli were reported[167].

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Abbreviations

BBD: Bladder bowel dysfunction, CI: Confidence interval, DMSA: Technetium-99m-labeled dimercaptosuccinic acid, GR:: Grade of recommendation, LE:: Level of evidence, LUTD: Lower urinary tract dysfunction, RCT: Randomized control study, RR: Relative risk, UTI: Urinary tract infection, VUR: Vesicoureteral reflux, VCUG: voiding cystourethrography

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Acute bacterial prostatitis

From AAUS

Contents

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Executive Summary

Epidemiology and pathogenesis

1. Prostatitis syndromes are a very common presentation in the clinical setting and tend to occur in young and middle-aged men.

Diagnosis

1. Patients with acute bacterial prostatitis present with typical signs and symptoms of an acute urinary tract infection including irritative and/or obstructive voiding complaints, and have additional symptoms of systemic infections like malaise, nausea, vomiting, chills and fever, and

sometimes present with signs of symptoms of urosepsis. They also complain of perineal and suprapubic pain due to a painful swollen prostate and may have associated pain or discomfort of the external genitalia (GR: B).

2. Digital rectal examination reveals a hot, boggy, and exquisitely tender prostate gland (GR: B).

3. Prostatic massage for the expression of prostatic fluid is not indicated and perhaps even harmful because it could precipitate bacteremia or sepsis (GR: B).

4. A midstream urine specimen is sufficient and will show prominent leukocyturia and bacteriuria with typical uropathogens (GR: B).

5. The sonographic determination of residual volume is an important diagnostic procedure, because infravesical obstruction may play an important pathogenic role in acute bacterial prostatitis (GR: B).

6. Transrectal ultrasound (TRUS) does not need to be performed on every patient with suspected acute bacterial prostatitis (GoR B), but can aid in the diagnosis or exclusion of a prostatic abscess (GR: B).

7. Computer tomography (CT) and magnetic resonance imaging (MRI) offer no advantage over TRUS, unless the abscess has penetrated the confines of the prostate gland or there are further abscess foci suspected (GR: B).

8. PSA is moderately to markedly elevated in a patient with acute bacterial prostatitis, but is not a diagnostic requirement (GR: C).

9. In patients with elevated PSA serial measurement is recommended as a useful tool for follow-up (GR: B).

10. Escherichia coli is the most common pathogen encountered in acute prostatitis (GR: B).

11. There is a significantly higher rate of mixed infection in prostatitis from prior manipulation as compared with spontaneous acute prostatitis (GR: B).

Treatment

1. Rapid initiation of broad-spectrum parenteral antibiotics and symptomatic support are mandatory for the patients with acute bacterial prostatitis (GR: B).

2. Supportive measures include i.v. hydration and catheter drainage if the patient cannot void (GR: B).

3. Insertion of a suprapubic cystotomy tube is the optimal therapy for relief from urinary obstruction (GR: B).

4. In-and-out catheterization to relieve the initial obstruction or short-term (< 12 hours) indwelling catheterization with a small-caliber Foley catheter is appropriate (GR: B).

5. The selection and course of antibiotics should be adjusted according to the pathogens isolated and the results of bacterial susceptibility testing (GR: B).

Prostate abscess

1. Suspicion of a developing abscess is raised if there is no response to appropriate antibiotic therapy, and can be confirmed by TRUS (GR: B).

2. If prostatic abscess is discovered, initiation of broad-spectrum antibiotics and prompt surgical drainage is crucial (GR: B).

Introduction

Acute bacterial prostatitis constitutes a urologic emergency. It is uncommon and usually occurs in concert with a UTI but can have a dramatic presentation. Usually, many clinicians diagnose and treat the acute bacterial prostatitis empirically. A correct diagnosis has therapeutic implications since acute prostatitis may require a longer course of treatment than other forms of urinary tract infection and because the choice of antibiotic to complete treatment after fever subsides should be based on its ability to penetrate into prostatic tissue. Thus, it is of great necessity to define detailed and consensual diagnosis and treatment criteria for acute bacterial prostatitis.

Methodology

We surveyed the extensive literature regarding acute bacterial prostatitis available in Medline via Pubmed and also considered other relevant publications up to July 2014. We used terms prostatitis, bacterial prostatitis, acute bacterial prostatitis, combined with the terms: diagnosis, evaluation, management or treatment, for the search strategy. For the purpose of this review a total of 72 possibly eligible publications were included into the analysis, which were screened by title and abstracts. The limitations for this literature search were English language (two eligible publications were not fully reviewed because just only abstracts were written in English). The papers were rated according to the level of evidence and the strength of recommendations according to ICUD standards. [1][2].

Definition of the disease

Overview

Acute bacterial prostatitis represents an acute infection of the prostate gland. It is a male urinary tract infection (UTI) that has some features in common with lower UTI in females, including the etiological organisms involved and some of their urovirulence factors. The host response, however, is very different from simple cystitis and the treatment course is more complicated[3]. The prostatitis syndrome is a common healthcare issue affecting 10–14% of men of all ages and ethnicities. Acute bacterial prostatitis is associated with severe, mainly Gram-negative infection[4]. In the 1999, NIH consensus statement on prostatitis, prostatitis and prostatitis-like symptoms were classified into four broad categories[5]. Type I prostatitis refers to acute bacterial prostatitis.

Epidemiology

Overall, prostatitis syndromes are a very common presentation in the clinical setting and tend to occur in young and middle-aged men. However, acute bacterial prostatitis accounts for the rarest category among the NIH classification. It is diagnosed in less than 0.02% of all patients seen for prostatitis[6]. However, the potential morbidity and mortality of acute prostatitis constitutes a true urologic emergency[7]. It is characterized by an acute onset of pain combined with irritative and obstructive voiding symptoms in a patient with manifestations of a systemic febrile illness. The hospital admission rate for acute bacterial prostatitis in the USA in 1994 was 12.7 in 100,000 as the first, second or third principal diagnosis for hospital admission[8](LE: 4).

Characterization

Etiology

Acute bacterial prostatitis is the result of severe infection of mainly Gram-negative bacteria, which can be easily isolated from the urine. *Escherichia coli* is the most common pathogen encountered in acute prostatitis, accounting for 87% of cases[9][10][11][12][13]. However, other pathogens include *Pseudomonas, Proteus, Klebsiella, Streptococcus, Enterobacter,* and *Staphylococcus*. Mixed flora infections can occur in 2.5% of cases[9]. Some investigators reported causative microorganisms as below. *Escherichia coli* (64%), *Enterococcus* (7%), *Pseudomonas* (6%) and other Gram-negative rods (12%)[11][14](LE: 3). The spectrum of microbial etiologies reported is similar to those found in complicated female UTI, both in the case of community-acquired infections (two third of *Enterobacteriacae* sp, 5–10% of *Enterococcus* sp and *P. aeruginosa*) as well as for nosocomial infections (large proportion of resistant bacteria) [15][16](LE: 3). The prevalence of venereal agents are low, reported as 2%. These results do not support the recommendations suggesting to treat first for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* in young adults[17][18][19].

Risk factors

The mechanisms of Acute bacterial prostatitis are reflux of infected urine into the ejaculatory and prostatic ducts, an ascending urethral infection from the distal urethra, meatus and bladder direct or lymphatic invasion from the rectum, and hematogenous infection[20][21] Although many patients with acute bacterial prostatitis have no clear risk factors, underlying functional or anatomical anomalies that predispose to urogenital infections might affect the development of prostatitis. Prior manipulation of the lower urinary tract including chronic indwelling bladder catheterization, intermittent bladder catheterization, urodynamic study, transurethral surgery and prostate biopsy could be predisposing factors[22][23][24][25].

Clinical Evaluation/risk assessment

Diagnostic and staging procedures

The diagnosis of acute bacterial prostatitis does not generally present much difficulty for the urologist[26](LE: 4) and it is usually based on typical signs and symptoms[27]. Patients with symptoms of acute bacterial prostatitis have to undergo urinalysis and culture of the urine. An initial imaging of the prostate is suggested to exclude prostatic abscess [28](LE: 4).

Symptoms and signs

There are no common key symptoms of acute bacterial prostatitis. The NIH revised classification of prostatitis deals more with pathophysiology and laboratory diagnosis and describes the clinical features of acute bacterial prostatitis only briefly as "signs of acute UTI"[5](LE: 4). Irritative and/or obstructive voiding complaints including dysuria, urinary frequency and urgency are typical[5](LE: 4). Obstructive voiding complaints including hesitancy, poor interrupted stream, and even acute urinary retention are common. The patients complain of perineal and suprapubic pain and may have associated pain or discomfort of the external genitalia. The patients have a swollen prostate that is extremely painful when investigated. Patients with acute bacterial prostatitis are often acutely ill and distressed. Symptoms of systemic infection like malaise, nausea, vomiting, chills and fever may vary. These patients may even be systemically toxic, i.e. flushed, febrile,

tachycardic, tachypnoic, hypotensive, and present even with all signs and symptoms of an urosepsis[5][6][21][29](LE: 4). Digital rectal examination reveals a hot, boggy, exquisitely tender and tense prostate gland. Fluctuation during palpation is suspicious for prostatic abscess. Defecation may cause pain[27]. Perineal pain and anal sphincter spasm may complicate the digital rectal examination[29][30](LE: 4). Although a gentle rectal examination can be performed in patients who have suspected acute bacterial prostatitis, prostatic massage for the expression of prostatic fluid is not indicated and perhaps even harmful because it is painful for the patient and it could precipitate bacteremia or sepsis[4][21][29][30](LE: 4).

Urine analysis and culture

In patients presenting with acute bacterial prostatitis, a midstream urine specimen will show prominent leukocyturia and bacteriuria[27]. Midstream urine culture is considered the only laboratory evaluation of the lower urinary tract and usually shows typical uropathogens [28][31](LE: 4).

The NIH revised classification of prostatitis does not include the "four-glass-test" for diagnosis[5], because prostatic massage is not recommended during the early phase of acute bacterial prostatitis (see above)[32][33]. Moreover, expressed prostatic secretion (EPS) or voided bladder 3 urine (VB3) are not necessary because the diagnosis can be made from symptomatic presentation and midstream urine culture[7](LE: 4, GR: C).

Functional findings

The sonographic determination of residual volume is an essential diagnostic procedure, because infravesical obstruction may play an important pathogenic role in acute bacterial prostatitis[34][35] (LE: 3). And the difference in voiding problems may reflect age differences and the prostate volume. In addition, the frequency of voiding problems, particularly urinary retention, was remarkably higher in the group that underwent prior manipulation[25](LE: 3). Some investigators suggested that bladder outlet obstruction might not be the main cause of acute bacterial prostatitis[36](LE: 3). For this reason, more evidence is necessary to clarify the relationship between obstructive bladder dysfunction and acute bacterial prostatitis.

Imaging studies

No routine clinical, biological or imaging test can currently provide evidence that adequately rules out prostatic involvement in male UTI[17]. The French guideline and one American guideline just consider that "any UTI in male has the potential for a prostatic involvement"[37][38][39][40][41] [42](LE: 4).

There are only a few studies that describe ultrasonographic findings in non-abscessed acute prostatitis[43][44][45][46]. Recently, in a prospective study of 45 patients with a clinical diagnosis of acute bacterial prostatitis, transrectal ultrasound (TRUS) was performed upon admission as well as one month after antibiotic therapy and the findings correlated with the clinical presentation of disease [40]. The authors conclude that TRUS does not need to be performed on every patient with suspected acute bacterial prostatitis (as only 47% had sonographically demonstrable lesions on admission and 61% had lesions improved or disappeared post treatment), but TRUS would be indicated to exclude the presence of prostatic abscess (LE: 2a, GR: B). In conclusion, carefully performed TRUS can aid in the diagnosis or exclusion of a prostatic abscess without increasing the risk for urosepsis[40](LE: 2a, GR: B).

Current reports indicate that the more cost-intensive computer tomography (CT) and magnetic resonance imaging (MRI) offer no advantage over TRUS, unless the abscess has penetrated the confines of the prostate gland or there are further abscess foci suspected[34][35] (LE: 3).

In some papers, the investigators stated that intraprostatic color flow in patients with acute prostatitis was greater than in the normal prostate, or those with chronic inflammation or carcinoma[47](LE: 3). According to the study, in most of the patients, the vascularity of the prostate was increased in the acute phase of inflammation (15-spot scale). With recovery from infection color flow in the prostate decreased to 15 spots, the pattern in healthy men[48](LE: 3). Hypoechoic areas in the peripheral zone of the prostate can persist for a long time in patients with acute prostatitis. Color doppler ultrasonography of these areas can helps to differentiate them from those with carcinoma[49].

There are also two interesting imaging studies – one performed with prostatic Indium-labeled leukocyte scintigraphy and one performed with a combination of PSA levels and TRUS-provided evidence supporting a frequent involvement of the prostate in male UTI[50][51](LE: 2a).

The former was carried out to determine whether indium-111 (111In)-labelled leukocytes (ILLs) accumulated in the infected tissue and whether uptake responded to treatment[52]. Scintigraphs prior to antibiotic treatment showed uptake in prostates of all patients with acute bacterial prostatitis; after treatment no uptake was noted in nine out of 10 patients, and one out of 10 had markedly decreased uptake. In the patients with UTI, if there was no involvement in the prostate, no uptake occurred in prostates. ILLs could be useful for detecting acute bacterial prostatitis in the future[28].

The latter showed the prostate is concurrently involved in men with febrile UTI with a transient increase in prostate volume and serum PSA during the acute stage of disease[43][51](LE: 3). With these two concepts, the presence of an inflammatory reaction within the prostate can inform us of acute prostatitis when the diagnosis is not clear[17].

Serum prostate-specific antigen (PSA)

Although prostate-specific antigen (PSA) levels are not a mainstay of diagnosis, they are generally moderately to markedly elevated in the setting of acute bacterial prostatitis[53][54][55](LE: 3). The role of serum PSA in the differential diagnosis and evaluation of acute bacterial prostatitis is not clear. But elevated levels of PSA have been described in 70% of men with acute bacterial prostatitis[56](LE: 3) as a consequence of increased vascular permeability and disrupted epithelium of the gland. In a prospective study of 39 men with pyrexia (>38.3 °C), serum PSA levels were used to categorize patients according to an initial diagnosis of acute bacterial prostatitis, pyelonephritis, urogenital infection or fever of unknown origin. All of the 20 cases with pyrexia and elevated PSA were diagnosed and treated as acute bacterial prostatitis[53]. Game´ et al. [57]demonstrated a decreased free-to-total (f/t) PSA ratio up to 30 days following adequate antimicrobial therapy, indicating the significance of increased bound PSA in acute prostatitis[57] (LE: 3). The decrease of f/t PSA ratio has been correlated to systemic inflammation as measured by serum C reactive protein (CRP) levels. In a prospective study of 70 men with febrile UTI with prostatic involvement as measured by tPSA, this marker has been proven useful to assess prostatic infection. Effective treatment with antibiotics resulted in significantly reduced serum PSA. A decline of tPSA levels in patients after appropriate antimicrobial treatment has been suggested to indicate a healing process[43](LE: 3). So the authors recommend PSA as a concise, accurate, rapid and cost-effective tool for identifying acute bacterial prostatitis and for follow-up[28](GR: B).

Treatment

Patients with acute bacterial prostatitis are easily diagnosed and successfully treated with appropriate antibiotic therapy and possible urinary drainage, as long as the clinician keeps a high index of suspicion for prostatic abscess in patients who fail to respond quickly[29][30](LE: 4).

Principles of management

Use of antibiotics

Appropriate management of acute bacterial prostatitis includes rapid initiation of broad-spectrum parenteral antibiotics and symptomatic support [49]. Treatment of acute bacterial prostatitis is well standardized. Current guidelines for the treatment of acute bacterial prostatitis have only been worked out by the EAU[37][42](LE: 4).

Pharmacologic penetration of antibiotics in the acutely inflamed prostatic tissue is considered to be sufficient in the case of susceptible bacteria. In severe cases, parenteral administration of high doses of bactericidal antibiotics, such as a broad-spectrum penicillin derivative, a third-generation cephalosporin with or without aminoglycosides, or a fluoroquinolone, is required until fever and other parameters of acute infection are normalized. It can be performed alone or in combination with supportive measures including i.v. hydration and catheter drainage if the patient cannot void[25][58](LE: 4).

In less severe cases, an oral fluoroquinolone for 10 days may be sufficient[34](LE: 4). The selection and course of antibiotics can be adjusted according to the pathogens isolated and the results of bacterial susceptibility testing[26].

In most cases the fever resolves in 36–48 h[49][49](LE: 2a-4). After successful initial therapy, switching to an oral regimen such as a fluoroquinolone is appropriate. The oral antibiotic therapy should be continued at least for a total of two to four weeks[37][42](LE: 4) although currently there is no consensus on the optimal treatment duration.

The duration of therapy for acute prostatitis has not been well studied. If the patient is responding clinically and the pathogen is sensitive to treatment, most experts recommend that antibiotic therapy be continued for three to four weeks to prevent relapse, although a longer course is sometimes necessary[59](LE: 4, GR: C). A patient with acute bacterial prostatitis must be over-treated rather than under-treated [60](LE: 4, GR: C). Kravchick et al. reported that three months after the end of a six-week therapy, EPS cultures were still positive in a third of the men. Prolonged therapy (at least six weeks) and subsequent follow-up with Stamey's test at the three-monthly visits are required to prevent early recurrence[49](GR: B).

Antibiotic resistance

In a recent guideline for antibiotic treatment of acute bacterial prostatitis, the administration of cephalosporins or a quinolone alone or in combination with an aminoglycoside has been recommended[37][42](LE: 4).

The susceptibility to ciprofloxacin of E. coli was shown to be relatively low (76.2%) in some local areas[25](LE: 3). A result as such probably reflects the increase in resistant bacteria owing to the recent excessive use of ciprofloxacin at that local area. The guidelines for the treatment of urinary tract infection of the Infectious Disease Society of America (IDSA) published in 1999 do not

recommend a specific antibiotic for empirical treatment when the local level of resistance among E. coli strains exceeds 20%. The IDSA also emphasizes that physicians should obtain information about local resistance rates[25][61](GR: C).

As in the previous report, ciprofloxacin alone may be an inadequate choice, especially in patients with prior manipulation of the urinary tract. Considering the very low susceptibility to cephalosporins (< 60%) in pathogens other than E. coli, and the relative high isolation rates (> 40%) of pathogens other than E. coli, cephalosporins as single therapeutic agents may have limited use in this community. Most commonly, antibiotic combination therapy for acute bacterial prostatitis includes a cephalosporin and an aminoglycoside. The second- and third-generation cephalosporins have been prescribed relatively frequently for this purpose. Administration of an aminoglycoside must be confined to the group of patients without prior manipulation owing to their susceptibility. In the group of patients with prior manipulation in which pathogens other than E. coli constitute a substantial number of isolates, a combination of a cephalosporin and amikacin should be recommended for empirical therapy[25](GR: B).

Additional points to be considered

Another supportive treatment options like alpha-blockers, antipyretics or anti-inflammatory agents may be beneficial, although current data are lacking.3 Stool softeners are also recommended[21](GR: C).

Some investigators reported that empirical antibiotic treatments lead to inadequate antibiotic treatment in 42% of the cases and a higher rate of bacteriological failure. Moreover, the clinical failure rate being much higher than the bacteriological failure rate suggests that antibiotic treatment frequently induces an incomplete resolution of the symptoms, even without any early infection relapse, possibly because of a persistent underlying urological disorder[17](GR: B).

In the previous study of acute prostatitis, the abnormalities requiring surgical correction were detected in 24% of the patients after a check-up including digital rectal examination, prostatic ultrasound, post-void residual urine measurement and uroflow measurement[51](GR: B).

Follow-up and monitoring

Although the role of serum prostate-specific antigen (PSA) in the differential diagnostic evaluation of acute bacterial prostatitis is not finally proven, elevated PSA is common. Effective treatment with antibiotics results in significantly reduced serum PSA. Therefore some authors recommend PSA as a concise, accurate, rapid and cost-effective tool for identifying acute bacterial prostatitis and for the follow-up[28][31] (LE: 4).

After antibiotic treatment, the long-term response is unclear. A prospective study found a bacterial persistence rate at three months of 33% [49] (LE: 2a). Therefore, prolonged therapy of fluoroquinolones for six weeks and reevaluation after that has been recommended[49](GR: B). In this manner, patients with acute prostatitis tend to have persistent infection. Acute prostatitis tends to persist and bacterial localization cultures should be taken at subsequent follow-up visits for at least three months[49]. Along with this, PSA levels could be high even up to three months after an acute episode[49](GR: B).

Morote et al.[62]showed that acute inflammation contributed to PSA increases but did not influence the percentage of free PSA in patients with cancer-free biopsies (LE: 3). Moreover, some patients with carcinoma could be missed during the acute phase of inflammation. Therefore, PSA and TRUS monitoring are strongly recommended (GR: B).

Special considerations

Prostate abscess

Prostatic abscesses are uncommon but potentially serious manifestations of acute infection of the prostate and demand prompt treatment. It represents a severe complication of acute bacterial prostatits with an estimated incidence of 2–18%[36](LE: 3) and a mortality rate of 3–30%. Antibiotic treatment of acute bacterial prostatitis is simple but abscess formation is well described and may have devastating sequelae. Its clinical diagnosis is somewhat difficult and suspicion of a developing abscess is raised if there is no response to appropriate antibiotic therapy, and can be confirmed by TRUS[59](LE: 4). TRUS should not be postponed for > 48 h in patients who do not respond to appropriate antibiotic therapy[49](GoR B). This is particularly important for the patients with immunocompromised disease or diabetes[28][40](GR: C). Patients who are immunocompromised, especially patients who have HIV/AIDS, seem to be more susceptible to the development of acute bacterial prostatitis and to the occurrence of a potentially life-threatening prostatic abscess. The incidence rate rises to roughly 14% in those who have developed AIDS[63](LE: 3). If a prostatic abscess is discovered, initiation of broad-spectrum antibiotics and prompt surgical drainage is crucial[7][64](GR: C).

Microbiology of prostatic abscess

E. coli and Staphylococcus species are the most commonly isolated pathogens in prostatic abscess, although other pathogens, such as *Mycobacterium tuberculosis, Actinomyces, Citrobacter, Bacteroides fragilis, Aeromonas aerophyla,* and *Klebsiella pneumonia* have been reported[35][65][66][67][68][69](LE: 3). Burkholderia pseudomallei overwhelmingly predominates in the Thai population[68].

How to treat the prostatic abscess

Recommended treatment of prostatic abscess consists of broadspectrum antibiotic coverage and, in most cases, drainage of the abscess. Several surgical procedures have been described to relieve abscess formation. Transurethral incision or resection, suprapubic adenectomy, perineal incision and transrectal or transperineal prostatic puncture and drainage under sonographic guidance have been applied according to location and extension of the abscess[34][35](GR: C & B).

Transperineal incision and drainage[70]must be considered when the abscess has penetrated beyond the prostatic capsule or penetrated through the levator ani muscle[29][30](GR: C). Although transurethral unroofing and perineal drainage were once the mainstays of surgical drainage, transrectal ultrasound-guided aspiration of prostatic abscesses has been increasingly used as an effective means of drainage that may avoid the potential morbidity associated with transurethral drainage[65][71](GR: B). Some authors also support urinary diversion with a suprapubic catheter[35][66].

In small abscesses, patients may be treated conservatively by the administration of antibiotic agents together with the placement of a suprapubic catheter. The follow-up requires regular TRUS controls[34][35](GR: C & B).

Relief from obstruction

In acute bacterial prostatitis, urinary obstruction is a very common symptom. Because patients can have significant obstruction from an acutely inflamed prostate, bladder scanning for postvoid residual urine is recommended. If the residual urine is less than 100 mL, the patient should be initiated on alpha blocker therapy; if the residual is large, consideration should be given to placement of a small urethral catheter if short-term drainage is required or a suprapubic catheter if longer-term drainage is required[6][7](GR: B).

Traditionally, it has been suggested that the insertion of a suprapubic cystotomy tube is the optimal therapy because an indwelling Foley catheter may further obstruct urethral ducts, resulting in the potential to develop prostate abscesses[62][63][64](LE: 4). In most patients, however, an in-and-out catheterization to relieve the initial obstruction or short-term (<12 hours) indwelling catheterization with a small-caliber Foley catheter is appropriate[30](GR: C).

Abbreviation

URI: urinary tract infection, EPS: expressed prostatic secretion, VB3: voided bladder 3 urine, TRUS: transrectal ultrasound, CRP: C reactive protein, PSA: prostate-specific antigen

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Epididymitis

From AAUS

Contents

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Executive Summary

Epidemiology and pathogenesis

1. Epididymitis is inflammation of the epididymis, causes pain and swelling. Acute epididymitis represents sudden occurrence of pain and swelling of the epididymis associated with acute inflammation of the epididymis. Chronic epididymitis represents 3-month or longer history of symptoms of discomfort and/or pain in the scrotum, testicle or epididymis that is localized to one or both epididymis.

2. 1% patients in the urologic clinic were identified with the diagnosis of epididymitis. Most patients (80%) could be classified as chronic epididymitis (LE: 3).

3. In sexually active men younger than 35 years of age, epididymitis is commonly the result of a sexually transmitted infection; the most common organisms causing epididymitis are *N. gonorrhoeae,* and *C. trachomatis* (LE: 3).

4. In elderly men, BPH and associated stasis, UTI, and catheterization are the most common causes of epididymitis; the most common causative microorganisms in the pediatric and elderly age groups are the coliform organisms that cause bacteriuria (LE: 3).

Diagnosis

1. The microbiologic diagnosis of epididymitis can usually be determined by examination of a Gram stain of a urethral smear and/or MSU for the detectionof Gram-negative bacteria. A urethral swab and MSU should be sent for culture and sensitivity testing before antimicrobial therapy (GR: C).

2. Acute epididymitis and spermatic cord torsion should always be differentiated as soon as possible (GR: B).

Treatment

1. In acute epididymitis, antimicrobials should be selected on the empirical basis.

2. For young, sexually active men, the regimen is ceftriaxone 1000 mg intramuscularly in a single dose, plus doxycycline 100 mg orally twice a day for 10 days (GR: C).

3. In older men, fluoroquinolones are recommended as first line agents: ofloxacin 300 mg twice a day for 10 days or levofloxacin 500 mg once a day for 10days (GR: C).

4 Supportive therapy includes bed rest, up positioning of the testes (GR: C).

5. In chronic epididymitis, a 4 to 6-week trial of antibiotics that would potentially be effective against possible bacterial pathogens and *C. trachomatis* (GR: C).

Introduction

The purpose of this guideline is to identify accepted criteria for definition, classification, diagnosis, and therapy of epididymitis based on the literature search. It will help Asian urologists and GPs on diagnosis and treatment of epididymitis, and may be necessary to the collaborative studies on this field in the future. The text focuses on an infectious or inflammatory disease of the human epididymis, while the conditions such as chronic epididymalgia, epididymo-orchitis or orchitis are not included.

Definitions

Epididymitis is inflammation of the epididymis, causes pain and swelling which is almost always unilateral and relatively acute in onset. In some cases, the testes are involved in the inflammatory process (epididymo-orchitis). On the other hand, inflammatory processes of the testicle, especially virally induced orchitis, often involve the epididymis[1].

Epididymitis are classified as acute or chronic processes according to the onset and clinical course. Acute epididymitis represents sudden occurrence of pain and swelling of the epididymis associated with acute inflammation of the epididymis. Chronic epididymitis represents 3-month or greater history of symptoms of discomfort and/or pain in the scrotum, testicle or epididymis that is localized to one or both epididymis on clinical examination[2].

1% patients in the urologic clinic were identified with the diagnosis of epididymitis. Most patients (80%) could be classified as chronic epididymitis (defined as duration of symptoms for 3 or more months) (LE: 3)[3]. Less than 1% patients undergoing TURP or other transurethral procedure (LE: 3), such as holmium laser enucleation of the prostate (LE: 3), TRUS-guided biopsy of prostate (LE: 2), prostate brachytherapy (LE: 2) occur epididymitis[4][5][6][7]. Urethral catheterization is one of the risk factors of epididymitis (LE: 3)[8][9].

Typically, in epididymitis due to common bacteria and sexually transmitted organisms, the infection is spread from the urethra or bladder. In sexually active men younger than 35 years of age, epididymitis is commonly the result of a sexually transmitted infection (LE: 3). In elderly men, BPH and associated stasis, UTI, and catheterization are the most common causes of epididymitis[10][11]. Bacterial prostatitis and/or seminal vesiculitis are associated with epididymal infection in postpubertal males of all ages (LE: 3)[12]. In infants and boys, epididymitis is often related to a UTI and/or an underlying genitourinary congenital anomaly (LE: 3) or even to the presence of a foreskin (LE: 3)[13][14].

In men younger than the age of 35 who are sexually active with women, the most common organisms causing epididymitis are *N. gonorrhoeae* and *C. trachomatis* (LE: 3)[10]. The most common causative microorganisms in the pediatric and elderly age groups are the coliform organisms that cause bacteriuria (LE: 3)[15].

Tuberculosis, mycobacteria, viral, fungal, mycoplasmal and parasitic microorganisms can be associated with epididymitis. Rarely, epididymitis could be a complication of brucellosis[16]. Chronic epididymitis may result from other disease such as Behçet disease (LE: 3) or treatment with amiodarone (LE: 4)[17][18].

Clinical Evaluation

All men with epididymitis that is caused by sexually transmitted organisms have a history of sexual exposure. Lower urinary tract surgery or catheterization may cause epididymitis.

In acute epididymitis, the inflammation and swelling usually begin in the tail of the epididymis, and may quickly spread to involve the rest of the epididymis. Physical examination localizes the tenderness to the epididymis. If it continues to the testis then the swollen epididymis becomes indistinguishable from the testis. The spermatic cord is usually tender and swollen. In chronic epididymitis, may result from inadequately treated acute epididymitis, the inflammation and pain in the epididymis is usually without swelling[2].

The microbiologic diagnosis of epididymitis can usually be determined by examination of a Gram stain of a urethral smear and/or midstream urine (MSU) for the detectionof Gram-negative bacteria. The presence of intracellular Gram-negative diplococci on the smear correlates with infection with N. gonorrhoeae. The presence of only WBC on a urethral smear indicates the presence of non-gonorrhoeal urethritis. A urethral swab and MSU should be sent for culture and sensitivity testing before antimicrobial therapy (GR: C). C. Trachomatis is isolated in approximately two-thirds of these patients. Blood cultures are valuable if the patient is febrile or has systemic signs of toxicity.

Acute epididymitis and spermatic cord torsion should always be differentiated as soon as possible using all available information, including the age of the patient, history of urethritis, clinical evaluation and Doppler (duplex) scanning of testicular blood flow. High-resolution ultrasonography is reliable for the differentiation between epididymitis and spermatic cord torsion (GR: B)[19][20][21]. Chronic epididymitis can sometimes be the first clinical manifestation of urogenital tuberculosis.

Treatment

In acute epididymitis, antimicrobials should be selected on the empirical basis. Before antimicrobial therapy, a urethral swab and MSU should be obtained for microbiological investigation. (1) For young, sexually active men, who are at risk of infection with C. trachomatis or N. gonorrhoeae, a therapeutic regimen that covers both these pathogens is mandatory. As antibiotic resistance in N. gonorrhoeae increased dramatically over the last years, fluoroquinolones should not be the drugs of first choice. The proper regimen is ceftriaxone 1000 mg intramuscularly in a single dose, plus doxycycline 100 mg orally twice a day for 10 days (GR: C). (2) In older men, with BPH or other micturition disturbances, the most common urinary tract pathogens are involved, fluoroquinolones are recommended as first line agents: ofloxacin 300 mg twice a day for 10 days or levofloxacin 500 mg once a day for 10days (GR: C)[22][23].

In chronic epididymitis, a 4 to 6-week trial of antibiotics that would potentially be effective against possible bacterial pathogens and particularly *C. trachomatis* may be appropriate (GR: C) [3].

Supportive therapy includes bed rest, up positioning of the testes (GR: C). Anti-inflammatory agents, analgesics and nerve blocks have all been recommended as empirical treatment (GR: C). If uropathogens are found as causative agents, a thorough search for micturition disturbances should be carried out to prevent relapse (GR: C). In case of C. trachomatis epididymitis, the sexual partner should also be treated (GR: C)[1][3]. Urethral catheter should be withdrawn or substituted by suprapubic catheterization (GR: B)[24].

In young men, epididymitis can lead to permanent occlusion of the epididymal ducts and thus to infertility, therefore, one should consider antiphlogistic therapy with methylprednisolone, 40 mg/day, and reduce the dose by half every second day (GR: C)[1].

Abbreviations

AAUS: Asian Association of UTI and STI, BPH: benign prostatic hyperplasia, CDC: Centers for Disease Control and Prevention, EAU: European Urological Association, GPs: general practitioners, ICUD: International Consultation on Urological Diseases, MSU: mid-stream urine, STD: sexually transmitted diseases, TRUS: transrectal ultrasonography, TURP: transurethral resection of prostate, UTI: urinary tract infection, WBC: white blood cells

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Antimicrobial prophylaxis for the prostate biopsy

From AAUS

Contents

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Executive summary

Epidemiology and pathogenesis

1. Incidence of infectious complications after TRUS-Bx is reported to be 0.1-7%, those requiring admission is 0.6-4.1%.

2. Overall, reported prevalence of fluoroquinolone resistance in infectious complications after TRUS-Bx is 24-100% and considering the recent trend of increasing antimicrobial resistance, fluoroquinolone resistance is expected to rise rapidly.

Diagnosis

1. The purpose of monitoring for fluoroquinolone resistant E. coli before TRUS-Bx would be to select appropriate prophylactic antibiotics that can specifically target antimicrobial-resistant organisms.

Treatment

1. Solutions for fluoroquinolone resistance are Identifying high risk patients with history taking, pre-biopsy rectal swab culture, and changing prophylactic antimicrobials for TRUS-Bx. If pre-biopsy rectal swab culture was done, susceptible antimicrobial agent targeting the suspected causative bacteria should be used. If not, 3rd generation cephalosporins and aminoglycoside may be the optimal choice, at least in Korea.

Introduction

Transrectal ultrasound–guided prostate biopsy (TRUS-Bx) is one of the most commonly performed urologic procedure in USA and Europe, with approximately one million biopsies performed annually in each continent. TRUS-Bx is a relatively safe procedure and chances of severe complication is low, but incidence of infectious complications is recently rising, along with the potential for more severe complications such as sepsis.[1][2] Escherichia coli is the most common pathogen found in infections after TRUS-Bx.[3][4][5][6] Randomized, controlled trials showed that antibiotic prophylaxis was effective in preventing infectious complications following TRUS-Bx.[7] Fluoroquinolone is the most commonly used antimicrobial agent for prophylaxis.[7][8] However, worldwide antimicrobial resistance is rising,[9][10][11] and as such, infectious complications after TRUS-Bx by fluoroquinolone resistant E. coli is rising as well.[9][12][13][14]

Incidence of infectious complications after TRUS-Bx

Incidence of infectious complications after TRUS-Bx is reported to be 0.1-7%, those requiring admission is 0.6-4.1%.[15] In Korea, reported incidence of infectious complications after TRUS-Bx was 0.65-3.1% [16][17][18] and in another Asia-Europe multicenter study that included Korea, the reported incidence of febrile urinary tract infection (UTI) was 3.5% and those requiring admission was 3.1%.[19] In Japan, the reported incidence of febrile UTI was 0.5%-0.76%,[20][21] and in Taiwan, the incidence was 5.4% before fluoroquinolone prophylaxis and 0.9% after fluoroquinolone prophylaxis.[22] Turkish study reported an incidence of 2% that required admission.[23] Incidence of infectious complications after TRUS-Bx has been rising in recent years. In a study that analyzed complications after prostate biopsy from SEER-Medicare data from 1991 to 2007, infectious complications after prostate biopsy have increased in recent years,[1]and in a Canadian report, incidence of infectious complications that required admission was 1.0% in 1996 but the incidence increased to 4.1% in 2005, 72% of which was sepsis.[2][13] Another recent Canadian report also stated that incidence of infectious complications was 0.52% from 2002 to 2009, but the incidence increased to 2.15% from 2010 to 2011.[24] The main reason for this increase in infectious complications is the rise of fluoroquinolone resistance.[9]

Prevalence of fluoroquinolone resistance in infectious complications

In one Korean study, acute bacterial prostatitis after TRUS-Bx occurred in 1.36% of the patients and prevalence of fluoroquinolone-resistant strain was 23.8%.[25] In a Japanese study, acute bacterial prostatitis developed in 1.3% of the patients and all urine and blood cultures yielded levofloxacin-resistant E. coli.[26] In another Japanese study, rate of genitourinary tract infection was 0.76% and *E. coli* was the most frequently isolated, of which 77.8% showed levofloxacin resistance.[21] In a North American cohort, 2.77% developed infection after biopsy, of which 55% had fluoroquinolone-resistant infection,[6] In a French prospective study, 0.67% had an acute bacterial prostatitis, of which 95% showed fluoroquinolone resistance.[27] In an Australian study that analyzed E. coli bacteremia that occurred after TRUS-Bx, 62% were fluoroquinolone resistant.[28] Overall, reported prevalence of fluoroquinolone resistance in infectious complications after TRUS-Bx is 24-100% and considering the recent trend of increasing antimicrobial resistance, fluoroquinolone resistance is expected to rise rapidly. Along with the problem of fluoroquinolone resistance, one should also be wary of the emergence of extended-spectrum beta-lactamase (ESBL) producing bacteria, which in one study reported an incidence of 43% of acute prostatitis occurred after TRUS-Bx.[29]

Rectal swab culture before TRUS Bx

Investigators from US[12] and Japan[30] monitored the rates of fluoroquinolone resistant E. coli before TRUS-Bx, with results of 23% and 13% respectively. The purpose of monitoring for fluoroquinolone resistant E. coli before TRUS-Bx would be to select appropriate prophylactic antibiotics that can specifically target antimicrobial-resistant organisms. Targeted prophylaxis may not only prevent infectious complications and sepsis after TRUS-Bx, but also suppress the rise of antimicrobial resistant bacteria. In a study conducted to evaluate targeted antimicrobial prophylaxis in men undergoing TRUS-Bx in US, there were no infectious complications in the 112 men who received targeted antimicrobial prophylaxis, while there were 9 cases (including 1 of sepsis) among the 345 on empirical therapy.[31] This study also evaluated the cost-effectiveness of targeted prophylaxis, which revealed that targeted prophylaxis yielded a cost savings of $4,499 per TRUS-Bx infectious complication averted. However, debate still exists whether rectal swab culture should be routinely performed before TRUS-Bx. In a Canadian study, despite a significant correlation between those patients who developed infections and the detection of ciprofloxacin-resistant organisms, only 9.0% of the total group with ciprofloxacin resistance developed an infectious complication.[32] Future studies will need to evaluate the cost effectiveness and clinical utility of a pre-biopsy rectal culture in targeted antibiotic prophylaxis.[32]

Solutions for fluoroquinolone resistance

Identifying high risk patients with history taking

Fluoroquinolone use in the previous 3-6 months prior to TRUS-Bx was the common risk factor for fluoroquinolone resistance found in several studies. [5][33][34][35] The longer the period of fluoroquinolone use, the higher the incidence of fluoroquinolone resistance.[35] Therefore, thorough history taking is of paramount importance in order to identify recent fluoroquinolone usage for other conditions such as urinary tract infection, chronic prostatitis, heart valve surgery, artificial instrument insertion surgery etc.

Pre-biopsy rectal swab culture

Evidence for routine rectal swab culture before all TRUS-Bx is still indeterminate. However, in cases of high risk of fluoroquinolone resistance, performing pre-biopsy rectal swab culture to identify rectal bacterial flora would be of great assistance in preventing or treating infectious complications. Pre-biopsy rectal swab culture should be done 1-2 weeks before TRUS-Bx and if the patient has history of recent antimicrobial use, pre-biopsy rectal swab culture should be postponed or its results should be interpreted cautiously.

Changing prophylactic antimicrobials for TRUS-Bx

Currently, fluoroquinolone is the recommended antimicrobial for TRUS-Bx in US and European guidelines. It is also the most widely used antimicrobial agent for antimicrobial prophylaxis for TRUS-Bx in practice. However, in regions such as Korea where rates of fluoroquinolone resistance is high, following the US and European guidelines may be less effective for antimicrobial prophylaxis. If pre-biopsy rectal swab culture is done, susceptible antimicrobial agent should be used, and if it is not done, prophylactic antimicrobial agent should be changed in patients suspected of fluoroquinolone resistance. For this, there are attempts of adding aminoglycoside such as amikacin to fluoroquinolone, or using 3rd generation cephalosporins for prophylaxis. However, this may cause another problem in addition to fluoroquinolone resistance; emergence of ESBL producing bacteria. In a Korean report, 20% of patients with infectious complications were found to have ESBL producing bacteria,[25] and in a Canadian report, the incidence of ESBL producing bacteria was 4.6%.[32] ESBL producing bacteria are usually resistant to most antimicrobials with the exception of carbapenems (imipenem, meropenem). However, it is not recommended to use potent antimicrobials such as imipenem or piperacillin/tazobactam for general prophylaxis because this may eventually cause emergence of carbapenem-resistant enterobacteriaceae that could potentially make us vulnerable to fatal infections.

Treating Fluoroquinolone resistant E. coli

Because infectious complications after TRUS-Bx could be fatal, immediate admission and implementation of antimicrobials is warranted in cases suspected of sepsis. If pre-biopsy rectal swab culture was done, susceptible antimicrobial agent targeting the suspected causative bacteria should be used. If not, 3rd generation cephalosporins and aminoglycoside may be the optimal choice, at least in Korea. Because resistance of gentamicin and tobramycin is already high in Korea, amikacin is the recommended aminoglycoside. If ESBL producing bacteria is suspected or cephalosporins are ineffective, use of carbapenems such as imipenem or meropenem should not be delayed. Once the results of antimicrobial susceptibility test is confirmed, de-escalation therapy is recommended, which consists of switching from a broad-spectrum empiric antimicrobial therapy to a narrower spectrum. After patient is discharged, continued treatment for a sufficient period of time is necessary to cure prostatitis.

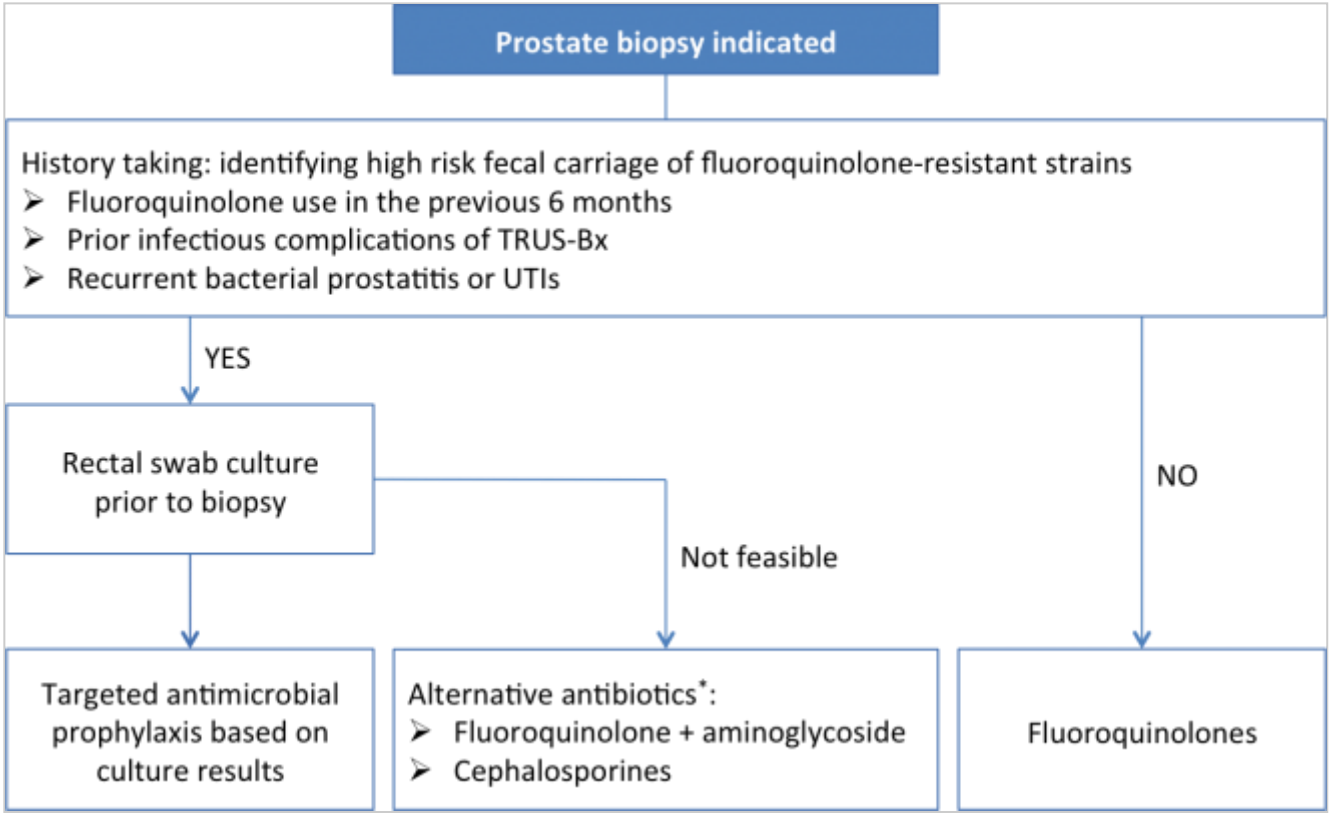

Figure 1. Flow chart to choose antibiotic prophylaxis for transrectal prostate biopsy. *Alternative antibiotics may be recommended in regions where the rate of fluoroquinolone resistance is high, but levels of evidence from clinical studies are not high.

Abbreviation

TRUS-Bx: transrectal ultrasound–guided prostate biopsy, UTI: urinary tract infection, ESBL: extended-spectrum beta-lactamase

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Diagnostic strategy for STIs

From AAUS

Contents

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Executive summary

Diagnosis

1. Diagnostic methods for *Trichomonas vaginalis* : Direct microscopic examination, Swab, and NAAT

2. Diagnostic methods for *Neisseria Gonorrhoea*: gram staining, culture, and NAAT

3. Diagnostic methods for *Chlamydia trachomatis*: culture, DFA (Direct immunofluorescence assay), EIA (Enzyme immunoassay), Rapid test, and NAAT.

Introduction

The strategies for diagnosis of sexually transmitted infections (STIs) in Asian countries are very important for the following reasons: curable STIs are frequently found in Asians; STIs can result in serious physical complications in some patients; and deplete a developing nation's economic reservoir for controlling the infections[1]. Practically, untreated early syphilis will result in a stillbirth rate of 25% and be responsible for 14% of neonatal deaths. Untreated gonococcal and chlamydia infections in women will result in pelvic inflammatory disease in up to 40% of cases. One in four of these cases will result in infertility[2][3].

STIs are not only medical problems, but also social, political, behavioral and economical problems.To solve these complicated and entangled problems, we must explore more comprehensive approaches as follows; international cooperation, national supports or international supports, and governmental or community supports. Furthermore, the strategies for detection of STIs should be designed within one's national ability or budget[4].

Clinical guidelines must be based on evidence and be of value to medical practitioners. From the review of previous guidelines, we can find that the ideal guidelines are not often practice[5][6]. Additionally, while there are very good STI or sexually transmitted diseases (STDs) guidelines around the world, STIs or STDs still thrive today.

The basic concept of a guideline is one rule for one fact with limited exceptions. However, a universal or multi-national guideline must capture the diversity of people across the Asian countries. To get an ideal STI guideline for Asian people, we must review some discrepant parts.

Which target is more appropriate for the diagnostic strategy: STDs or STIs ?

STIs have a broader meaning than STDs. The STDs get a small portion on the top of STIs ice bug. Unfortunately, some people who are STI incubators or asymptomatic can spread the pathogens to others as well as hurt themselves. Recently, the term "STIs"has been used more commonly in medical journals. Scientifically, the concept of STIs is more reasonable rather than the concept of STDs. However, while this inference is ideal in the medical sector, it is not always true in an economical perspective. In addition, etiological diagnosis of STIs is problematic for general health care providers in clinical setting and this approach increases the medical costs and reduces access to treatment.

If the strategy's target is STDs, this approach may be simple and beneficial, and the patients may show higher compliance to specific treatment. If the strategy's target is STIs, this approach may be complicated and the medical or social costs are very expensive, and we would require highly sensitive laboratory tests or screening tests to detect non-symptomatic pathogensby qualified personnels with adequate training for performing technically demanding procedures.

There are many methods for etiological diagnosis of STIs. While the standard bacterial culture method for Neisseria gonohoeae or Trichomonas vaginalis arewell established around the world, the culture method for cryptic organisms such as Chlamydia trachomatis or Mycoplasma

genitaliumare difficult to set up, time-consuming, and demanding highly qualified cell culture techniques. Many health care facilities in Asian countries lack the cell culturing equipment and trained personnel required for etiological diagnosis of STIs.

The screening tests on the base of pathogens, nucleic acid amplification technique (NAAT), can be alternative method for etiological detection of STIs. Though it is customized and the whole procedures can be automatically performed, the cost isvery expensive to test for every person who wants to check for STI, and wide use of NAAT, in practice, is not acceptable in less developedAsian countries. However, we cannot overlook serious complications of asymptomatic STIs in Asian countries. Hence, I propose a mixed step for diagnosing the STIs or STDs in Asian countries: the STI concept for the core groups or people with the high complication risk of STIs, and the STDs concept for lower prevalence groups for STIs and people with lower complication risk of STIs.I strongly recommend that the STIs core group or people with potentially serious risks after STIs infection should be tested with STIs screening tests regardless of symptoms. We should provide the NAAT for all symptomatic patients whatever the risk for STIs (Fig. 1)[7][8][9].To successfully implement this concept, we must decide "Who should be tested for screening tests in each country?" and "Who are the STI core groups in each country?"

Another important issue is that "Which STIs we should impose the weight"

There are many defined STIs in the literatures. The common pathogens or diseases are bacterial vaginosis, *Chlamydia trachomatis* (CT), genital herpes, *Neisseria gonohoeae* (NG), hepatitis B and C viral infections, human papillomavirus, HIV/AIDS, pubic lice, syphilis, and *Trichomonas vaginalis* (TV)[10].The three pathogens (CT, NG, TV) are very well known organisms for male urethritis. Today, we can definitively add on *Mycoplasma genitalium* as a urethritis pathogen, while there are many disputes that the *Ureaplasma pavum* or *U. urealyticum* can be pathogens for urethritis[9][11][12][13].

Diagnostic methods for urethritis pathogens

We need valid laboratory assays to confirm STDs from the symptomatic patients, to detect infections in asymptomatic high STIs risk individuals, and to investigate the cases of resistance to empirical treatment or to monitor the changes of antibiotics resistance patterns. The ideal diagnostic methods for STIs must be simple to perform, highly sensitive and highly specific, reproducible, rapid, and inexpensive. However, there is no one rule for covering all pathogens. Medical practitionersmust understand the feasibility and weakness of each test for each pathogen within their national ability or budget. In recent years, new methods have been developed, using molecular biology techniques. Even though the newly developed NAATs meet the criteria of optimal test for STIs, they also some disadvantages for general use in Asian countries. Additionally, we must understand the limitation of not validated in-house NAATs in Asian markets. Furthermore, the genetic sequence mutations in the target area are a critical issue or serious limitation for NAATs[14]. Interestingly, some old fashioned tests are still valid and used as a gold standard for detecting the STIs pathogens.

Trichomoniasis

Direct microscopic examination

Direct microscopic examination by medical exporters is made from a swab or urethral discharges. One drop of a physiological saline is placed into a sample on slide and immediately examined under a light microscope (x100).

Swab

A swab of secretions is taken from the urethral orifice within six hours of sample collection to inoculate a tube of Diamond's modified medium.The culture is incubated at 35°C for 3-4 days with daily examination by wet prep for motile *trichomonas*. Recently, a culture system with a two-chambered bag is available[15].

NAAT

Even though some assays are commercially available, the feasibility has not scientifically evaluated.

Table 1. Diagnostic methods for *Trichomonas vaginalis*

	Wet smear	Culture	NAAT
Sensitivity	38-82%	98%	Unknown
Specificity	100%	100%	Unknown
Sample	Urethral discharge	Urethral discharge	Urethral discharge Urine
Target	Motile *Trichomonas*	*Trichomonas*	DNA
Advantage	Rapid	Sensitive	Viable or non-viable Extremely sensitive Variable samples
Disadvantage	Very low sensitivity	Takes 3-4 days	Require expertise Amplification inhibitors
Performance	Easy	Easy	Extensive
Cost	Cheap	Cheap	Expensive

Chlamydia trachomatis

Culture

Chlamydia culture is labor-intensive, time-consuming and expensive. It also needs considerable technique to perform. For these reasons, culture techniques are not generally recommended for clinicians. Practically, some national research laboratories may be required for monitoring of antibiotics resistance or genetic mutations.

DFA (Direct immunofluorescence assay)

The urethral secretion is collected with cotton swabs,and rolled on glass slides. Fixed and stained with fluorescein-labelled antibodies for major outer membrane protein of *Chlamydia trachomatis*. The stained *Chlamydia trachomatis* can be detected with immuno fluorescence microscopy by

the trained person.

EIA (Enzyme immunoassay)

The common target of EIA for diagnosing the *Chlamydia trachomatis* is chlamydial genus-specific lipopolysaccharide (LPS) antigen. Because of sharing the structure of LPS in chlamydial genus or other Gram-negative bacteria, blocking process are needed for enhancing the specificity. The basic equipments for successful performance are commercial kits by certain companies and a microwell plate reader.

Rapid test

The main advantage for rapid test is simple and rapid in chlamydial detecting process. In addition, rapid detection and onsite treatment can be an ideal method to stop spreading the infection. However, major drawback of this test is very lower sensitivity. Furthermore, the cost for doing the test is expensive. For these reasons, we do not recommend the test for diagnosing chlamydia infection anymore.

NAAT

Today, the NAAT for *Chlamydia trachomatis* is a newly developed gold standard for detecting the infection. While the major disadvantage of the NAAT is a complicated procedure, requiring training or expertise for successful operation; today, the drawback has been solved with a semi- or full automated format. With high sensitivity for detecting the organisms, we can use various clinical samples such as urine, tampons, swabs, and direct smeared samples. With the multiple targeting ability, we can detect many STIS pathogens in one sample. However, we still consider the disadvantages of NAATs for molecular diagnosis of STIs. First of all, the cost is very expensive for routinely performing in under developed countries. Second, we must consider the technical failure with amplification inhibitors and cross-over contamination. Finally, if genetic mutation in the targeted area happens during genetic evolution, we cannot detect the infection with NAATs system.

Table 2. Diagnostic methods for *Chlamydia trachomatis*

	DFA	EIA	Rapid	NAAT
Sensitivity	80-85%	60-80%	52-85%	Unknown
Specificity	99-100%	97-99%	>95%	Unknown
Sample	Urethral discharge	Urethral discharge	Urethral discharge	Urethral discharge Urine
Target	*Chlamydia* LPS *Chlamydia* MOMP	*Chlamydia* LPS *Chlamydia* MOMP	*Chlamydia* LPS *Chlamydia* MOMP	DNA
Advantage	Rapid	Rapid	Rapid	Viable or non-viable Extremely sensitive Variable samples
Disadvantage	Require expertise Fluorescent microscope	Require expertise Microwell plate	Insensitive Expensive	Require expertise Amplification inhibitors
Performance	Moderate expensive	Moderate	Easy	Extensive
Cost	Cheap	Cheap	Expensive	Expensive

Neisseria Gonorrhoea

Gram staining

A direct Gram staining on the urethral discharge and examining under an oil immersion (X1000) has been a traditional laboratory test for *Neisseria gonorrhoeae* detection. The presence of Gram-negative diplococcic inside polymorphonuclear leukocytes is a significant diagnostic critera for *Neisseria gonorrhoeae* infection. The main advantages of Gram staining are rapid and inexpensive. This is the first recommended evaluation test for the male urethritis.

Culture[16]

Inoculating the urethral secretion on *Neisseria Gonorrhoea* selective media such as Thayer-Martin or blood agar plate is the next step after a direct Gram smear. Typical colonies are tested with Gram-stain, oxidase and catalase and/or superoxal tests for presumptive identification of *N. gonorrhoeae*. Additionally, the minimal inhibitory concentration (MIC) of antibiotics such as cefixime, ceftriaxone, fluoroquinolone, azithromycin, spectinomycin and et al are determined to establish the antimicrobial susceptibility of the strain.

NAAT

The NAATs systems are designed to combo types for detecting *Neisseria Gonorrhoea* and *Chlamydia trachomatis*. Target genes are both DNA and RNA, and the molecular techniques are polymerase chain reaction (PCR) and ligase chain reaction (LCR). Please see the section of *Chlamydia trachomatis* for understanding advantages and disadvantages.

Table 3. Diagnostic methods for *Neisseria Gonorrhoea*

	Gram smear	Culture	NAAT
Sensitivity	90-95%	81-100%	98-100%
Specificity	95-100%	100%	98-100%
Sample	Urethral discharge	Urethral discharge	Urethral discharge Urine
Target	Gram-negative diplococci in PMN	*N. gonorrhoeae*	DNA RNA
Advantage	Rapid, inexpensive	Drug resistance	Viable or non-viable Extremely sensitive Variable samples
Disadvantage	Lower sensitive in asymptomatic people	Stringent handling requires up to 3 days	Require expertise Amplification inhibitors
Performance	Easy	Moderate	Extensive
Cost	Cheap	Cheap	Expensive

Mycoplasma genitalium

Only culture and NAAT method can detect the organism and we can definitely make diagnosis of this infection. However, unfortunately, the culture method is very difficult, time-consuming, and expensive. In addition, while there are many NAATs methods for detecting the organism, we do not have authorized commercial kits to diagnose the infection[13]. *Mycoplasma genitalium* has ability for genetic mutation under evolutional pressure. One of frequent mutation sites is determining areas for antimicrobial resistance. For this reason, we must consider unique national laboratory research center for tracking the mutation and antimicrobial susceptibility. If it is not available due to either some technical problems or national medical budget problems, we can consider one or two Asian reference centers.

How to evaluate the male urethritis patient?[17][18]

Symptomatic patients

All male patients with urethral discharge must examine the gonococal infection. The first step is a Gram smear that is simple and rapid test. If Gram-negative diplococci in PMN cells are detected, we should do Neisseria Gonorrhoea culture. NAATs can be available to detect STIs from various samples. If NAATs test are positive in gonococal infection, we must do Neisseria Gonorrhoea culture.

Asymptomatic people or risk groups

Screening tests for STIs can be indicated in pregnant women, sexually active adolescents, persons in correction facility, homeless adolescents, and sex workers. While they have not shown symptoms, the risk of vertical STIs infection transmission is underestimated. In addition, the potential risk of STIs core groups for spreading the infections into bridging people must be considered. In conclusion, to establisha good Asian STIs guideline, we must consider the heterogeneous characteristics of Asian countries, and the draft must be reviewed by wide spectrums of national specialists to adjust their performance. In near future, we should set up regional or international central laboratoriesto support the diagnosis and treatment of STIs.

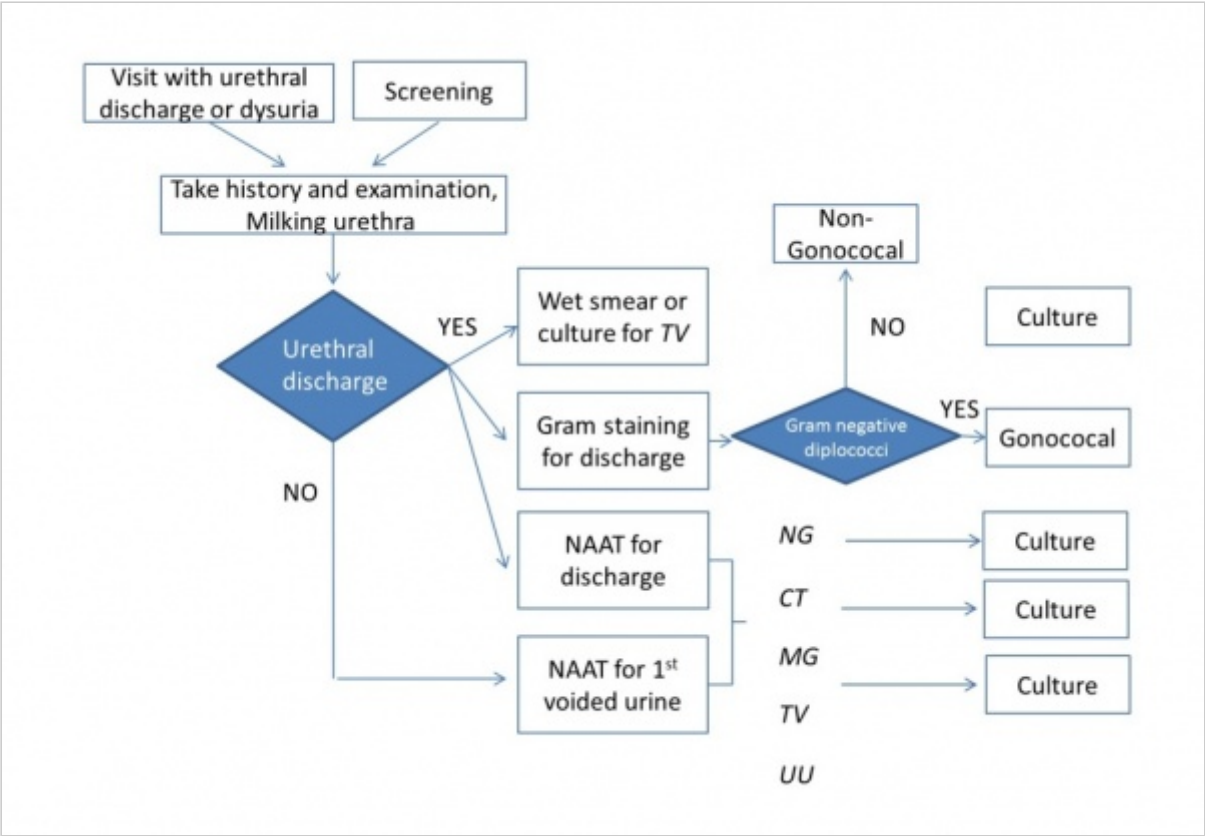

Fig. 1. Flow chart for diagnosing of male urethritis

Abbreviations

STIs: sexually transmitted infections, STDs: sexually transmitted diseases, NAAT: nucleic acid amplification technique, CT: *Chlamydia trachomatis,* TV: *Trichomonas vaginalis,* NG: *Neisseria gonohoeae,* MIC: minimal inhibitory concentration, PCR: polymerase chain reaction, LCR: ligase chain reaction

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Gonococcal urethritis

From AAUS

Contents

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Executive summary

Epidemiology and pathogenesis

1. The World Health Organization (WHO) estimated the 106.1 million of new cases of the gonococcal infections in 2008 in adults between the ages of 15 and 49 worldwide

Diagnosis

1. Diagnostic methods for *Neisseria Gonorrhoea*: gram staining, culture, and NAAT

Treatment

1. Ceftriaxone, maximum dose for *gonorrhea* in each country, intramuscularly or intravenous as a single dose. If there is an allergy to ceftriaxone or ceftriaxone is not available in the country, azithromycin 2 g orally once a day or azithromycin (extended release) 2 g orally once a day is recommended. If dual therapy to prevent antimicrobial resistance is considered, maximum dose of each drug should be used.

Introduction

A variety of antimicrobial agents have been used for the treatment of gonorrhea. The introduction of new drugs to treat gonorrhoea has repeatedly brought about the emergence and spread of Neisseria gonorrhoeae with resistance to these drugs. After clinical strains of N. gonorrhoeae became resistant to penicillin or tetracycline, ceftriaxone was recommended as the primary regimen for thetreatment of gonorrhea with ciprofloxacin as an alternative treatment option in 1989[1]. In addition to ceftriaxone, single doses of fluoroquinolones and a third-generation cephalosporin were recommended as primary treatment regimens in 1993[2]. However now oral regimens of fluoroquinolones or third-generation cephalosporins are no longer recommended because of the continuous increase in clinical strains of N. gonorrhoeae with decreased susceptibilities to these agents[3][4]. Since the early 1990s, however, clinical strains with decreased susceptibility to azithromycin have emerged in several countries worldwide[5][6]. Furthermore, high resistance to azithromycin was reported from Argentina[7]. Furthermore, the high-level ceftriaxone-resistant strain H041 was isolated from the pharynx of a female commercial sex worker in Japan in 2009[8]. The emergence and spread of N. gonorrhoeae with resistance or decreased susceptibility to these agents have led to difficulty in treating gonorrhea.Thus, other drugs for gonococcal infections are required.

Epidemiology

The World Health Organization (WHO) estimated the 106.1 million of new cases of the gonococcal infections in 2008 in adults between the ages of 15 and 49 worldwide[9]. The 2008 estimate of the number of new cases for the gonococcal infections is 21% higher than the estimate for 2005.

Clinical features

The signs and symptoms of male gonococcal urethritis include micturition pain, burning sensation of urethra,or a white or yellow purulent urethral discharge that usually appears 1 to 10 days after infection. Rectal infection may be asymptomatic. When present, symptoms of rectal infection may include discharge, anal itching, soreness, bleeding, or painful bowel movements. Pharyngitis caused by *N. gonorrhoeae* is rare and many cases are pharyngeal infection. Pharyngeal infection may cause a sore throat, but usually is asymptomatic.

Diagnosis

See chapter "Diagnostic Strategy for Sexually Transmitted Infections"

Treatment

Oral regimens of penicillin, tetracycline, fluoroquinolones or thirdgenerationcephalosporins are no longer recommended to treat *gonorrhea* because of the continuous increase in clinical strains of *N. gonorrhoeae* with decreased susceptibilities to these agents[3][4]. Single-dose intramuscular gentamicin for the treatment of uncomplicated gonococcal urethritis in men were reported cure rates of 62% to 98%[10].

Spectinomycin is good for gonococcal urethritis,[11] but clinical efficacy is low for pharyngeal infection of N. gonorrhoeaeby less tissue penetration.[12],[13] Even in heterosexual men with gonococcal urethritis, 20% have been reported to be positive for *N. gonorrhoeae* in the

pharynx[14]. Treatment of pharyngeal gonorrhea with antibiotics is more difficult than that of urethritis. Most cases of pharyngeal infection are asymptomatic, and no point-of-care tests for identifying N. gonorrhoeae from pharyngeal specimens are available in practice. The antibiotic regimens that treat not only urogenital but also pharyngeal gonorrhea should be adopted in all patients with gonorrhea. Therefore spectinomycin is not recommended to treat gonococcal urethritis.

Ceftriaxone is good for gonococcal infections including urethritis, pharyngeal infection[15]. The high-level ceftriaxone-resistant strain H041 was isolated from the pharynx of a female commercial sex worker in Japan, in 2009. Fortunately, such isolates to resistant for ceftriaxone were reported only several cases in the world afterwards. Selection of ceftriaxone resistance could occur more frequently in the pharynx than at the urogenital and anorectal sites. However, it is necessary to use high dose of ceftriaxone as much as possible to prevent antimicrobial resistance.

A single 1 g dose of azithromycin was a good efficacy of treating *gonorrhea*[16]. However, clinical strains with decreased susceptibility to azithromycin have emerged in several countries worldwide since the early 1990s[17][6]. Furthermore,high resistance to azithromycin was reported[7]. Therefore a single 1 g dose of azithromycin for g*onorrhea* is not recommended because of several reports of treatment failures, and concerns about possible rapid emergence of macrolide resistance.

A single 2 g dose of azithromycin immediate-release formulation has been reported to be effective against urethritis or pharyngeal infection[18][19][20]. And, with a single 2 g dose regimen of azithromycin (extended release) , the eradication rate of N. gonorrhoeae was high in men with gonorrhea[21][22]. However, the widespread use of the high-dose regimen of azithromycin might lead to the development of further resistance to this agent. Therefore the use of a single 2 g dose of azithromycin immediate-release formulation or a 2 g dose of azithromycin (extended release) in monotherapy would not be recommended as the first-line treatment and should be restricted to limited cases of *gonorrhea.*

Dual therapy to prevent antimicrobial resistance has recommended in several guidelines or papers[23]. However the evidence of efficacy to prevent antimicrobial resistance with dual therapy is few. Furthermore, in vitro, no synergy was found for combination therapy including azithromycin + ceftriaxone[24][25]. Therefore dual therapy to prevent antimicrobial resistance is not recommended at a present. Higher doses of antibiotics might be required to prevent the emergence of antimicrobial resistance. If dual therapy to prevent antimicrobial resistance is considered, maximum dose of each drug should be used[26].

Recommended treatment regimen

Ceftriaxone, maximum dose for gonorrhea in each country, intramuscularly or intravenous as a single dose.

If there is an allergy to ceftriaxone or ceftriaxone is not available in the country, azithromycin 2 g orally once a day or azithromycin (extended release) 2 g orally once a day is recommended. If dual therapy to prevent antimicrobial resistance is considered, maximum dose of each drug should be used.

Abbreviation

N. gonorrhoeae: Neisseria gonorrhoeae

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Chlamydial urethritis

From AAUS

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Executive summary

Epidemiology and pathogenesis

1. The high-level ceftriaxone-resistant strain H041 was isolated from the pharynx of a female commercial sex worker in Japan in 2009 (LE: 5).

Diagnosis

1. Diagnostic methods for C*hlamydia trachomatis*: culture, DFA (Direct immunofluorescence assay), EIA (Enzyme immunoassay), Rapid test, and NAAT.

Treatment

1. Oral regimens of fluoroquinolones or third-generation cephalosporins are no longer recommended because of the continuous increase in clinical strains of N. gonorrhoeae with decreased susceptibilities to these agents (LE: 2a).

2. A single 2 g dose of azithromycin has been reported to be effective against urethritis or pharyngeal infection. However clinical strains with decreased susceptibility to azithromycin have emerged in several countries worldwide (LE: 5).

3. Spectinomycinregimen is effective for gonococcal urethritis, but clinical efficacy is low for pharyngeal infection of *N. gonorrhoeae* by less tissue penetration (LE:1b).

4. Ceftriaxone regimen is effective for gonococcal infections including urethritis, pharyngeal infection (LE: 1b).

5. No synergy was found for combination therapy including azithromycin plus ceftriaxone in vitro (LE: 6).

6. Ceftriaxone, maximum dose for gonorrhea in each country, intramuscularly or intravenous as a single dose is recommended at a present (LE: 2a, GR: C1).

Introduction

A variety of antimicrobial agents havebeen used for the treatment of gonorrhea. The introduction of new drugs to treat gonococcal infections has repeatedly brought about the emergence and spread of *Neisseria gonorrhoeae* with resistance to these drugs. After clinical strains of *N. gonorrhoeae* became resistant to penicillin or tetracycline, ceftriaxone was recommended as the primary regimen for thetreatment of gonococcal infections with ciprofloxacin as an alternative treatment option in 1989.[1] In addition to ceftriaxone, single doses of fluoroquinolones and a third-generation cephalosporin were recommended as primary treatment regimens in 1993.[2] However now oral regimens of fluoroquinolones or third-generation cephalosporins are no longer recommended because of the continuous increase in clinical strains of N. gonorrhoeae with decreased susceptibilities to these agents.[3][4] Since the early 1990s, however, clinical strains with decreased susceptibility to azithromycin have emerged in several countries worldwide.[5][6] Furthermore, high resistance to azithromycin was reported from Argentina.[7] Afterwards, similar reportsfor high level resistance to azithromycin was reported in Scotland, Wales and Rome.[8][9] [10] The high-level ceftriaxone-resistant strain H041 was isolated from the pharynx of a female commercial sex worker in 2009in Japan.[11] Afterwards, F89 ceftriaxone-resistantstrains like a H041 strain were reported from France and Spain.[12][13] Furthermore, ceftriaxone treatment failuresagainst pharyngeal infection caused by *N. gonorrhoeae* were reported in several countries.

The emergence and spread of *N. gonorrhoeae* with resistance or decreased susceptibility to these agents have led to difficulty in treating gonococcal infections.Thus, other drugs for gonococcal infections are required.

Definition

Urethritis

The signs and symptoms of male gonococcal urethritis include micturition pain, burning sensation of urethra, or a white or yellow purulent urethral discharge that usually appears 1 to 10 days after infection.

Rectal infection

Rectal infection may be asymptomatic. When present, symptoms of rectal infection may include discharge, anal itching, soreness, bleeding, or painful bowel movements. Prevalence of *N. gonorrhoeae* infection per anatomic site in MSM is higher in anorectal infection than urethral or oropharyngeal infection.[14][15]

Pharyngeal infection

Pharyngitis caused by *N. gonorrhoeae* is rare and many cases are pharyngeal infection. Pharyngeal infection may cause a sore throat, but usually is asymptomatic. In heterosexual men, the prevalence of pharyngeal infection caused by *N. gonorrhoeae* with urethritis was 19.8%.[16][17][18]

Epidemiology

The World Health Organization (WHO) estimated the 106.1 million of new cases of the gonococcal infections in 2008 in adults between the ages of 15 and 49 worldwide.[19] The 2008 estimate of the number of new cases for the gonococcal infections is 21% higher than the estimate for 2005. There was a significant increase in the incidence of gonococcal infections in all of the regions including Asian region apart from the WHO European Region and the WHO Eastern Mediterranean Region.

Diagnosis

See chapter "Diagnostic Strategy for Sexually Transmitted Infections"

Treatment

Antimicrobial susceptibility

In many countries, the decreased susceptibilities for various antimicrobial agents against *N. gonorrhoeae* have been reported.In Japanese surveillance from 2012 to 2013, the susceptible rate of *N. gonorrhoeae* for PCG, CFIX, CTRX, SPCM and CPFX were 0,89.3, 100, 100 and 20.4%, respectively.[20] The MIC90 of AZM was 0.25mg/L and the rate of 1.0 mg/L was 1.9%. In Korea, the susceptible rate of *N. gonorrhoeae* for PCG, TC, CFIX, CTRX, SPCM, CPFX, and AZM were 0, 50, 91, 97, 100, 3, and 95% respectively in 2011-2013.[21] The similar reports were published in other Asian countries.[22][23][24][25][26][27][28]

Clinical study and recommended treatment

Oral regimens of penicillin, tetracycline, fluoroquinolones or third generation cephalosporins are no longer recommended to treat gonorrhea because of the continuous increase in clinical strains of *N. gonorrhoeae* with decreased susceptibilities to these agents.[3][4] Therefore, aminoglycoside, macrolide, or injectable cephalosporin are candidate of treatment for gonococcal urethritis at present. Single-dose intramuscular gentamicin for the treatment of uncomplicated gonococcal urethritis in men were reported cure rates of 62% to 98%.[29] The acceptable clinical efficacy for treatment of *gonorrhoea* is a cure rate of ≥95% with a lower 95% CI of at least 90%.[30] Thus single-dose intramuscular gentamicin is not recommended to treat gonococcal infections.

Spectinomycin is effective for gonococcal urethritis,[31] but clinical efficacy is low for pharyngeal infection of N. gonorrhoeaeby less tissue penetration.[32][33] Even in heterosexual men with gonococcal urethritis, 20% have been reported to be positive for N. gonorrhoeae in the pharynx.[16][17][18] Treatment of pharyngeal gonorrhea with antibiotics is more difficult than that of urethritis. Most cases of pharyngeal infection are asymptomatic, and no point-of-care tests for identifying N. gonorrhoeae from pharyngeal specimens are available in practice. The antibiotic regimens that treat not only urogenital but also pharyngeal *gonorrhea* should be adopted in all patients with gonorrhea. Furthermore, spectinomycin is not available in several countries. Therefore spectinomycin is not recommended to first-line treatment for gonococcal urethritis.

A single 1 g dose of azithromycin was a good efficacy of treating *gonorrhea.*[34] However, clinical strains with decreased susceptibility to azithromycin have emerged in several countries worldwide since the early 1990s.[5][6] Furthermore,high resistance to azithromycin was reported.[7][8][9][10] Therefore a single 1 g dose of azithromycin for gonococcal infections is not recommended because of several reports of treat¬ment failures, and concerns about possible rapid emergence of macrolide resistance.

A single 2 g dose of azithromycin immediate-release formulation has been reported to be effective against urethritis or pharyngeal infection.[35][36][37] And, with a single 2 g dose regimen of azithromycin (extended release) , the eradication rate of N. gonorrhoeae was high in men with gonococcal urethritis.[38][39] However, the widespread use of the high-dose regimen of azithromycin might lead to the development of further resistance to this agent. Therefore the use of a single 2 g dose of azithromycin immediate-release formulation or a 2 g dose of azithromycin (extended release) in monotherapy would not be recommended as the first-line treatment and should be restricted to limited cases of gonococcal infections.

Ceftriaxone is effective for gonococcal infections including urethritis, pharyngeal infection.Muratani et al reported that the cure rate of CTRX 1g iv therapy for gonococcal urethritis and pharyngeal infection are 100% each.[40] On the other hand, the high-level ceftriaxone-resistant strain H041 was isolated from the pharynx of a female commercial sex worker in Japan, in 2009.[11] Fortunately, such isolates to resistant for ceftriaxone were reported only several cases in the world afterwards[12][13], most N. gonorrhoeae strainsare susceptible for CTRX in the world at present.

Thus, CTRX is recommended for treatment of gonococcal infections for monotherapy. How should the dose of CTRX be recommended? The CTRX therapy for gonococcal infections is recommended in each guideline, but the doses of CTRX are variety. In CDC guideline, ceftriaxone 250 mg in a single intramuscular dose is recommended.[41] In EAU guideline, ceftriaxone, 1 g intramuscularly as a single dose is recommended.[42] In this way, the recommended dose of CTRX ranges from 125 mg to 1 g.[43] Although not spread worldwide, the high-level CTRX-resistant strain was reported.[11][12][13] However, treatment failure with CTRX therapy had reported in several articles.[11][44][45][46][47][48][49] The site of infection was pharynx in all cases

with CTRX treatment failure. Furthermore, dose of CTRX are 250 or 500mg in most cases[44][45][50][47][48][51], and in 4 reports, pharyngeal infections were cure with 1g dose of CTRX.[44][45][48][49] Selection of ceftriaxone resistance could occur more frequently in the pharynx than at the urogenital and anorectal sites because of less tissue penetration of antimicrobial agents. In addition, the single dose therapy is recommended concerning drug compliance in the treatment of the sexually transmitted infections. Thus, because of other antimicrobial agents including penicillin, tetracycline, aminoglycoside, quinolone, macrolide and other cephalosporin are notindicated for less efficacy, it is necessary to use high dose of ceftriaxone as much as possible to treat infections and to prevent antimicrobial resistance for monotherapy,

Dual therapy to prevent antimicrobial resistance has recommended in several guidelines or papers.[47] However the evidence of efficacy to prevent antimicrobial resistance with dual therapy is few. Furthermore, in vitro, no synergy was found for combination therapy including azithromycin plus ceftriaxone.[52][53] Therefore dual therapy to prevent antimicrobial resistance is not recommended at a present. Higher doses of antibiotics might be required to prevent the emergence of antimicrobial resistance. If dual therapy to prevent antimicrobial resistance is considered, maximum dose of each drug should be used.[54]

Recommended treatment regimen

Ceftriaxone, maximum dose for *gonorrhea* in each country, intramuscularly or intravenous as a single dose.

If there is an allergy to ceftriaxone or ceftriaxone is not available in the country,azithromycin 2 g orally once a day or azithromycin (extended release) 2 g orally once a dayis recommended. If dual therapy to prevent antimicrobial resistance is considered, maximum dose of each drug should be used.

Abbreviations

WHO: World Health Organization, PCG: penicillin G, CFIX: cefixime, CTRX: ceftriaxone, SPCM: spectinomycin, CPFX: ciprofloxacin, AZM: azithromycin, TC: tetracycline, MSM: men who have sex with men

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Mycoplasmal and non-chlamydial non-gonococcal urethritis

From AAUS

Contents

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Executive summary

Epidemiology and pathogenesis

1. Urethritis that occurs when neither *Neisseria gonorrhoeae* nor *Chlamydia trachomatis* is detected is called NCNGU.

2. Several microorganisms such as bacteria, viruses, or protozoa are thought to be associated to NCNGU, but only *Mycoplasma genitalium* (LE: 1a) and *Trichomonas vaginalis* (LE: 1b) have been confirmed as pathogens for male urethritis.

Diagnosis

1. *M. genitalium* is detected from urine specimens of 10-25% of male patients with symptomatic urethritis by NAATs (LE: 1a).

2. *T. vaginalis* can be detected from the urine specimens of patients who have some urethral symptoms or whose sexual partners are infected with *T. vaginalis* by microscopic examination or NAATs (LE: 1b).

Treatment

1. Azithromycin has strong activity against *M. genitalium*, and azithromycin regimens such as azithromycin 1 g orally as a single-dose or an extended azithromycin regimen such as 500 mg on day 1 followed by 250 mg daily for the following 4 days are recommended for *M. genitalium* urethritis (LE-2). However, macrolide-resistant M. genitalium strains are spreading throughout the world. Then, azithromycin-regimens would be unavailable in the future, because it is known that azithromycin can induce mutations which are closely related macrolide-resistance on the target gene of macrolides such as 23S rRNA. Therefore, some doctors argue that tetracycline regimens such as doxycycline 200 mg/day for 7 days are recommended as the first line treatment for *M. genitalium* urethritis. If azithromycin- or doxycycline-regimens fail, newer fluoroquinolone regimens such as moxifloxacin 400 mg orally per day for 10 days (LE: 3) or sitafloxacin 100 mg twice a day for 7 days (LE: 3) are recommended.

2. For *T. vaginalis* urethritis, metronidazole 2 g orally as a single dose or tinidazole 2 g as a single dose is recommended (LE: 1b). If these regimens fail, metronidazole 500 mg twice a day for 7 days is recommended (LE: 3).

3. The associations of other microorganisms such as *Ureaplasma urealyticum, Ureaplasma parvum, Mycoplasma hominis, Neisseria meningitidis,* or others with male urethritis remain unclear (LE: 4).

Introduction

Urethritis is classified as gonococcal urethritis or NGU by the presence or absence of *N. gonorrhoeae*. NGU in which *C. trachomatis* is detected by any diagnostic method is called "chlamydial urethritis", and NGU in which *C. trachomatis* is not detected is called "NCNGU". The pathogens for NCNGU have been examined, and some microorganisms such as *M. genitalium, T. vaginalis, U. urealyticum, U. parvum, M. hominis, N. meningitidis, Gardnerella vaginalis, Haemophilus* species, herpes simplex virus, adenovirus, and others are thought to be possible pathogens[1][2][3][4][5][6][7][8][9][10][11][12][13][14][15][16]. Among these, the pathogenicity of M. genitalium and T. vaginalis to the male urethra has been confirmed[16][17][18]. In this chapter, male urethritis associated with M. genitalium or *T. vaginalis* is called "*M. genitalium* urethritis" or "*Trichomonas urethritis*", respectively, and the treatment recommendations for these types of urethritis are described. In addition, the treatments for NGU are also described, because tests for detecting microorganisms related to NGU have not been available in some countries.

Pathogenicity of microorganisms for NCNGU and epidemiology

There have been several studies that have detected some micro-organisms from the urine specimens of patients with NCNGU[1][2][3][4][5][6][7][8][9][10][11][12][13][14][15][16]. *M. genitalium* is detected from 10-25% of patients with urethritis by NAATs, but it is detected from 1-7% of asymptomatic controls who attend STI clinics or who have other diseases. Taylor-Robinson proposed a modification to the Henle-Koch postulates, which focused on epidemiological studies, animal model studies, antimicrobial susceptibility testing in vitro, clinical responses to antimicrobials, and transmissibility to determine the pathogenicity of M. genitalium to the male urethra[19]. Many studies supported the pathogenicity of M. genitalium to the male urethra, and it has been finally confirmed that M. genitalium is one of the pathogens for male urethritis[17][18][20][21][22]. However, the relationships between M. genitalium and prostatitis, epididymitis, and balanoposthitis are unclear.

T. vaginalis is detected from urine specimens of 1-20% of patients with urethritis by microscopic examination or NAATs[6][9][10][11][12][13][15][23][24][25][26][27]. *T. vaginalis* is usually detected from patients whose sexual partner has trichomonal vaginitis, and most male patients are asymptomatic. However, T. vaginalis is also detected from patients who have urethral symptoms, such as urethral discomfort or dysuria, or patients whose urethritis has not been treated with antimicrobials[26]. It is thought that the pathogenicity of *T. vaginalis* to the male urethra has been confirmed[16][18].

U. urealyticum is detected from urine specimens of patients with symptomatic urethritis by NAATs, and the prevalence rates of *U. urealyticum* from urine specimens of patients with symptomatic urethritis are 7-33%[3][4][9][14][15][24][25][28][29][30][31][32][33]. The possibility of pathogenicity of *U. urealyticum* to the male urethra has been described for a long time; infection can be treated by antimicrobials that U. urealyticum is sensitive to in vitro. However, *U. urealyticum* is also detected at higher rates from men who are asymptomatic or normal control men[14][34] and these are unresolved problems. At the present time, we cannot determine the pathogenicity of *U. urealyticum* to the male urethra.

Other microorganisms such as herpes simplex virus, adenovirus, or *N. meningitidis* are possible pathogens for NCNGU. However, comparative studies between patients with urethritis and controls have not been performed to determine the pathogenicity of these microorganisms. *U. parvum* and *M. hominis* have also been detected from urine specimens of patients with urethritis, but they are also detected in normal controls at high rates, and the pathogenicity of these bacteria has yet to be determined.

Diagnosis

M. genitalium is detected only by NAATs. In some Asian countries, commercial-based tests using FVU are available, and these tests are multiplex-PCR based on including *N. gonorrhoeae, C. trachomatis, U. urealyticum, T. vaginalis*, and others[22][35][36]. *T. vaginalis* can be detected as actively motile organisms on the urinary sediments of FVU, urethral discharge, or prostate secretions on microscopy[37]. Direct immunofluorescent antibody staining or culturing is also available. Recently, NAATs have become available in some of the countries described above[36]. However, *M. genitalium* and *T. vaginalis* cannot be detected by commercial-based NAATs in many countries[21][22][27][37].

Treatment

Treatment for M. genitalium urethritis

Antimicrobial susceptibility of *M. genitalium* in vitro

The isolation of *M. genitalium* from clinical specimens has been difficult, and there are not many strains available for testing antimicrobial susceptibility[38][39]. Macrolides, tetracyclines, or fluoroquinolones are thought to have activities against *M. genitalium*. Among these antimicrobials, macrolides such as azithromycin, clarithromycin, and erythromycin have stronger activity against M. genitalium than fluoroquinolones or tetracyclines[38]. The activities of fluoroquinolones such as moxifloxacin and sitafloxacin are stronger than other fluoroquinolones such as norfloxacin, ciprofloxacin, and levofloxacin. However, antimicrobial-resistant M. genitalium strains have emerged; macrolide-resistant strains in particular are spreading throughout the world[25][39][40][41][42]. Macrolide-resistant strains have been isolated from urethral swab specimens in patients with *M. genitalium* urethritis in Australia and southern Europe[39][41]. Resistance to macrolides is strongly related to point mutations of 23S rRNA, and the detection of these mutations in *M. genitalium* DNA from urine specimens is reported from many countries. Some authors have reported treatment failure by moxifloxacin, and some mutations of the gyrA or parC gene, which are related to fluoroquinolone resistance in some bacteria, have been reported[42][43][44]. However, reports of resistant *M. genitalium* strains to fluoroquinolones have not been published.

Clinical studies of *M. genitalium* urethritis

For *M. genitalium* urethritis, more than 30 clinical trials including double-blind, randomized, control studies, comparative studies, single-arm studies, and retrospective observational studies have been reported. Between macrolides and tetracyclines, the microbiological efficacy of macrolide-regimens such as azithromycin 1 g single dose or the extended-azithromycin regimen (500 mg on day 1 followed by 250 mg daily for the following 4 days)[45] were superior to that of tetracycline-regimen such as doxycycline 100mg twice a day for 7 days[40][46]. However, the efficacy of macrolides is decreasing in recent studies because of the emergence of macrolide-resistant *M. genitalium* strains. In some countries, the microbiological efficacies of azithromycin against M. genitalium urethritis have deceased dramatically[25][40][42]. Some macrolide-resistant strains with a point mutation of 23S rRNA emerged after treatment with azithromycin 1 g as a single-dose, and it is possible that azithromycin can induce macrolide resistance[39]. Some are thinking that the azithromycin-regimens would be unavailable in the future. Therefore, some doctors argue that tetracycline regimens such as doxycycline 200 mg/day for 7 days are recommended as the first line treatment for *M. genitalium* urethritis.

Among the fluoroquinolones, the efficacy of levofloxacin was low[47][48]. Moxifloxacin 400 mg per day for 10 days or sitafloxacin 100 mg twice a day for 7 days showed good efficacy against M. genitalium urethritis[41][45][49]. Moxifloxacin was especially effective against azithromycin-treatment failure cases[39][41]. In Asia, sitafloxacin is available only in Japan and Thailand, but there is no evidence for its effectiveness in azithromycin-treatment failure cases.

Treatment for *Trichomonas* urethritis

Antimicrobial susceptibility of *T. vaginalis* in vitro

Nitroimidazoles (metronidazole or tinidazole) are the only drugs recommended for treating *T. vaginalis* infection. However, nitroimidazole-resistant strains have emerged from persistent or recurrent trichomoniasis. Metronidazole resistance was found in 4-10% of cases of vaginal trichomoniasis, and tinidazole resistance was found in 1% of cases in the USA[50][51].

Clinical studies for *T. vaginalis* urethritis

Clinical studies for trichomonas infection were performed using metronidazole or tinidazole in the period from the 1970s to the 1990s[18][52][53][54]. Metronidazole 2 g orally as a single dose or tinidazole 2 g orally as a single dose was effective, and the cure rates were 84-98% for the metronidazole regimen and 92-100% for the tinidazole regimen. For nitroimidazole-resistant strains in treatment-failure cases by single-dose regimens with metronidazole or tinidazole, an alternative regimen, metronidazole 500 mg orally twice a day for 7 days, is recommended[18][55].

Treatment regimens for NGU

The main pathogen for NGU is C. trachomatis, and azithromycin regimens such as azithromycin 1 g orally as a single dose or azithromycin 2 g orally as a single dose, or a tetracycline regimen, such as doxycycline 100 mg twice a day for 7 days or minocycline 100 mg twice a day for 7 days, is recommended. The microbiological efficacy of the doxycycline regimen for *M. genitalium* is lower, but recently the efficacy of azithromycin against *M. genitalium* has also decreased[25][40][56]. In this sense, the efficacies of azithromycin or doxycycline are almost similar. Therefore, either an azithromycin regimen or a doxycycline regimen is also recommended for NGU. If *M. genitalium* or *T. vaginalis* is detected by any method, appropriate treatment regimens for them are recommended. If these treatments fail, fluoroquinolone regimens such as moxifloxacin 400 mg a day for 10 days are recommended as the second line.

Recommendations for treatment for M. genitalium urethritis, T. vaginalis urethritis, or NGU

M. genitalium urethritis

Azithromycin regimens, including azithromycin 1 g orally as a single dose, or an extended azithromycin regimen such as 500 mg on day 1 followed by 250 mg daily for the following 4 days, are recommended as the first line treatment.

If the azithromycin regimens fail, a moxifloxacin regimen such as 400 mg orally once a day for 7 days is recommended. A sitafloxacin regimen, such as 100 mg twice a day for 7 days, is also recommended in some Asian countries.

However, the microbiological efficacies of azithromycin against *M. genitalium* are extremely low in some countries, such as the USA[25][40], Australia, Northern Europe, and others. In the near future, azithromycin regimens might not be appropriate for *M. genitalium* urethritis. The doxycycline regimen such as doxycycline 100mg twice a day for 7 days would be recommended as the first line treatment and fluoroquinolone regimens will be recommended for failure cases for doxycycline regimen.

T. vaginalis urethritis

If *T. vaginalis* is detected from specimens of patients with symptomatic urethritis or asymptomatic patients whose partners have trichomonal vaginitis, metronidazole 2 g orally as a single dose or tinidazole 2 g orally as a single dose is recommended. If the single-dose regimen fails, metronidazole 500 mg orally twice a day for 7 days is recommended.

NGU

For NGU, an azithromycin regimen such as azithromycin 1 g orally as a single dose or azithromycin 2 g orally as single dose or a tetracycline regimen such as doxycycline 100 mg twice a day for 7 days or minocycline 100 mg twice a day for 7 days is recommended for chlamydial urethritis. If one of these fails, regimens for M. genitalium or T. vaginalis regimens are recommended.

Abbreviations

NCNGU: non-chlamydial non-gonococcal urethritis, NAATs: nucleic acid amplification tests, NGU: non-gonococcal urethritis, FVU: first voided urine

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Syphilis

From AAUS

Contents

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Executive summary

The present guidelines aim to provide comprehensive information on syphilis, including the epidemiology, clinical features, diagnosis and management. The guidelines provide evidence-based recommendations on the diagnosis, prevention and treatment of syphilis in adults in Asia, including patients with HIV co-infection.

Methodology

A PubMed search was performed, using the keywords “syphilis”. A total of 3044 results were found in the last five years’ publications. A careful review of the titles and abstracts was done to find all the studies pertaining to epidemiology, clinical features, diagnosis, treatment and prevention of syphilis. After review, 262 studies were selected for analysis of full text.

Diagnosis

Dark field microscopy (LE: 2a)

Serology

1. Non-treponemal test (e.g. Rapid plasma reagin and Venereal Disease Research Laboratory) confirmed by TPHA (a treponemal test) (LE: 2a)
2. Reverse algorithm of syphilis serologic screening (LE: 2a)
3. IgM/IgG sensitive enzyme immune-assay (LE: 2a)
4. Plasmonic enzyme-linked immunosorbent assay (LE: 2b)
5. Western blotting (LE: 2b)

Point of care tests (LE: 1a)

Polymerase chain reaction (LE: 1a)

CSF analysis in suspected neurosyphilis (LE: 2a)

Treatment

Penicillin

Benzathine penicillin 2.4 million units single dose is used for early syphilis and three weekly doses are recommended in late syphilis. (LE: 1a) Similar schedule for HIV-positive population, although, for the treatment of early infectious syphilis, enhanced therapy with three dosages of benzathine penicillin G has been under consideration. (LE: 3)

Azithromycin

Azithromycin 2.0 gm administered orally as a single dose in early syphilis. (LE: 1a)

Tetracycline group

Oral doxycycline (100 mg twice daily) or oral tetracycline (500 mg 4 times a day) for 14 days for early syphilis. (LE: 3)

Cephalosporins

Ceftriaxone 1-2gm per day, given intravenously for 10-21 days in early syphilis. (LE: 2a)

Drug resistance

Azithromycin

Due to A2058G and the A2059G mutation in 23s ribosomal RNA. (LE: 2b)

Prevention

Interleukin-2 expression plasmid (pIL-2) enhanced a TpGpd DNA vaccine. (LE: 2b)

Introduction

Syphilis is a complex, systemic disease caused by the spirochete *Treponema palladium*. Syphilis is most commonly transmitted sexually or congenitally and can involve nearly every organ system. Its clinical course involves several well-characterized stages: an incubation period, a primary stage, a secondary stage, a latent stage and a late or tertiary stage.[1]

Epidemiology

According to the World Health Organization estimation, at least 12 million people worldwide are currently infected with syphilis.[2]

In 2014, baseline HIV and syphilis prevalence in China were 0.49% and 17.29% respectively. Syphilis incidence rate was 7.22 per 100 person-years.[3] Syphilis prevalence increased steadily from 5.1% in 2008 to 8.4% in 2012.[4] Unprotected receptive anal intercourse and multiple sexual partners in the last six months were the most important risk factor noted incrosssectionalanalysis of 570 patients.[5]LE(3)In the Chinese population, the HLA-DRB1*14 allele was more prevalent in syphilis patients than in the healthy controls.[6] (LE: 2a)

In India, *Treponema pallidum* was confirmed as the etiologic organism in 23% of genital ulcer, in a study of 194 patients.[7] In the Nagaland state of India, 426 female sex workers (FSWs) were recruited in 2006 and the prevalence of syphilis was found to be 21.1% and HIV prevalence was 11.7%. Being married, widowed/divorced/separated, illiterate or having a history of drug use increases the likelihood of syphilis infection.[8] (LE: 3) In India, targeted FSW interventions and STI treatment, resulted in reductions in syphilis risk.[9] (LE: 3)

In Bangkok, Thailand, during 2005-2011, a prevalence of HIV infection among 4,762 men having sex with men (MSM) was 28.3% and of syphilis was 9.8%.[10] In Hyderabad, Pakistan, fifty female sex workers were studied. Syphilis was identified in 22 (44%) females.[11]

The risk of syphilis is increased in HIV-positive population. In a study of the 402 consecutive HIV-positive patientsfrom China, the prevalence of syphilis was 12.4% and latent syphilis was the most common form. Men who have sex with men (MSM) were the largest group. (LE: 3) [12]Prevalence of syphilis infection was 16.5% in a cross-sectionalsurvey of 200 HIV-positive patients in China. Factors associated with syphilis seropositivity included receptive anal sex with a male partner in the last six months, illicit drug use in the last six months and use of antiretroviral medications . [13] (LE: 3)

An outbreak of syphilis was noted in Darkhan-Uul Province of Mongolia in 2012, the total notification rate was 62.3 per 100,000. Only 10% of cases reported using condoms during their last sexual encounter, with 65.5% reported having casual sex or multiple sex partners.[14]

Clinical

Primary syphilis

The classic solitary chancre (ulcer) of primary syphilis is seen approximately 9 to 90 days after exposure to the disease. Commonly affected sites include penis, vulva, cervix, anus, nipple, fingers, hand, eyelid, arm or oral cavity depending on the type of sexual exposure.[15][16][17][18][19][20] Because chancres are painless, presentation is usually delayed. Indurated chancre results in difficulty in retraction of the prepuce which flips over on retraction (dory-flap sign).[21] Chancre at the urethral meatus and development of stricture are rare complications of syphilis.[22] Chancres are often associated with painless local lymphadenopathy. Multiple chancres may occur and up to one-fourth may be painful, especially if superinfected with skin flora or with herpes simplex virus.[23]

Syphilitic balanitis of Follmann is a rare condition which is considered as a manifestation of primary syphilis. It presents with diffuse indurated dark red erythema of the glans penis accompanied by bilateral inguinal lymphadenopathy.[24]

Secondary syphilis

Secondary manifestations of syphilis usually begin after 3–5 months of initial infection and in a third of patients with a secondary disease, a residual chancre will be present. It presents with the classical triad of skin rash, mucosal ulceration and lymphadenopathy. It may be associated with a headache, malaise, mild fever, lymphadenopathy or sore throat. The typical maculopapular and subsequently scaly rash affecting the palms and soles occurs in over 75% cases. Other common forms of the cutaneous rash are pustular and psoriasiform lesions. Papulonodular lesions are also seen.[25][26][27] Nodular secondary syphilis simulating lepromatous leprosy have been reported.[28] It can also mimic cutaneous lymphoma[29][30] or Kaposi sarcoma.[31][32] Vesicular lesions are seen rarely.[33] Syphilitic alopecia occurs in only 4% of patients with syphilis.[34][35] Presentation as depigmented macules is known as "leucoderma syphiliticum".[36] Erythema multiforme and pityriasis lichenoides like lesions can also be seen.[37][38]

Other features of the secondary disease include condylomata lata (pale elevated papules over moist body orifices), oral mucosal erosions, mild hepatosplenomegaly and raised liver function tests, in particular, alkaline phosphatase. Cardiovascular, bone and renal complications are seen occasionally. Diffuse polyostotic osteitis with skull involvement was seen in a case of secondary syphilis in an HIV-infected patient.[39] Neurological and ophthalmological complications can occur rarely and it can also cause adrenal insufficiency and Addison's disease.[23][40][41]

Oropharyngeal involvement is common in syphilis. In one study of HIV-infected MSM, nine out of forty-four patients of syphilis had oropharyngeal manifestations. Lesions involving the anterior tonsillar pillar were the most common.[42] In a retrospective review of 23 reports describing 34 patients, the oral lesions described were non-specific ulcers, mucosal patches, keratosis, pseudomembranes and gumma. In a case series of 12 patients with oral syphilis, polymorphic types of oral lesions were found such as white patches, blistering mucositis, chronic non-specific ulcers, gumma, and necrosis of the dorsum of the tongue.[43]

Secondary syphilis can be a presenting feature secondary to an immune reconstitution syndrome in an HIV-positive patient.[44] It can also be acquired through blood transfusion, presenting without preceding primary stage, known as Syphilis d' emblee.[45]

Latent syphilis

Latent syphilis is arbitrarily divided into early or late latent infection. In early latent syphilis, the patient do not have any signs of primary or secondary disease and have positive syphilis serology, preceded by negative serology within the last two years or recent contact with an infectious case. Early latent syphilis is considered infectious to sexual partners, whereas late infection is probably not.[23] (LE: 3) Asymptomatic patients with no evidence of recent negative serology or previous treatment are classified as having late latent infection or syphilis of unknown duration. Because syphilis serology may remain positive for life even after successful treatment, a reasonable effort should be made to exclude prior infection.

About one-third of patients with latent syphilis progresses to symptomatic late disease (tertiary syphilis), which may manifest as neurosyphilis, cardiovascular syphilis or late benign syphilis (gummatous disease).[23] In a hospital-based five-year survey in STD clinic in India, describing 570 cases, 7.36% cases were diagnosed with syphilis. Primary syphilis was diagnosed in 21 (50%), secondary in 10 (24%), and latent in 11 (26%) cases. Concomitant primary chancre and lesions of secondary syphilis were seen in 2 (20%) patients.[46]

Neurosyphilis

This is a rare complication of syphilis, which affected 10% of men and 5% of women in the preantibiotic era. A detailed classification of neurosyphilis was proposed by Merritt in 1946. In asymptomatic neurosyphilis, CSF abnormalities may be present in the absence of symptoms or signs of neurological disease.

Meningovascular neurosyphilis typically occurs 5–12 years after initial infection. It usually affects the territory of the middle cerebral artery and may cause a stroke-like syndrome. Focal or generalised seizures can also occur sometimes.

Parenchymatous neurosyphilis is the cause of general paresis of the insane. Early symptoms include irritability, memory loss, personality change and insomnia. These may progress over many years to result in depression, confusion, disorientation, delusions of grandeur, paranoia and seizures. Dementia progresses to death within months to years.

Tabes dorsalis is seen as a consequence of untreated parenchymatous neurosyphilis. It is characterised by lightning pains, reduced deep tendon reflexes, paraesthesias, sensory abnormalities, Charcot's joints, and Argyll-Robertson pupils. Bladder and bowel disturbances are common. The classic visceral crises of tabes may result in severe gastrointestinal pains or laryngeal pain and hoarseness.[23]

Clinical profiles of 16 patients with neurosyphilis in north-east India was studied, between August 2008 and December 2010. The clinical spectrum included: neuropsychiatric syndromes (10), myelopathy (5), and posterior circulation stroke (1). Neuropsychiatric symptoms were dementia, behavioural abnormalities, chronic psychosis, and myelopathy syndromes including acute transverse myelitis (ATM), chronic myelopathy and syphilitic amyotrophy.[47]

A retrospective review was performed for 149 patients with neurosyphilis in China, 16.8% patients were found asymptomatic for neurosyphilis, 15.4% with syphilitic meningitis, 24.2% with meningovascular neurosyphilis, 38.9% with general paresis, 4.0% with tabes dorsalis and 0.7%

with gummatous neurosyphilis.[48]

Cardiovascular syphilis

Cardiovascular syphilis is seen after 15–30 years of initial infection and results in the proximal aortic aneurysm and aortic regurgitation. It was seen in 25% of patients with symptomatic late infection in pre-antibiotic era, but is uncommon in current practice.[23]

Late benign syphilis (gumma)

Gummas are proliferative granulomatous lesions which represent an inflammatory response to small numbers of treponemes. They may occur in the skin or within any viscera or bone. Gummas may occur as early as in the first year but usually the incubation period is over five years.[23] Nodular tertiary syphilis has been reported as the presenting manifestation of HIV.[49]

In HIV era, syphilis may promote HIV acquisition and transmission and HIV infection may alter the course and response of syphilis to treatment.[50] Malignant syphilis or lues maligna is a severe form of secondary syphilis, which is seen in HIV-infected individuals.[51] In this case of secondary syphilis, pustular lesions progress rapidly to painful ulcerative lesions associated with severe constitutional symptoms.[52][53][54]

Diagnosis

Dark field microscopy is considered as a point of care test for syphilis. (LE: 2a)[55] It becomes positive before the serological response, therefore, has diagnostic utility in very early chancre.

Serology

Nontreponemal serological tests are traditionally used for the screening followed by a treponemal specific confirmatory test. A non-treponemal test such as RPR and VDRL reactivity are known to decrease in response to therapy, in contrast to the lifelong persistence of treponemal test positivity. (LE: 2a)[56] To improve the accuracy of detection and confirmation of syphilis, it is recommended that all sera reactive in VDRL positive results regardless of their titre, should be confirmed by TPHA, a treponemal test, and low titre positivity should not be ignored. (LE: 2a)[57]

The reverse algorithm of syphilis screening using initially a treponemal assay instead of the non-treponemal assay and those who are tested positive are confirmed using non-treponemal assay. It detects a higher number of patients with positive results compared to traditional screening by rapid plasma reagin (RPR). This screening algorithm facilitates the detection of latent and early syphilis, but it also results in overtreatment and higher cost. (LE: 3)[58] On comparison of traditional and the reverse screening algorithm, reverse algorithm has higher diagnostic efficacy than the traditional algorithm with high sensitivity and specificity. (LE: 2a)[59], (LE: 2b)[60] The 2-step algorithms of nontreponemal followed by treponemal (Nontrep-First) and treponemal followed by nontreponemal (Trep-First) were compared with the 1-step algorithms (treponemal only [Trep-Only] and nontreponemal only [Nontrep-Only]) test, in a cohort of 10,000 individuals. Overtreatment rates were seen substantially higher (more than three times) for the 1-step algorithms. Among the 2-step algorithms, Nontrep-First was found to be more cost-effective. (LE: 2a)[61]

Biological false positive (CBFP) results can be seen in serological testing. Among the 63,765 tested blood samples, 206 (0.32%) had the CBFP reaction. Female sex and old age were associated with an increased likelihood of the CBFP reaction. (LE: 2b)[62] An IgM/IgG sensitive enzyme immuno-assay (EIA) can be an effective alternative to VDRL for syphilis screening. Six hundred seventy four specimens were tested by VDRL and EIA and TREP-SURE EIA was found to be marginally less sensitive than the VDRL test for screening, but it was significantly more specific. (LE: 2a)[63]

In a case series of 52 patients of primary syphilis, twenty-eight (53.8%) had a positive TS-EIA. Forty patients (76.9%) had a positive RPR including 15 patients (37.5%) with negative TS-EIA results. Thus, RPR was found to be significantly more sensitive than the EIA. (LE: 2a)[64] Plasmonic enzyme-linked immuno-assay is an enzyme-linked immuno-assay involves antibody induced enzyme-mediated surface plasmon resonance (SPR) of gold nanoparticles (AuNPs).This allows the quantitative assay of *T. pallidum* antibodies due to the remarkable colour and absorption spectral response changes of the reaction system. Sensitivity of this test is 1000-fold higher than a conventional ELISA.: (LE: 2b)[65] Western blotting is done with the serum of affected patients and is analysed for the expression of IgM and IgG against the four protein antigens Tp15, Tp17, Tp45, and Tp47. (LE: 2b)[66]

The incidence of the prozone phenomenon is low (0.83%) and it is seen particularly during primary and secondary syphilis. Pregnancy and neurosyphilis were also associated with the prozone phenomenon. It usually occurs due to high titres of antibodies, but it has also been seen in patients with a moderate/low titre. (LE: 3)[67]

Point of care tests

In resource-limited settings with poor access to laboratories for syphilis screening, rapid point-of-care (POC) tests can help in increasing the coverage of syphilis screening tests. Four POC tests most commonly used are: (i) Determine Syphilis TPH (Inverness Medical Japan Co, Ltd, Chiba, Japan); (ii) Onsite Syphilis Ab Combo Rapid TestH (CTK Biotech, San Diego, CA, USA); (iii) SD Bioline Syphilis 3.0H (Standard Diagnostics Inc, Kyonggi-do, Korea); and (iv) DPP Syphilis Screen and Confirm AssayH (Chembio Diagnostic Systems Inc, Bedford, NY, USA). All four tests use an immunochromatographic strip design where a visible coloured line appear if treponemal antibodies are detected in the specimen. The DPP Syphilis test, in addition, simultaneously detects non-treponemal antibodies by a separate coloured line on the same test strip. All four tests are almost equally sensitive and specific though sensitivity for the primary syphilis is highest with the Determine test. (LE: 2b)[68]

A systematic review and meta-analysis were conducted to evaluate the sensitivity and specificity of rapid and POC tests in blood and serum samples and rapid and POC treponemal tests showed comparable sensitivity and specificity to laboratory-based treponemal tests. (LE: 1a)[69] In India, between December 2007 and February 2008, rapid point of contact diagnostic tests (Syphicheck-WB, Qualpro Diagnostics, India) using finger-prick samples were introduced for syphilis screening. The introduction of rapid tests significantly increased the uptake of syphilis screening in this high-risk population in India. (LE: 2a)[70]

In a comparison of treponemal and nontreponemal serological tests, treponemal tests are found to be more sensitive and are recommended for clinical routine screening of syphilis. However, nontreponemal tests perform better in therapy response assessment. (LE: 2a)[71] Polymerase chain reaction

The real-time polymerase chain reaction (PCR) is sensitive and specific in the detection of T. pallidum and herpes simplex virus and it appears superior to serology in early T. pallidum infections. (LE: 2a)[72] A nested PCR (nPCR) assay specifically amplifying the tp47 gene of T. pallidum from swab and blood specimens was evaluated in a cohort of 294 patients and was found to be highly sensitive and specific for all stages of syphilis. (LE: 2a)[73]

In a systematic review of polymerase chain reaction (PCR) technique in syphilis, sensitivity was highest in the swabs from the primary genital or anal chancres and in blood from neonates with congenital syphilis. Thus PCR is a useful diagnostic tool in ulcerative lesions of syphilis, especially when serology is still negative. (LE: 1a)[74]

Diagnosis of neurosyphilis

In CSF analysis, the CSF white blood cell levels, the CSF-LDH levels, the albumin quotient and the IgA index are associated with high risk of NS. Optimal cut-off values are 10 × 106 cells/L for the CSF-WBC concentration, 19.3 U/L for the CSF lactate dehydrogenase concentration, 7.08 for the albumin quotient and 0.14 for the IgA index. LE(2a)[75] A correlation was found between CSF CXCL2 concentrations with neurosyphilis and it was shown that the CSF level of CXCL2 can be used to distinguish those with and without neurosyphilis in HIV-infected patients. (LE: 2b)[76]. Patients with asymptomatic neurosyphilis had significantly higher levels of IL-17A (8-fold) and IFN-γ (7.8-fold) in the CSF compared with patients in the no-neurosyphilis group in a case series of 33 patients with secondary and early latent syphilis. (LE: 2a)[77]

Treatment

Penicillin

Benzathine penicillin 2.4 million units (MU) single dose is used for the treatment of all persons with early syphilis. (LE: 1a) 2,78 Three weekly doses are recommended in late syphilis. (LE: 1a)[2] [78]

Enhanced therapy with three dosages of benzathine penicillin G for the treatment of early infectious syphilis has been under consideration, particularly in the human immunodeficiency virus type 1 infected population. In a study of HIV-1 infected individuals, cure rates were 97% after three dosages of benzathine penicillin G compared to 88% after a single dose. (LE: 3)[79] In an another study, HIV-positive patients with early syphilis were treated with three doses of benzathine penicillin (2.4 MU I.M.) and 92.2% cases showed a successful response. (LE: 3)[80] However, there is limited data to recommend the use of enhanced therapy.

Jarisch- Herxheimer (JH) occurs occasionally after treatment with the penicillin group. Risk factors for JH reaction include high rapid plasma reagin titers, early syphilis and prior penicillin treatment. Penicillin treatment was given to 240 patients of syphilis in a case series and the overall rate of JH reaction was 31.5% (34.6% in HIV-infected patients and 25.2% in HIV-uninfected patients). (LE: 2b)[81]

Tetracycline group

A 14-day course of oral doxycycline (100 mg twice daily) or oral tetracycline (500 mg four times a day) is recommended in early syphilis. In a study of 641 patients, a similar serological treatment success rate was observed in penicillin-treated patients and in patients treated with

doxycycline/tetracycline. (LE: 3)[82]

Azithromycin

In a multicentre randomized clinical trial of early syphilis patients, similar efficacy was observed with azithromycin 2.0 g administered orally as a single dose and benzathine penicillin G at a dosage of 2.4 million units administered intramuscularly. (LE: 1a)[2][83] Similarly, in a meta-analysis, the efficacy of azithromycin and benzathine penicillin was found to be similar in the treatment of syphilis.[2]

Drug resistant T. pallidum strains, caused by the mutations in the 23S ribosomal RNA (23S rRNA) gene are widespread and increasingly prevalent. It is most common in men who have sex with men. A2058G and A2059G mutations are the commonly found mutations. (LE: 2b)[84]

Azithromycin resistance due to the A2058G mutation was also noticed in T. pallidum in Australia. (LE: 2a)[85] Treatment failure with azithromycin has been noted in China, in both primary and secondary syphilis. Clinical as well as serological failure occurred with doses of azithromycin used for treatment in a range from four to thirty gram. This suggests that azithromycin has limited therapeutic value in this setting. (LE: 2b)[86]

Cephalosporins

Ceftriaxone 1-2 gram per day, given intravenously for 10-21 days have shown a comparable efficacy with penicillin in active syphilis in HIV-infected patients. (LE: 2a)[87] Similarly, equal efficacy with doxycycline has been seen in the treatment of early syphilis. (LE: 2b)[88] Five hundred and sixty HIV-positive syphilis patients were treated with cephalosporins and treatment failure was noticed in 51 (9.0%) patients. Multivariate logistic regression modelling demonstrated that the predictive factors associated with treatment failure were baseline RPR titer ≤ 1:16, a previous history of syphilis and a CD4 T-cell count below 350 cells/ml. (LE: 2b)[89]

Vaccine

Interleukin-2 expression plasmid (pIL-2) enhanced TpGpd DNA vaccine (pTpGpd) has been used in a rabbit Tp skin challenge model. It has shown to increase anti-TpGpd antibodies and T-cell proliferation. Clinically, it resulted in the decrease in a number of ulcer lesions and the fastest recovery. Thus, these vaccines efficiently improve the protective effect against T. pallidum spirochete infection and attenuate syphilitic lesion development. LE(2b)[90]

Abbreviations

CBFP: Chronic biological false positive results, CSF: Cerebrospinal fluid, DNA: Deoxyribonucleic acid, EIA: Enzyme immunoassay, ELISA: Enzyme-linked immunosorbent assay, FSW: Female sex worker, HIV: Human immunodeficiency virus, JH: Jarisch- Herxheimer reaction, MSM: Men who have sex with men, NS: Neurosyphilis, PCR: Polymerase chain reaction, POC: Point of care test, RNA: Ribonucleic acid, rRNA: Ribosomal ribonucleic acid, RPR: Rapid plasma reagin, STI: Sexually transmitted infection, TPHA: Treponemal haem agglutination test, VDRL: Venereal Disease Research Laboratory

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Genital herpes

From AAUS

Contents

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Executive Summary

Prevention

1. Regular male condom usage is effective in reducing the transmission risk of genital HSV-2 infection (LE: 2A, GR: B), there is no added advantage of vaginal diaphragm (LE: 1B, GR: A).

2. Circumcision can be used as an effective preventive measure in males (LE: 1A). Circumcision in spouses seems to confer protection from acquiring genital herpes in their wives (LE: 3, GR: B).

3. Oral valacyclovir and acyclovir and tenofovir1% gel can reduce the risk of sexual transmission in susceptible partners (LE: 1B, GR: A).

4. Limited data on the use of anti-HSV vaccines suggests that it is not significantly effective in preventing genital herpes (LE: 1B, GR: B).

Diagnosis

1. Tzanck smear is a rapid point-of-care test. (LE: 3)

2. Virus antigen can be detected using either DIF or antigen capture EIA. (LE: 3). It is important to perform HSV typing in patients with first-episode genital herpes. (LE: 3)

3. Viral culture has been traditionally considered as 'Gold standard' in the diagnosis of genital herpes. (LE: 4)

4. PCR is more sensitive than viral culture. (LE: 1B) It is widely regarded as the test of choice for the diagnosis of genital herpes in symptomatic patients. (LE: 4)

4. Serology: Seroconversion or a rising titre of antibodies has diagnostic significance. (LE: 2A) Type-specific assays which detect antibodies against antigenically unique glycoproteins G1 and G2 should be used. (LE: 3)

Treatment

First episode genital herpes

1. Oral acyclovir, valacyclovir and famciclovir are effective in reducing the severity and duration of symptoms (LE: 1B, GR: A). Topical antivirals are less effective than systemic agents (LE: 1B, GR: A) and topical acyclovir has been shown to be associated with resistance to oral acyclovir (LE: 3, GR: B).

Recurrent genital herpes

1. Episodic therapy with oral acyclovir, valacyclovir and famciclovir can be utilised to treat recurrent episodes (LE:IB, GR:A).

2. Suppressive therapy with all the three antiviral agents (acyclovir, valacyclovir and famciclovir) has been found to reduce the frequency of recurrences significantly in patients having six or more recurrent episodes per year (LE: 1B, GR: A), though it can benefit patients with fewer recurrences as well.

3. The suppressive therapy may be discontinued after a year to assess the recurrence frequency. It may be reasonable to re-start suppressive therapy for patients who continue to have high recurrence rates. (LE: 4, GR: C)

4. Suppressive therapy with valacyclovir is more effective than episodic therapy in reducing the frequency of recurrent episodes and improving the quality-of-life (LE: 1B, GR: A).

Management of partner

1. Adequate sexual history and history of genital herpes should be taken. Examination of the partner should be done (LE: 4, GR: C).

Genital herpes and HIV

1. There is epidemiological synergy between HSV and HIV. HSV infection is associated with increased HIV shedding and increases the risk of acquiring HIV infection (LE: 1A). HIV infection may lead to increased severity of genital herpes (LE: 3) and is associated with increased genital HSV shedding (LE 3).

2. First episode genital herpes can be treated with the same doses of antivirals as for non-HIV infected patients, but has to continued till complete resolution of lesions (LE:IIB, GR:B). Twice the standard doses for 10 days have also been recommended by some experts (LE: 4, GR: C).

3. Episodic therapy for recurrent genital herpes comprises of the standard doses as for HIV-negative patients if no significant immunosuppression; or double-the-standard dosage, if advanced HIV disease (LE: 1B, GR: A).

4. Standard doses of acyclovir and valacyclovir have been used effectively in suppressing recurrent episodes (LE: 1B, GR: A). If inadequate response, double the dose or use famciclovir 500 mg twice daily (LE: 2A, GR: B).

Drug resistance

1. Drug resistant HSV-2 is more common in HIV co-infected patients in comparison to HIV-negative individuals (LE: 3).

2. Intravenous foscarnet 40 mg/kg every 8 hours has been found to be effective in treating drug-resistance genital herpes (LE: 1B, GR: A).

3. Intravenous cidofovir has also been found to be useful in treating drug-resistant cases, even in foscarnet resistance (LE: 4, GR: C).

4. Topical cidofovir gel 0.3, 1% (LE: 1B, GR: A) and foscarnet 1% cream (LE: 2A, GR: B) have shown good response in treating drug-resistant genital herpes.

Introduction

The present guidelines aim to provide comprehensiveinformation on genital herpes, including the epidemiology, clinical features, diagnosis and management. The guidelines provide evidence-based recommendations on the prevention and treatment of genital herpes in adults in Asia, including patients with HIV co-infection.

Methodology

A PubMed search last performed on March 23, 2014, using the terms "genital herpes", "herpes genitalis", "human herpes virus type 2" and "HSV-2" was carried out. A careful review of the titles and abstracts was done to find all the studies pertaining to epidemiology, clinical features, diagnosis, treatment and prevention of genital herpes. In addition, the 2007 British Association for Sexual Health and HIV (BASHH) National Guideline for the Management of Genital Herpes, the 2010 European guidelines for management of genital herpes and the 2010 US Centers for Disease Control and Prevention (CDC) Sexually Transmitted Disease Guidelines were reviewed in detail.

Epidemiology

According to 2003 WHO estimates, the number of people aged 15–49 years who were living with HSV-2 worldwide was 536 million, or roughly 16% of the world's population in this age range. The prevalence of HSV-2 infection varies greatly with different geographic regions. Generally, the prevalence was found to be higher in developing countries as compared to developed countries. The lowest prevalence was seen in Western Europe (18% in women, 13% in men) while the highest was seen in Sub-Saharan Africa (70% and 55% in women and men, respectively).[1] Because of larger population size, Asian countries contribute more prevalent infections to the global total as compared to countries with a smaller population.

Though globally, women were found to have a higher prevalence than men, a sub-data analysis suggests that men are more commonly infected with HSV-2 in South and South-East Asia. This difference from the global scenario is more likely to be due to fewer seroprevalence studies in Asia than a true result.[1] The prevalence of HSV-2 infection increases with age and reaches a peak in the age-group 35-39 years, after which it decreases slightly.[1] Genital herpes infection is primarily caused by HSV-2, but the causative role of HSV-1 has increased over the years. In a study conducted in British Columbia, the proportion of genital herpes due to HSV-1 increased over time from 31.4% to 42.8% over a period of 8 years (1997-2005). Additionally, HSV-1 infection was more likely in females, younger age groups, and later time periods.[2] In an Australian study, cases of first-episode anogenital herpes the proportion attributable to HSV-1 increased from 29% to 42% over a 15-year period, this increase being statistically significant for heterosexual women and MSM younger than 28 years of age.[3] In the developing countries, the proportion of genital herpes caused by HSV-1 is not known, but is presumed to be low.[4] The sero-prevalence of HSV-2 in Asian countries is around 10-30% in general population,[5]with the prevalence being highest in Eastern Asian countries. The prevalence has been found to be lowest

in Japan and countries of the pacific region.[1] In India, a cross-sectional study conducted in 2006, the prevalence of HSV-2 infection was found to be 10.1% with significant differences in geographical prevalence. Females (11.3%) had a higher prevalence than males (8.9%), but the difference was not statistically significant.[6] In a cross-sectional study, the prevalence of HSV-2 infection among males in six major cities of Pakistan was 3.4%.[7]

Special population groups

In a retrospective analysis done on 500 pregnant women in Goyang, Korea, the HSV-2 sero-prevalence rate was found to be 17%,[8] while in North-East India the overall prevalence was 8.7% in pregnant women.[9]

The incidence rates for HSV-2 infection in female sex workers in Yunnan, China was found to be 21.9 per 100 person years (95% confidence interval 17.8-26.3) in an open cohort study.[10] The prevalence rates for HSV-2 infection in female sex workers in the border area between China and Vietnam was 58.3%.[11]

In a seroprevalence study done in India among 170 STI clinic attendees, 15.88% of the patients tested positive for HSV-2 IgM serology.[12] HSV-2 seroprevalence in HIV-positive individuals has been found to vary from 55-70%.[13][14][15][16][17] However, only about 20-30% of the cases manifest themselves clinically in HIV infected patients.[18][19] In MSM population, the rate of co-infection with HIV was found to be 3.2% in a Chinese study.[20] A Chinese study found that the prevalence of HSV-2 infection in MSM population was 16%.[20]

Risk factors and Prevention

Risk factors

The risk of acquiring HSV-2 infection increases with age and number of sexual partners, including sex partner concurrency. HSV-2 infection occurs more frequently in individuals with a history of other sexually acquired infections including HIV. Women and men who have sex with men (MSM) have been found to have a higher prevalence of HSV-2 infection.

Prevention

Barrier contraceptives

In a large pooled analysis of six prospective studies with individual-level condom use data, it was found that consistent condom users (those who used condom 100% of the time) had a 30% lower risk of HSV-2 acquisition as compared to those who never used condoms ($p = 0.01$) (IIA). Risk for HSV-2 acquisition increased steadily and significantly with each unprotected sex act. There was no gender difference in condom efficacy.[21] In a case-crossover study where data was pooled from six prospective studies, it was found that each unprotected act leads to a 3.6% increase in the odds of HSV-2 acquisition (odds ratio = 1.036; 95% confidence interval: 1.021-1.052), but no increase in the odds of acquisition associated with protected acts (odds ratio = 1.008; 95% confidence interval: 0.987-1.030).[22] In another study, more frequent use of condoms was found to be protective against HSV-2 acquisition, but not against HSV-1 acquisition.[23]

Additional use of vaginal diaphragm and lubricating gel has not been found to offer any additional benefit in preventing HSV-2 transmission as compared to male condom use only (LE: 1B).[24]

Circumcision

In a meta-analysis of observational studies, the reduced risk of HSV-2 acquisition among circumcised males was only borderline statistically significant (RR=0.88, 95% CI 0.77-1.01) (IA).[25] Similary, in an Indian prospective cohort study, no statistically significant protection against HSV-2 was found to be conferred on circumcised males.[26] However, in a RCT (immediate circumcision versus delayed circumcision at 24 months) done on rural Ugandan population, circumcision was found to prevent HSV-2 infection by 28% (LE: 1B).[27] In another study, male circumcision was found to reduce the HSV-2 sero-incidence by about 55%.[28]

In a small study on 40 patients, (therapeutic) circumcision appeared to reduce the frequency of recurrent genital herpes episode and prolong the disease-free interval between the two recurrences.[29] In a study done in North-east India to determine the efficacy of male circumcision in HSV-2 acquisition by spouses, the seroprevalence of HSV-2 in women with circumcised spouses (1.7%) was found to be significantly lower than those with uncircumcised spouses (9.2%).[30]

Antivirals

Valacyclovir 500mg once daily has been demonstrated to significantly reduce the risk of HSV-2 transmission among serodiscordant couples by 48% and clinical disease in the susceptible partner by 75%.[31] In another study, daily acyclovir 400mg twice daily in HIV-1/HSV-2 discordant couples failed to decrease the risk of HSV-2 transmission in susceptible partners.[32] A double-blind RCT (CAPRISA-004 trial) found vaginal tenofovir1% gel to reduce the acquisition of HSV-2 by 51% in females.[33] In another prospective trial, daily oral emtricitabine/tenofovir did not prevent HSV-2 transmission in MSMs, but reduced the proportion of patients with moderate-severe genital ulcer by half.[34]

Anti-HSV Vaccines

In a RCT, a vaccine consisting of 20 µg of glycoprotein D from HSV-2 with alum and 3-O-deacylated monophosphoryl lipid A as an adjuvant given at 0, 1 and 6 months was found to be only 20% efficacious in preventing genital herpes disease. It was more effective in preventing HSV-1 infection and disease as compared to HSV-2, though it was able to generate a humoral response against HSV-2.[35]

Classifications and Natural history

Genital herpes manifest as grouped vesicles which later become pustular and ulcerate. The erosions are superficial and have characteristic polycyclic margins. New lesions may continue to form for a few days. Complete re-epithelisation can take 1-3 weeks and usually occurs without scarring.

First episode

This is the first time an individual develops genital herpes. It can be further subdivided into true primary and non-primary.

True primary episode

The first episode is considered a true primary episode if the patient does not have antibodies against both HSV-1 and HSV-2, that is in a seronegative individual. It is usually more severe, prolonged (lasting 2-4 weeks) and associated with systemic symptoms.

Non-primary episode

The first episode is considered a non-primary episode if the patient is infected by one HSV type and has antibodies against other type. For example, a patient who has antibodies against HSV-1 and gets infected with HSV-2. Previous infection with HSV-1 reduces the severity of clinical manifestations due to HSV-2 and increases the likelihood of asymptomatic seroconversion by a factor of 2.6 ($p<0.001$).[36]

Recurrent episode

A recurrent episode is said to occur in an individual if he/she has a past history of genital herpes lesions. It is shorter than the first episode, lasting for 7-12 days before spontaneously resolving. Sometimes, a patient may have an asymptomatic first episode and may manifest as recurrent episode for the first time.

Etiology

Genital herpes is caused by a DNA virus, Herpesvirus hominis. The genital lesions are usually caused by HSV-2, though the incidence of genital HSV-1 infections is increasing.[2][3]

Natural history

The incubation period ranges from 5-14 days. Transmission often occurs in the absence of clinically detectable lesions, with asymptomatic shedding accounting for majority of viral transmission.[37][38]

HSV establishes a latent infection in the sensory ganglia which is re-activated by a trigger leading to a recurrence. The recurrence may not be clinically detectable (asymptomatic recurrence). Asymptomatic recurrence or asymptomatic viral shedding is usually more following a clinical episode and during the initial years of infection. PCR-based studies (which are more sensitive than culture-based studies) suggest that asymptomatic viral shedding occurs 12-25% of days.[39] [40]Another study suggests that only 7% of anogenital viral reactivation may manifest itself clinically. About half of such viral reactivation lasts for 12 hours or less.[41]

Clinical recurrences are more common and earlier in HSV-2 infections than HSV-1 infections. Ninety percent patients with HSV-2 infection have atleast one recurrence during the first year. Though the average number of recurrences is 4-5 per year in HSV-2 infections, it is quite variable with upto 20% patients experiencing more than 10 recurrences. Men were found to have about 20% more recurrences than women.[42] In a cohort study, the rate of HSV-1 recurrences was found to be 1.3/year in the first year of infection which fell to 0.7/year in the second year.[43] The number of recurrences gradually decreases with time at a variable rate.

Diagnosis

Genital herpetic infection is usually diagnosed clinically, especially when the clinical picture is classical, with the presence of polycyclic erosions associated with local adenitis and in recurrent cases preceded by prodrome. However, clinical diagnosis of genital herpes is not a 100% accurate and is highly dependent on clinician' skill and experience.

Tzanck smear

It is a point-of-care test which does not require expensive equipments, can be easily done in the clinician's office and yields rapid results, but is highly operator skill-dependant. In a study, the sensitivity of tzanck smear (viral culture as gold standard) in diagnosing anogenital lesions of herpes was found to be 79% for skin lesions and 81% for mucous membrane lesions in men and 52% in women. The specificity was 93%.[44] (LE: 3)

Virus antigen detection

As the natural course of HSV-2 infection is different from that of HSV-1, it is important to perform HSV typing in patients with first-episode genital herpes. (LE: 3)

HSV antigen can be detected and typed by DIF assay using fluorescein-labelled type-specific monoclonal antibodies on smears. It can be classified as a rapid diagnostic test and performs satisfactorily in symptomatic patients. However, its sensitivity may drop to less than 50% (viral culture as 'gold standard') when testing asymptomatic patients.[45][46] In a study to determine the utility of DIF test in genital herpes, there was concordance between DIF and viral culture in 85% patients whereas in about 15% patients DIF was positive when viral culture was negative. This method proved to be highly sensitive (97%) in patients with clinically suspected infection. High negative predictive value (99%) proves the clinical utility of the DIF in this group of patients. (LE: 3)[47]

Antigen capture EIA is another method which can be used to detect HSV antigen, however unlike DIF test, most of the commercially available assays do not differentiate HSV-1 from -2. The sensitivity of this method, as compared to viral culture, is atleast 95% while specificity ranges from 62-100% in symptomatic patients.[48][49][50] (LE: 3)

Viral culture

Viral culture has traditionally been considered as the 'Gold standard' in diagnosis of genital herpes (LE: 4). The sensitivity depends on the nature of the lesion, being 90% from vesicular/pustular lesions, 70% from ulcerative lesions and 27% from crusted lesions. The sensitivity further depends upon the transport and storage facilities.[51] The characteristic cytopathic effect usually appears in 24-72 hours but may take as long as 5 days. The specificity is virtually 100%. Though it is labour-intensive and takes time, the advantage is it can be used for performing anti-viral sensitivity testing. Commonly used cells, sensitive to different viruses, include mainly primary human diploid fibroblasts, such as MRC-5 cells, and cell lines, such as Vero cells (monkey kidney), HEp-2 cells (laryngeal squamous cell carcin-oma), baby hamster kidney and rabbit kidney cells. The CAM of chick embryo has been found to be a simple, cheap and efficient method of cultivation of HSV and can be used in settings where cell culture facilities are not available. (LE: 3).[52] In a study on correlating pock sizes produced on CAM with HSV typing, a 100% concordance of small pock sizes with HSV-1, and of large pock sizes with HSV-2 was found. (LE: 3)[53]

Molecular methods

PCR allows multiplication and detection of the HSV genome in clinical samples. Not only the sensitivity of PCR has been shown to be better than that of viral culture (11-71% superior to viral culture), another advantage is the requirement of less stringent transport conditions as compared to that for viral culture.[54][55][56] (LE: 1B) It is widely regarded as the test of choice for the diagnosis of genital herpes in symptomatic patients. (LE: 4) Compared with traditional PCR, rt-PCR is faster, less labor-intensive with minimal technical hands-on time and a lower risk of molecular contamination.[57] A rapid quantitative rt-PCR was found to give the result in 2 hours (range 1.5-3.5 hours). The correlation between the rapid test and conventional TaqMan PCR was excellent (R=0.96, P<.001). (LE: 2B).[58]

Serology

Serological tests detect antibodies in the serum against the virus and have traditionally plated a limited role in the management of genital herpes. They are unreliable in differentiating a primary infection from a recurrent infection as IgM antibodies are not always increased in a primary infection. Conversely, IgG antibodies can be sometimes elevated in a recent infection posing a diagnostic difficulty. In such a setting, a seroconversion or a rising titre of antibodies can help in resolving the issue. (LE: 2A) Additionally, as it is important to know whether the patient has HSV-1 or -2 infection, the serology tests which are not type-specific are not useful in the management of genital herpes. Type-specific assays which detect antibodies against antigenically unique glycoproteins G1 and G2 should be used.[59] (LE: 3)

Western blot is considered as the serological gold standard, but is not commercially available. ELISAs, which are commercially available, have about 95% sensitivity and specificity when compared to western blots.[59][60] However, the specificity of the tests varies with the population being tested, as even a highly specific test can have a poor predictive value in a population with a low prevalence. Hence, the test results should be interpreted keeping in mind the local epidemiology and the patient demographic profile. (LE: 3)

Three FDA approved kits are available now to perform type-specific serology. Diagnology's POCkittrade mark HSV-2 is a point of care test for herpes simplex virus type 2 (HSV-2) antibodies. Focus Technologies' HerpeSelect ELISAs can be used for distinguishing between HSV-1 and HSV-2. Focus Technologies' HerpeSelect Immunoblot is a novel strip immunoblot test.

Treatment

First-episode genital herpes

First-episode genital herpes can be quite severe, prolonged and usually associated with constitutional symptoms. Additionally, there is an increased risk of local and systemic complications as compared to the recurrent episodes.

All patients presenting within 3-5 days of disease onset or if still forming new lesions should be started treatment with oral antivirals.[61] Antiviral therapy does not alter the natural course of infection. Acyclovir, valacyclovir and famciclovir have been found to be effective in reducing the severity as well as the duration of symptoms.[62][63] (LE: 1B) Intravenous therapy is indicated only in certain situations, when the patient is not able to swallow, has vomiting or has a complicated infection. Topical antivirals are inferior to oral antiviral drugs.(LE: 1B) Moreover, topical acyclovir has been shown to be associated with resistance to oral acyclovir in HIV-negative individuals.[62] [64] (LE: 3)

All the recommended regimens are for 7-10 days. These are:

- Acyclovir 200 mg five times a day, or
- Acyclovir 400 mg three times a day,or
- Famciclovir 250 mg three times a day, or
- Valacyclovir 1000 mg two times a day

The choice of an antiviral agent should be based upon the cost and compliance of the therapy. The duration of therapy can be extended depending on the clinical response. Maintain hygiene by saline bathing and local anaesthetics like lignocaine can be used to alleviate pain. Benzocaine should be avoided as it is a potential sensitizer. Hospitalisation may be required in cases complicated by urinary retention, meningismus or severe constitutional symptoms. If catheterisation is necessary for urinary retention, a supra-pubic approach may be preferred over the per-urethral approach as it prevents the risk of ascending urinary tract infection.

Recurrent genital herpes

The recurrent episodes of genital herpes tend to be milder and shorter. Many episodes can be managed with supportive therapy alone.Other treatment options include episodic therapy and suppressive therapy. Treatment for the patient should be individualised taking into account patients' symptoms, frequency of recurrences and concerns.

Episodic antiviral treatment

Starting therapy within 48 hours of the onset of lesions has been shown to have a greater clinical benefit than initiating treatment later in the disease.[65] Oral acyclovir, valacyclovir and famciclovir have been found to be effective in reducing the severity and the duration of symptoms, with no advantage of one drug over the other. (LE: 1B) The mean reduction in the duration of symptoms is 1-2 days.[66][67][68] Ultra-short treatment course (1-3 days) not only has similar degree of clinical improvement as the 5-day course, but is also more convenient for the patient.[69][70] The reegimens include[71]:

Five-day regimens

- Acyclovir 800 mg twice daily
- Acyclovir 400 mg three times daily
- Valaciclovir 1000 mg once daily
- Famciclovir 125 mg twice daily

Ultra-short regimens

- Acyclovir 800 mg three times daily for 2 days
- Famciclovir 1gm twice for 1 day
- Valaciclovir 500 mg twice daily for 3 days

Suppressive antiviral therapy

Most of the earlier studies evaluating the efficacy of suppressive antiviral therapy were done on patients having six or more recurrences per year; this number has been chosen arbitrarily. Suppressive therapy may reduce the number of recurrences even in patients experiencing less frequent episodes. The decision to start suppressive therapy is a subjective one, and should be made in consultation with the patient considering the patient's needs, concerns, compliance and cost of therapy.

About half of patients on suppressive therapy become symptom-free while the other half experience a significant reduction in the frequency of recurrent episodes (by 70-80%).[61][72] Suppressive therapy with valacyclovir leads to a better QOL than episodic therapy.[73][74][75] (LE: 1B) If a patient develops a breakthrough lesion while on being suppressive therapy, the dose of antiviral should be increased to that of the episodic therapy till the lesion lasts, following which the patient is continued on the suppressive doses.

The suppressive therapy should be discontinued after a year to assess the recurrence frequency. The minimum time to assess the clinical benefit should be two recurrences. It is reasonable to re-start suppressive therapy for patients who continue to have high recurrence rates. (LE: 4)

All the three agents seem to have comparable clinical efficacy.[72][76] (LE: 1B) The recommended regimens are

- Acyclovir 400 mg twice daily
- Famciclovir 250 mg twice daily
- Valacyclovir 500 mg once daily OR 1000 mg once daily (if 10 or more recurrences per year) [72]

Counselling

As genital herpes is a recurrent disease and has a significant psycho-social burden on the affected patients, medical treatment should be supplemented with counselling. The patients should be educatedregarding the natural course of disease, available treatment options, sexual route of transmission, sexual abstinence during active lesions and safe sexual practices including promotion of condom use to prevent transmission to partner.

Management of partners

There is no evidence on which recommendations for partner notification can be based. However, we recommend examining the partner for any genital lesionsand taking history of genital herpes as it can help in the counselling process (LE: 4).

Genital herpes in HIV

There is epidemiological synergy between HSV and HIV infections. Epidemiological studies demonstrate that the seroprevalence of HSV-2 infection is disproportionately higher in HIV patients as compared to HIV-negative individuals with comparable demographic profile and a similar risk-behaviour for HSV-2 acquisition.

HSV is known to activate the replication of HIV and is associated with increased HIV shedding. This is supported by the fact that valacyclovir suppressive therapy for HSV-2 significantly reduced the plasma and genital HIV RNA levels.[77] In addition, genital HSV infection increases the risk for

HIV acquisition by 2-3 times[78] as it can facilitate HIV transmission, possibly due to a local inflammatory response at the site of herpetic lesions and breach in the genital epithelium. (LE: 1A) Conversely, increased HSV shedding has been documented in HIV positive patients, thus HIV infection can lead to an increased risk of sexual transmission of HSV.[79] HIV-associated immunosuppression can also lead to increased severity of infection, more clinical reactivations, persistence of lesions and atypical manifestations of reactivation episodes.[80][81][82] (LE: 3) The degree of immunosuppression due to HIV dictates the clinical morphology, healing time and the degree of recurrence. In untreated HIV patients, herpetic lesions can be severe, prolonged and can develop into chronic non-healing anogenital ulcers with a verrucous morphology, sometimes simulating a tumour.[83][84][85] Genital herpes can also be a manifestation of immune reconstitution inflammatory syndrome (IRIS) following initiation of anti-retroviral therapy.[86]

Though systemic antiviral drugs are effective in treating genital herpes in HIV patients as well, drug resistance is encountered more frequently in PLHIV. In a study, about 5% of HIV-patients had acyclovir-resistant HSV-2 isolates, in contrast to 0.2% in HIV-negative individuals.[64]

First-episode

Controlled trials on the optimum antiviral dose and duration are lacking for patients with genital herpes and HIV co-infection. The antiviral dose for acyclovir, valacyclovir and famciclovir is the same, but given till complete resolution of lesions.[87] (LE: 2B) If the lesions continue to persist or new lesions continue to appear after 3-5 days of treatment, increase the antiviral dose and rule out drug resistance by performing viral culture and drug-susceptibility testing.[71] Some researchers recommend using twice-the-standard dose of antivirals for a 10-day period, especially in advanced HIV infection with low CD4 counts.[88] (LE: 4) In severe cases, intravenous acyclovir 5 mg/kg thrice daily may be required for the initial few days followed by oral acyclovir to complete a minimum of 10-day course.[71]

Recurrent episode

Genital herpes recurrences are more frequent in PLHIV. Initiation of ART decreases the recurrent episodes but has less effect on the asymptomatic viral shedding. Recurrent episodes can be managed with episodic or suppressive treatment. There are no clinical trials comparing the two strategies.

Episodic treatment

Standard doses of antivirals for 5 days can be effective in patients without profound immunosuppression. The dose may have to be doubled and may have to be given for more than 5 days in patients with advanced immunosuppression.[88] (LE: 1B)

Suppressive treatment

All three antivirals have been tried for HSV suppression in PLHIV with good effect. Standard suppressive dose of acyclovir (400 mg BD) has been found to be effective. Valacyclovir 500 mg BD has been found to be better than 1g OD, while 500 mg OD has not been tried in PLHIV. It has been suggested to double the standard dose of these agents if patient continues to develop recurrences. (LE: 1B) If the suppression is still inadequate, famciclovir 500 mg twice daily can be tried.[88] (LE: 2A)

An advantage of suppressive therapy is that it has been shown to decrease not only the plasma HIV levels, but also limit the HIV disease progression in patients with dual infection. In a RCT, suppressive acyclovir therapy (400mg twice daily) was shown to reduce the risk of HIV disease progression (i.e., sustaining the CD4 count above the levels necessitating the initiation of ART) by 16% at 2 years.[89] But we feel that the data is insufficient for it to be routinely preferred over episodic therapy. The decision should be made on a case-to-case basis.

Genital herpes and drug-resistance

Drug resistance to common antiviral agents used to treat genital herpes (acyclovir, valacyclovir, famciclovir) is rare in immunocompetent individuals, but is increasingly becoming common in immunosuppressed patients. A study demonstrated that only about 0.18% HIV-negative patients had drug-resistant HSV-2, in contrast to 5.3% in HIV positive patients.[64] (LE: 3)

Acyclovir is a nucleoside analogue which is phosphorylated by the viral-thymidine kinase to form acyclovir monophosphate. This monophosphate derivative of acyclovir is then converted to acyclovir triphosphate, which in turn causes competitive inhibition of the viral DNA polymerase. Thus, HSV lacking thymidine kinase (TK-deficient strains) would demonstrate drug resistance. Because valacyclovir and famciclovir are also nucleoside analogs, acyclovir resistance confers resistance against these agents as well.

The TK-deficient viral strains have been shown to be less virulent as compared to drug-sensitive strains. The clinical reactivation of TK-deficient strains is less frequent, possibly due to a less effective establishment of latent infection.[90][91] Hence further clinical reactivations are likely to be acyclovir sensitive, despite the previous episode being acyclovir resistant (episodic drug resistance).

Drug resistant HSV isolates have shown to be associated with history of prior oral acyclovir use (especially in sub-optimal doses), persistent lesions, recurrent episodes and a low CD4 count.[64]

Drug-resistance should be suspected if lesions are not improving or the patient continues to develop new lesions while on therapy, especially in the setting of immunosuppression.

How to document and manage drug resistance?

If drug-resistance is suspected clinically, a sample should be sent for viral culture and drug-sensitivity testing. Simultaneously, a sample for viral PCR should also be sent to document HSV infection. Currently, a molecular method to test drug resistance is not available.

As partially-resistant strains can respond to higher doses of acyclovir, one approach is to treat the patient with high doses of intravenous acyclovir while waiting for the sensitivity report. Once resistance is confirmed, switching to an alternative agent like foscarnet or cidofovir is required. Foscarnet 40mg/kg every 8 hourly until complete clinical resolution has been shown to be effective in treating acyclovir-resistant genital herpes.[92] (LE: 1B) Intravenous cidofovir 5mg/kg over 1-2 hours till complete healing of lesions is another agent which has been found to be useful. It may even be effective in cases of foscarnet resistance.[93][94][95] (LE: 4) Topical cidofovir gel (0.3%, 1%) once daily for 5 days was found improve lesions of acyclovir-resistant genital herpes in HIV patients in a RCT.[96] (LE: 1B) Fifty percent (10 out of 20) patients in cidofovir arm had >50% improvement, out of which 30% (6 out of 20) had experienced complete subsidence. In an open-label non-randomised trial, topical foscarnet 1% five times a day for a mean duration of 34.5 days led to improvement in 65% (13/20) of lesions in AIDS patients with acyclovir

unresponsive genital herpes.[97] (LE: 2A) There are anecdotal reports of beneficial response with topical foscarnet 2.4%,[98] topical imiquimod 5%,[99] intralesional cidofovir[100] and oral thalidomide[101][102] in drug-resistant herpes. (LE: 3)

Abbreviations

AIDS: Acquired immunodeficiency syndrome, ART: Anti-retroviral therapy, CAM: Chorioallantoic membrane, EIA: Enzyme immunoassay, ELISA: Enzyme linked immunosorbent assay, DIF: Direct immunofluorescence, FDA: Food and drug administration, HIV: Human immunodeficiency virus, HSV: Herpes simplex virus, IRIS: Immune reconstitution inflammatory syndrome, MSM: Men having sex with men, PCR: Polymerase chain reaction, PLHIV: People living with HIV, RCT: Randomised controlled trial, rt-PCR: Real time PCR, TK: Thymidine kinase, QOL: Quality of life, WHO: World Health Organisation

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Condyloma acuminatum

From AAUS

Contents

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Executive summary

The present guidelines aim to provide comprehensive information on genital condyloma acuminata, including the epidemiology, clinical features, diagnosis and management. The guidelines provide evidence-based recommendations on the diagnosis, prevention and treatment of genital condyloma acuminata in adults in Asia, including patients with HIV co-infection.

Methodology

A PubMed search was performed, using the keywords "condyloma acuminata", "anal wart", "anogenital wart", "genital wart" and "genital HPV". A total 3291 results were found in publications during last five years. A careful review of the titles and abstracts was done to find all the studies pertaining to epidemiology, clinical features, diagnosis, treatment and prevention of conduloma acuminata. After review, 190 studies were selected for detailed analysis.

Diagnosis

Various diagnostic procedures described are

1. PCR (LE: 2b)

2. Serology (LE: 2b)

3. Immunohistochemistry (LE: 3)

Prevention

1. Vaccination (LE: 1a)

2. Male circumcision (LE: 1a)

3. Condoms (LE: 3)

Vaccination

According to AdvisoryCommittee on Immunization Practices (ACIP) recommendations, 2011, following protocol should be followed:

1. Females: Either routine vaccination with 3-dose series at age 11-12 years or through age 13-26 years if not vaccinated previously

2. Males: Routine vaccination with 3-dose series at age 11-12 years or if previously unvacci-nated through age 13-21 years

3. Vaccination is recommended through age 26 years for immuno-compromised men (including those with HIV infection) and men who have sex with men.

HIV and Condylomaacuminata

In HIV-affected individuals, the course of HPV is more aggressive, with a greater risk of treatment resistance, increased chances of intraepithelial neoplasia as well as cancers.

Treatment

Physician administered

1. Photodynamic therapy (LE: 1a)

2. Immunotherapy (LE: 1a) 3. Cryotherapy (LE: 1b)

4. Podophyllin (LE: 1b)

5. Laser (LE: 2)

6. Surgery (LE: 3)

Provider administered 1. Polyphenon 10% (LE: 1a)

2. 5- Fluorouracil (LE: 1a)

3. Interferon (LE: 1a)

4. Imiquimod 5%(LE: 1b)

5. Podophyllotoxin (LE: 1b)

6. Sinecatechins (LE: 3)

7. Cidofovir (LE: 3)

Introduction

Human papilloma virus (HPV) is the most common sexually transmitted disease in the world. Almost 80% of the world's population is exposed by the age of 50 years. HPV causes not only anogenital warts (AGW), but also oropharyngeal, genital and anal cancers.[1]

HPV infections most commonly affect young adults, females being more commonly affected than males. Over a 100 HPV types have been identified, with HPV types 6 and 11 being re-sponsible for approximately 90% of genital warts, and HPV types 16 and 18 for 70% of inva-sive cervical cancers. An important complication of genital warts is substantial psychosocial and economic burden. Apart from the inconvenience and discomfort of treatment, the fear of recurrence, transmission, and the possible threat of cancer, patients are also burdened by the shame and embarrassment related to the diagnosis of genital warts. Costs relate to routine screening for cervical cancer, treatment of genital warts, and the management and follow-up of malignancies. [2]

External genital warts or condylomata acuminata are extremely common, with between 500,000 to one million new cases diagnosed each year in the United States alone.[3] Not enough data is available for Asia.

Anal wart is another common manifestation. In a study from Spain, a prevalence of 25% was reported in 640 HIV-infected men (473 MSM and 167 heterosexuals), with most common HPV types involved were type 1 and 6.[4]

Epidemiology

In a review study, the annual incidence of AGW (including new and recurrent) ranged from 160 to 289 per 100,000 of the adult population, with a median of 194.5. New AGW incidence rates among males ranged from 103 to 168 per 100,000, with a median of 137 and among females from 76 to 191 per 100,000, with a median of 120.5 per annum. Incidence was not iced to peak before 24 years of age in females and between 25-29 years among males.[5] In a survey of 167,767 patients in a Urology clinic in Korea, the prevalence of condylomaa-cuminata was 0.37%.[6] In a study from NewDelhi, India, HPV DNA was detected in 84 (94.4%) of 89 patients of AGW by the Linear Array HPV Genotyping Test. HPV-6 and -11 were the commonest HPV types, presentin 55.05% and 41.57% of cases respectively. HPV high-risk types were present in 25.84% of cases, mostly in combination with low-risk types.[7]

In a study from Korea, HPV genotyping was done in 150 patients of genital warts, showed high-risk HPV types in 31 cases (23.5%), and of these, 27 cases (20.5%) contained both high-risk and low-risk HPV types. In the multivariate analysis, location of the lesions (base of the penis or the pubic area), morphology of the warts (papular or mixed genital warts), and lack of circumcision significantly increased the association with high-risk HPV infection in male genital warts.[8]

Risk factors

Risk factors for persistent HPV infection include multiple sex partners, sex at an early age, history of sexually transmitted infections and smoking. Condom use is only partially protective against HPV infection.[9] In a meta-analysis, in Spain, 21 studies with 8046 circumcised and 6336 uncircumcised men were included and male circumcision was associated with a sta-tistically significant reduced genital HPV prevalence.[10]

Transmission

Transmission occurs by way of skin-to-skin contact through sexual intercourse, oral sex, anal sex, or other contact involving the genital area. The virus may remain latent for months to years until a trigger causes replication of viral DNA, leading to the clinical manifestation of AGWs.

Clinical features

Human papilloma virus is the most common sexually transmitted infection in the world. Genital HPV infection can be divided into low-risk infections (causing AGWs) and high-risk infections (causing cervical intraepithelial neoplastic (CIN), and cervical and other cancers). External genital warts occur at multiple sites in nearly 50% of patients and typically appear in anogenital areas, such as the vulva, penis, groin, perineum, perianal skin, or mucosal surfaces.

Four main morphological types are condylomatous, keratotic, papular, and flat. Papular warts are skin-colored, dome-shaped papules of 1- to 4-mm size, that occur only on the fully keratinized skin. Flat warts can occur on the fully keratinized skin or moist skin and are macules or barely elevated papules. Keratotic warts have thick horny layer and are seen only on the fully keratinized skin. Condyloma acuminata are a cauliflower shaped lesion, seen only on the moist surfaces. 10 Physical symptoms may also accompany warts, such as pruritus, burning, pain, and obstruction. [11]

Patients with anal condyloma acuminata may be asymptomatic or present with painless papules, itching, and discharge or bleeding per rectum. It is not uncommon to have involvement of more than one area; multiple lesions may also be present and extend into the anal canal or rectum.[12] Various studies support the importance of an exhaustive proctological examination in patients suffering from condylomatosis of the genital area, as it was found that out of 362 patients with both endoanal and perianal condyloma, only half of them were detectable by perianal clinical examination.[13]

HPV-associated intermediate malignancy or premalignant conditions include giant condyloma acuminata (also called Buschke-Loewenstein tumor), anal, penile and vaginal or vulvar intraepithelial neoplasia while frankly malignant diseases include invasive anal, penile, or vulvar carcinoma. In HIV-infected individuals, the course of HPV is more aggressive, more risk of treatment-resistant with increase chances of intraepithelial neoplasia as well as can-cers.[14]

Diagnosis

Most condylomata are diagnosed clinically on the basis of their characteristic morphology and location. Investigations for diagnosis and management are needed only in a small proportion of cases.

Histopathology

A Biopsy is indicated in the case of atypical lesions, lesions with doubtful diagnosis, larger lesions, lesions that are not responsive to therapy and in immuno-compromised patients. In immuno-histochemistry, P16 staining is found to be useful in differentiating condyloma acuminate from bowenoid papulosis. In a study, 36 skin biopsy specimens (24 samples of condy-loma and 12 of bowenoid papulosis) were stained with an antibody to p16 protein and all cas-es of bowenoid papulosis showed diffuse while 75% of condyloma lesions showed sporadic and focal positive staining for p16 protein. (LE: 3)[15]

In situ hybridisation

Rarely, in some cases, additional confirmation of HPV infection or typing maybe desired, where in-situ hybridization (ISH) test maybe useful. It can detect a very low copy number of HPV DNA sequences in paraffin-embedded tissue sections. In a study, 210 cervical tissue specimens were evaluated to detect HPV DNA using ISH and PCR, and a concordance rate of 78.2% was found between these two modalities.(LE: 3)[16]

Polymerase chain reaction

HPV L1 sequencing and type-specific HPV-6, 11, 16, and 18 real-time polymerase chain reaction for identification and typing of HPV can be done, however this test is useful only for research settings and has not much diagnostic or prognostic value. (LE: 2b)[17]

Serology

Serology is used occasionally. When measured in cases of suspected HPV infection, 36% (18/50) of sera were positive for type-specific neutralizing antibodies. It is not used routinely, and use is limited to research setting. (LE: 2b)[18]

Preventive Vaccine

The current generation of HPV vaccines, Cervarix and Gardasil have demonstrated a high degree of efficacy in clinical trials against HPV serotypes.[19] Cervarix and Gardasil are two prophylactic HPV vaccines designed primarily for cervical cancer prevention. Cervarixis effective against HPV-16, -18, the two most common cancer-causing types. Gardasilis also effective against HPV-16, 18, in addition, itisalso effective against HPV-6 and -11, most common causes of genital warts and respiratory papillomatosis. According to ACIP, 2011 recommendation, for females, either routine vaccination with 3-dose series at age 11 or 12 years can be done or it can be done through age 26 years if not vaccinated previously. The most important determinant of vaccine impact to reduce cervical cancer isits duration of efficacy. As per current evidence, Cervarix's efficacy has been proven for 6.4 years and Gardasil's for 5 years.[20] In Australia national HPV vaccination programme, the percentage of genital-warts declined from 11.5% and 11.3% in women under 21 years and 21-30 year-old respectively to 0.85% and 3.1%, respectively. Similarlythe percentage of men under 21 yearsand 21-30 yearage group reducedfrom 12.1% and 18,2% respectively in 2007 to 2.2% and 18.2% respectively in 2011. No significant difference was seen in age group more than 30 years. (LE: 1a)[21]

The results show high efficacy against detection of new anogenital lesions in males 29 months after receiving the quadri valent HPV vaccine.[22][23][24] The ACIP recommended routine use of quadrivalent HPV vaccine in males aged 11 or 12 years. The ACIP also recommended vaccination with HPV for males aged 13 through 21 years who have not been vaccinated pre-viously or who have not completed the 3-dose series. (LE: 1a) males aged 22 through 26 years may also be vaccinated.[25]

In a randomized controlled trial in the per protocol susceptible population, vaccine efficacy against condyloma was 99% (96% to 100%).(LE: 1b)[26] There is a definite risk of viral transmission to the asymptomatic partners in HPV infection, as HPV DNA wasdetected in 34.5% of asymptomatic male partners of infected women. Thus, partner protection should be recommended to minimize the viral transmission.[27] (LE: 2b). The genital HPV infections are multifocal and they can be clinically evident at one site and mayremain dormant at other.[28] Though it has been proved now that HPV infection is a transient infection with a median duration of 8 months, and after 24 months, only 9% of the infection persist.[29] This emphasizes that extensive investigations to detect asymptomatic infection may not be required.

Treatment

Provider administered

Photodynamic therapy

A 5-amino levulinic acid-mediated photodynamic therapy (ALA-PDT) is an effective technique in the treatment of condylomata acuminata. ALA-PDT is proposed to act by selective destruction of subclinical virus-shedding area and activation of specific immune cells in the lesional skin. (LE: 1a)

[30] It has also been used in combinationwith CO2 laser, withdecreasedrecurrence rate and increased clearance rate. (LE: 1a)[31] Safety and efficacy have been documented for condylomataacuminata on the distal urethra. (LE: 1b)[32] In a randomized con-trolled trial, the group receiving PDT showed 95.3% clearance of AGW with only 9.38% pa-tients showed recurrence. (LE: 1b)[33] The cervical condylomatous lesions have also shown good improvement with a low recurrence rate. (LE: 3)[34]

Laser

The CO2, Pulsed-dye, Argon, Holmium, and Nd:YAG lasers have been described as treat-ment options for AGW. Single-period CO2 laser therapy was found beneficial for vulvar condylomata acuminata. (LE: 3)[35] The combination treatment using CO_2 laser and photodynamic therapy shown good results for HIV seropositive men with intra-anal warts (LE: 3)[36] The Nd:YAG and Thulium lasers have been used for external and urethral condylomas in 115 patients with complete clearance, however, 34% patients developed recurrences. (LE: 2)[37] Recurrent Buschke-Löwenstein tumours found to be treatable with CO2 laser vaporization with complete remission. (LE: 3)[38]

Surgery

Surgical excision is considered as the treatment of choice in large pedunculated lesions. (LE: 3)[39]

Cryotherapy

Cryotherapy act by crystallizing the cytosol of the cells, resulting in cell necrosis and activation of immune system. It has a reported efficacy of 79-88% for wart clearance with recurrence in 25-39% of cases. Weekly sessions are done usually up to 12 weeks for external genital warts. (LE: 1b) [40] It is an inexpensive, easy method with no serious side effects and is also a safe therapy in pregnant women. Mild side effects as blistering, local necrosis, scarring and hypo pigmentation can occur.

Immunotherapy

Intralesional antigen immunotherapy has been used for the treatment of warts. Induced delayed type hypersensitivity is the proposed mechanism of action. L1-virus like particles (VLP) immunotherapy was found to be associated with a significantly reduced rate of recurrence of genital warts when used in combination with conventional destructive therapy. (LE: 1b)[41] In a randomized control trial of 89 patients, intralesional Mycobacterium w (Mw) vaccine showed similar efficacy and safety as of imiquimod 5% cream, with a complete clearance in 66.7% of patients and a mean reduction in size of 83.23%. (LE: 1b)

Podophyllin

Topical solution of 20%, is applied by physician , once a week for up to eight weeks. It is an antimitotic and antiproliferative agent. Local side effects in form of edema, inflammation and erosions can be seen. (LE: 1b)[42]

Patient administered therapy

Imiquimod 5%

Imiquimod 5% cream is a topical immune response modifier, which has antiviral and anti-tumorous properties by inducing the production of cytokines (interleukins,interferon, TNF-alpha). Imiquimod is recommended therapy for AGW as topical application 3 times every week till complete clearance of wart or maximum 16 weeks. (LE: 1b)[43]

Imiquimod 3.75% cream is also available in many countries and appears to be as effective as 5% when applied daily for 8 weeks and is said to increase tolerability, decrease treatment du-ration and side effects. (LE: 3)[44]

Podophyllotoxin

Podophyllotoxin inhibits the proliferation of human skin keratinocytes and cures genital warts by inhibiting proliferation of HPV-infected cells. Podophyllotoxin is used 2 times on 3 consecutive days every week until warts completely cleared, or for a maximum period of 4 weeks. Local side effects in the form of erythema, edema and inflammation can occur. (LE: 1b)[45]In a randomized controlled trial to compare the effectiveness of self applied podophyllotoxin 0.5% solution and podophyllotoxin 0.15% cream, compared to clinic applied 25% podophyllin in the treatment AGW, complete clearance was seen in 75%, 64.5% and 53.1% of patients respectively. (LE: 1b)[46]

Sinecatechins and Polyphenon E 10% ointment

15% Sinecatachins ointment is used for the treatment of external genital warts. Three times daily application is recommended till complete wart clearance or maximum 16 weeks. Anti-viral, immune stimulation and anti carcinogenic activity are proposed mechanism of actions. Mild local side effects can be noted as redness, burning, pain, itching and swelling. (LE: 3)[47]

Polyphenon E is a botanical agent consisting predominately of catechins extracted from Camellia sinensis. The exact mechanism of action of polyphenon E is unknown but proposed mechanism are keratinocytes growth inhibition potential and its antioxidative activity. Recommended frequency of application is three times daily until complete clearance of all warts, but for no longer than 16 weeks. Polyphenon E 10% ointment is generally well tolerated in adults with external genital and perianal warts, local skin reactions as erythema, irritation, pain, and pruritus can occur rarely. Clearance rate of 50-70% was noted in a meta-analysis with approximately 10% recurrence rate. (LE: 1a)[48]

Cidofovir

Cidofoviris a nucleotide analog of deoxycytidine monophosphate. It selectively competitively inhibits viral DNA polymerase. Topical cidofovir has been successfully used in the management of condyloma acuminatum and other HPV-mediated diseases. (LE: 3)[49]

5-Fluorouracil (5-FU)

5-Fluorouracil is a pyrimidine anti-metabolite that functions as an anti-neoplastic agent by blocking DNA synthesis. Daily application of 5% 5-FU cream has been found effective in external genital and perianal wart. (LE: 1a)[50]

Interferon

It acts in HPV infections by virtue of its antiviral, anti-proliferative mechanisms and, in addition, it also stimulates the immune system of the body.It can be used either intralesional route or by systemic routes (subcutaneous or intramuscular), former is more effective. (LE: 1a)[51] Biphasic vesicles for topical delivery of interferon alpha are also available.[52]

Other treatment modalities (single or combination)

- Low-dose oral cyclophosphamide therapy: (LE: 3)[53]
- Systemic interleukin 2 and topical cidofovir: (LE: 3)[54]
- Local hyperthermia 44°c: (LE: 3)[55]
- Oral retinoid and intramuscular interferon-γ therapy: (LE: 3)[56]
- Combination of radiofrequency surgical dissection and oral acitretin: (LE: 3)[57]
- A 32P application device for the treatment of condyloma acuminatum in the rectum: (LE: 3) [58]
- Oral pidotimod plus vitamin C after laser vaporization: (LE: 3)[59]
- Chemoradiotherapy used for large Buschke-Lowenstein tumor: (LE: 3)[60]

Treatment summary

- Few smaller lesions: topical patient administered therapy as imiquimod, 5-FU cream, poly-phenon ointment
- Few larger lesion: Surgery, cryotherapy, podophyllin
- Multiple lesions: Immunotherapy, Interferon, PDT, laser, combination therapies

Table 1. Efficacy of various treatments for genital condyloma acuminata

Treatment modality	Clearance rate (%)	Recurrence rate (%)
Photodynamic therapy	85.7-95.3	9.38-14.3
Cryotherapy	79-88	25-40
Laser	23-52	60-77
Surgery	72	19-29
Immunotherapy	66.7	No after 3 months
Podophyllin	42-46.9	46-60
Imiquimod	56-84.5	13-16
Podophyllotoxin	45-77	38-65
Sinecatechecin	40-58	6-10
5-Fluorouracin	10-50	50
Interferon	17-67	9-69

Abbreviations

HPV: Human papilloma virus, AGW: anogenital warts, ISH: in-situ hybridization, 5-FU: 5-Fluorouracil

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Prevention of STIs, including education

From AAUS

-Standardized slides in youth education for the prevention of sexually transmitted infections-

Contents

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Executive summary

The best strategy for preventing the spread of sexually transmitted infections (STIs) is by educating the young. It is considered effective to provide such education by the age of 15 to 16 years, ideally before teenagers become sexually active. This guideline describes the framework and discusses the educational points for standard educational slides created by the Japanese Society for Sexually Transmitted Infections and the Japan Society of Adolescentology. A discussion of sexuality is also a discussion of human life, and the prevention of STIs is an important part of sex education. The Japanese Society for Sexually Transmitted Infections has a certification system for doctors and experts, and considers prevention education to be one of its key programs.

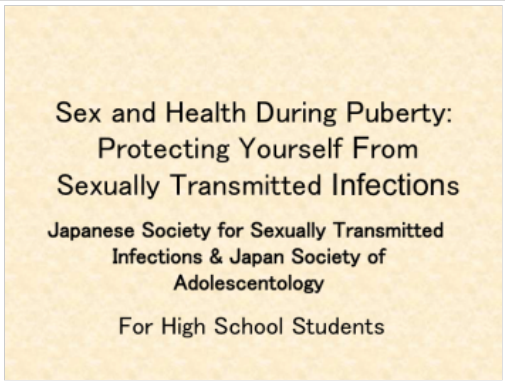
Introduction

The prevention of sexually transmitted infections (STIs) in the young is an important mission, as these are the future leaders of the coming generations who will be responsible for bearing and raising healthy children. What should be done to protect young people from contracting STIs? The Japanese Society for Sexually Transmitted Infections collaborated with the Japan Society of Adolescentology to create standard slides for teaching STI prevention to primarily teenagers around the age of 15 to 16 years. The following is a discourse on a strategy for preventing STIs from the position of an educator who participated in the preparation of these slides and who teaches STI prevention classes annually to teenagers mostly between the ages of 14 and 16 years at local high schools.

How to cope with sexual awakening

The purpose of knowledge and virtue education is to promote the development of reason and intellect in individuals who will become fully-fledged adult members of society that must be capable of making unwavering judgments. However, it is also critical to nurture rich emotions and help young people develop the ability to both understand and control their emotions. That being said, humans are also part of the animal kingdom, and thus have “natural instincts” such as appetite that are difficult to control. It goes without saying that when sexual desire exceeds the limits of control, we catch a glimpse of the difficulties humans face in self-control. Schools are the primary setting for education, and therefore must teach young people objectively about sexual awakening with the hope that they do not blindly follow their impulses and instead transfer their energy into other activities, putting energy to good use. This is one clear challenge faced by boys and girls entering puberty (and especially boys, who are typically the active sexual agents), and an answer to the question of how far education can help resolve this universal challenge remains unclear. However, some factors, including the risk of pregnancy and STIs, are thought to be helpful in meeting this challenge. Educators and medical professionals alike must teach young people in the midst of puberty about the potential adverse events that may occur when sexual desire leads to sexual activity, and must actively strive to cool the passionate emotions that young people are developing to some extent. This is not intended to be a form of intimidation, but rather one fact that must be communicated as common sense in a scientific society. It should be seen as an element of education for STI prevention that is also a key part of sex education in general.

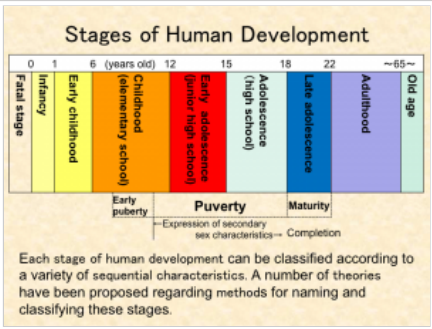
Detailed education for STI prevention (for high school students) (Slide 1)



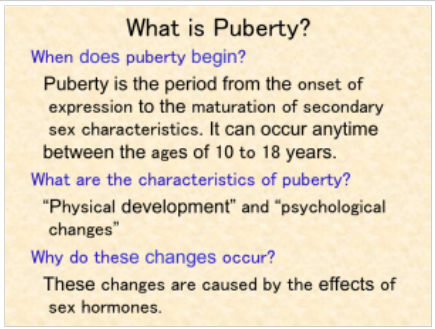
Slide 1. Sex and Health During Puberty: Protecting Yourself From Sexually Transmitted Infections

1. Introduction (Slides 2, 3, and 4)

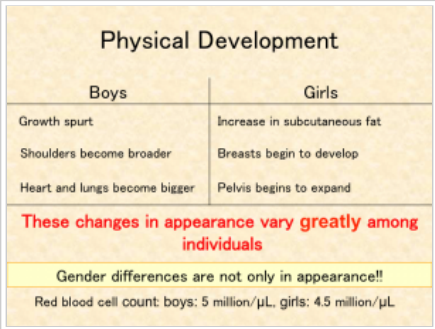
How would you describe your (the junior and senior high school students receiving the lesson) current stage of development? This is a detailed explanation of puberty and the other developmental stages, including physical changes in both boys and girls.



Slide 2. Stages of Human Development



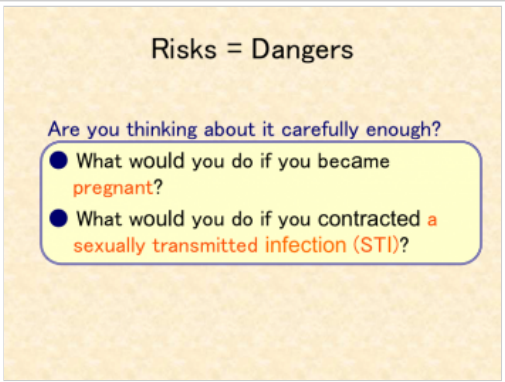
Slide 3. What is Puberty?



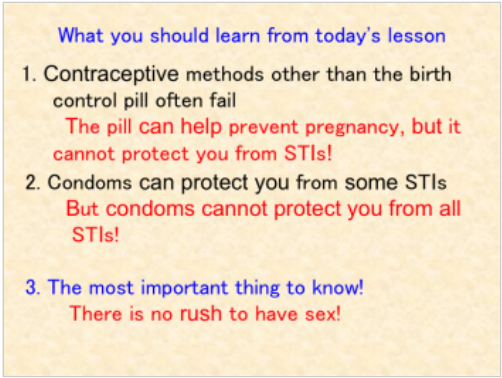
Slide 4. Physical Development

2. Presentation of the risks of sexual activity and main topics of the class (Slides 5 and 6)

Point out the presence of undesired adverse events such as STIs and pregnancy. Do not use the term "adverse event" in the classes. Use the term "risk" instead.



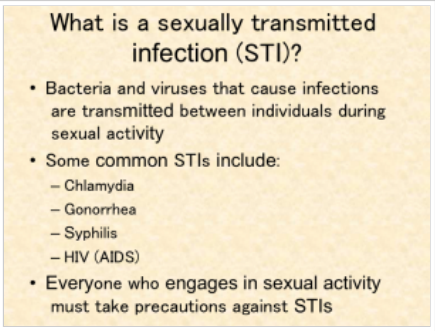
Slide 5. Risks = Dangers



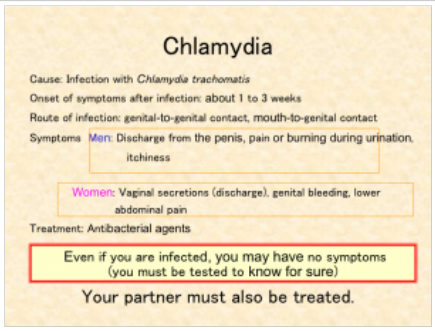
Slide 6. What you should learn from today's lesson

3. Detailed explanation about STIs (Slides 7, 8, and 9)

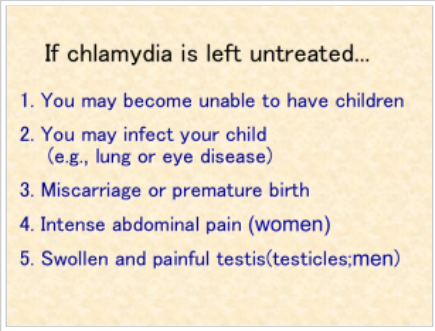
Describe the symptoms and route of infection for specific diseases such as chlamydial infection, how they may be present without symptoms, and problems they can lead to such as infertility, ectopic pregnancy, miscarriages or premature birth, or related infections in women, and swollen and painful epididymis in men.



Slide 7. What is a sexually transmitted infection (STI)?



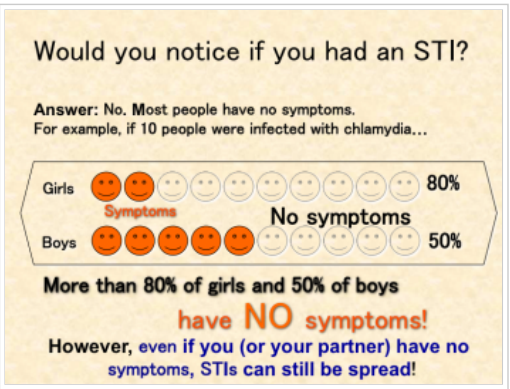
Slide 8. Chlamydia



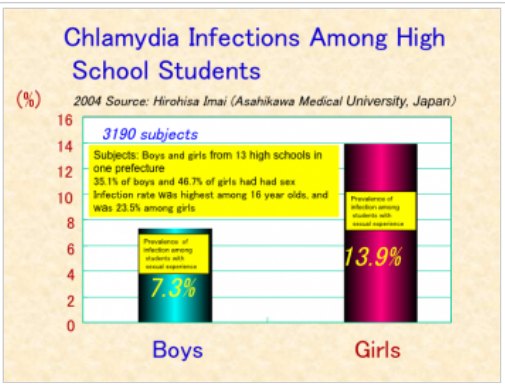
Slide 9. If chlamydia is left untreated...

4. Warning about the high prevalence of asymptomatic infections (Slides 10 and 11)

Use chlamydial infection or other types of infections as an example to explain the problem of disease spread, even when no symptoms are present.



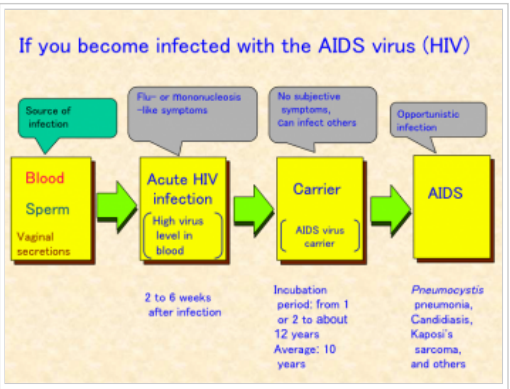
Slide 10. Would you notice if you had an STI?



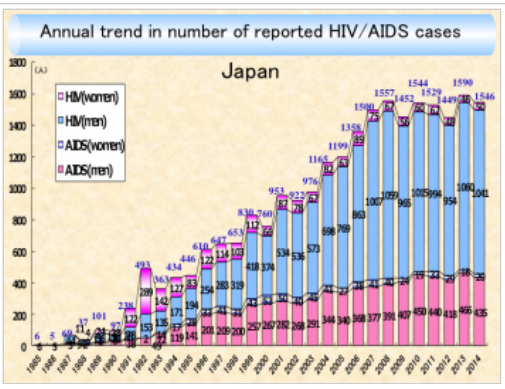
Slide 11. Chlamydia Infections Among High School Students

5. Information about the acquired immunodeficiency syndrome (AIDS) (Slides 12 and 13)

Provide information about the actual conditions and progression of this infectious disease, using data to explain that the incidence of human immunodeficiency virus (HIV) infections and AIDS is increasing annually in Japan, for example.



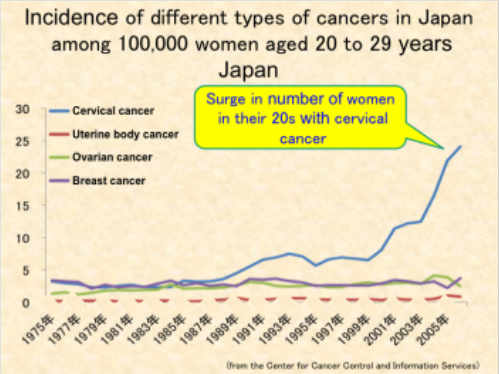
Slide 12. If you become infected with the AIDS virus (HIV)



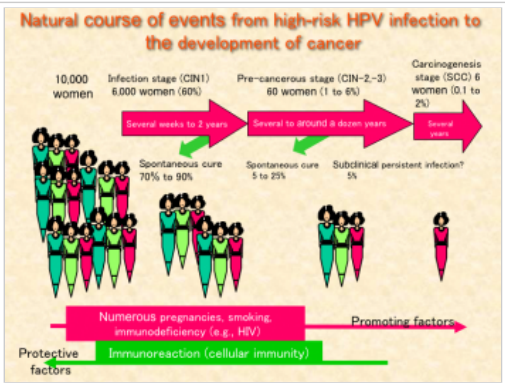
Slide 13. Annual trend in number of reported HIV/AIDS cases

6. The relationship between human papillomavirus (HPV) infection and cervical cancer (Slides 14 and 15)

Show them that the incidence of cervical cancer among young women in their 20s is on the rise, and that one reason for this is the presence of high-risk HPV infection. In other words, explain that many cases of cervical cancer are a type of STI in the broad sense of the term.



Slide 14. Incidence of different types of cancers in Japan among 100,000 women aged 20 to 29 years Japan

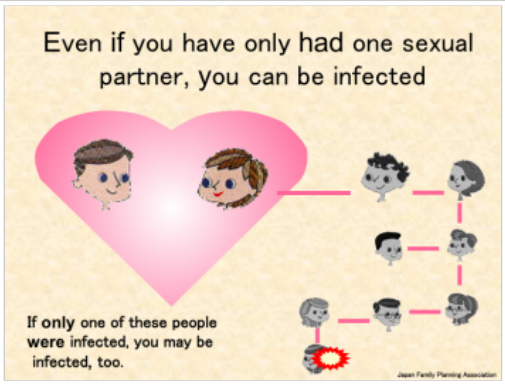


Slide 15. Natural course of events from high-risk HPV infection to the development of cancer

7. Are you safe if you have had only one sexual partner? (Slides 16 and 17)

The answer is no. Even if you have only had one sexual partner, you are still at risk of infection due to the existence of a hidden sexual activity network.

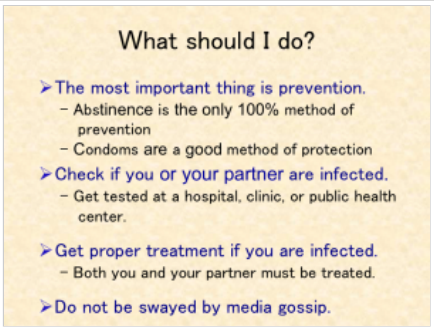
Slide 16. Are you safe if you have had only one sexual partner?



Slide 17. Even if you have only had one sexual partner, you can be infected

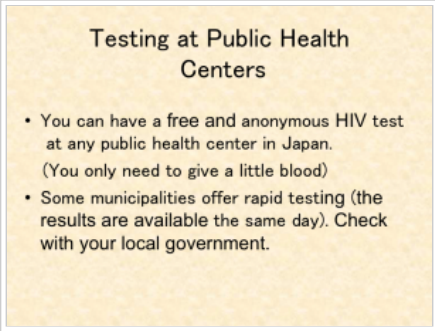
8. How can we solve this problem? (Slides 18, 19, and 20)

The most important thing is prevention. Abstinence from sex is the best form of prevention. If young people are going to have sex, they should use condoms. Teach them the proper way to put on a condom as a common sense. Explain that they can have a free and anonymous HIV test at a public health center if they think they may be infected.



Slide 18. What should I do?

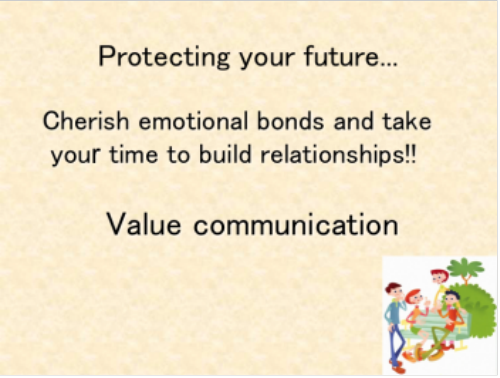
Slide 19. How to properly put on a (male) condom



Slide 20. Testing at Public Health Centers

9. Final message (Slide 21)

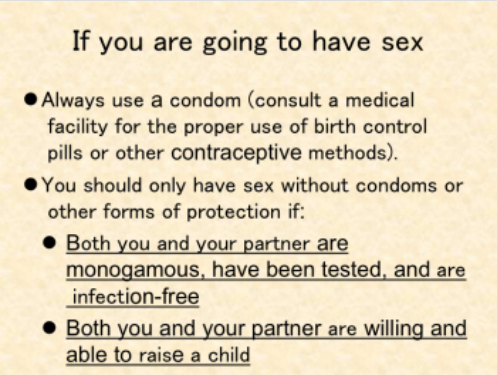
There is no need to rush into sexual activity. Start with heart-to-heart communication.



Slide 21. Protecting your future...

Education for STI prevention in pubescent students also applies to adults (Slide 22)

It is not necessarily true that most adults have accurate knowledge of STIs. "If you are going to have sex □ Always use a condom (consult a medical facility for the proper use of birth control pills or other contraceptive methods). You should only have sex without condoms or other forms of protection if both you and your partner are monogamous, have been tested, and are infection-free, and if both you and your partner are willing and able to raise a child." This conclusion applies to adults as well.



Slide 22. If you are going to have sex

Conclusions

Providing junior and senior high school students with accurate knowledge about STIs against the background of a steadily increasing incidence of HIV and other types of infections is an absolutely essential mission from a societal perspective. The Japanese Society for Sexually Transmitted Infections launched a system for certifying doctors and experts in STI in 2009. Although about 370 doctors have been certified in four tests conducted up to 2012, only about 20 experts have been certified during that period. We plan on stepping up recruitment for certified experts with the goal of increasing their numbers and improving STI prevention education for junior and senior high school students. STIs are an increasing threat for young people around the world. Education in schools for young people in their mid-teens may represent the best strategy for STI prevention, and collaboration between medical and educational professionals is essential. It is important to link the study of infectious disease with epidemiology to conduct ongoing investigations, to inform the public and young people of the results, and to take effective measures. Societies for the prevention of STIs around the world should act as mediators to increase the number of expert certification systems, for example. The slides we developed show promise for use as standard educational materials.

Abbreviation

STIs: sexually transmitted infections, HPV: human papillomavirus, HIV: human immunodeficiency virus, AIDS: acquired immunodeficiency syndrome

References

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