Lower Genitourinary Infections in Women

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Vaginitis, cystitis, urethritis, and cervicitis are common diagnoses made in women attending family physicians' offices. Recent research has fundamentally altered available information on the diagnosis and management of these common genitourinary infections. This clinical review discusses presenting symptoms, physical findings, laboratory diagnostic aids, treatment, and follow-up for each lower genitourinary syndrome in women concluding with a summary flow chart illustrating an overall recommended approach.

Vaginitis, cystitis, urethritis, and cervicitis collectively account for between 5 and 15 percent of all visits by women to family physicians.[1] Women rarely, however, volunteer such diagnoses as complaints: appointments are made for vaginal discharges and malodor, dysuria, urgency, vulvar pruritus, and other symptoms. Translating symptoms into treatable diagnoses is an important part of the physician's task during the office visit. Unfortunately, clinical syndromes overlap, physical findings may be nonspecific, and microbiological confirmation of diagnoses may be both expensive and untimely. The picture is further complicated by recent challenge to many long-held beliefs about the diagnosis and treatment of these common problems. This article reviews recent diagnostic and therapeutic advances in managing lower genitourinary infections in women and outlines some of the unanswered questions that hamper physicians' ability to deal with these problems and that require further investigation.

PRESENTING COMPLAINTS

Symptoms are the ticket for admission to an office visit and largely determine the physician's initial approach. The list of potential complaints for lower genitourinary infections is long: dysuria, vaginal discharge or itching, urgency, frequency, incontinence, dyspareunia, hematuria, and many others. The immediate question for the physician is whether any combination of symptoms predicts diagnosis accurately enough so that one or more diagnoses can be eliminated from consideration at the outset. Evidence is mixed. Komaroff[2] found that differentiating dysuria into external and internal was helpful in establishing diagnoses of vaginitis and cystitis-urethritis, respectively. He further identified three clinical groups that would allow the physician to focus the remainder of the examination:

1. Vaginal discharge and irritation absent, internal dysuria and frequency present. This group had a very low probability of vaginitis and high probability of urinary tract infection, thus allowing the elimination of pelvic examination and urinalysis, and necessitating only urine culture.
2. Vaginal discharge or irritation present, internal dysuria and frequency absent. This group had a low probability of urinary tract infection, allowing the elimination of urinalysis and culture.
3. Vaginal discharge or irritation present, internal dysuria or frequency present. This group had equal probabilities of both vaginitis and urinary infection, thus requiring pelvic examination, urinalysis, and urine culture.

Generalizability of Komaroff's recommendations to other primary care settings is hampered by patient selection and by the lack of uniform database on all patients seen. A more recent study performed in Seattle[3] found that up to one third of women could not distinguish between internal and external dysuria or claimed to have both. In the same study, although Komaroff's clinical strategies were generally helpful, some women were misclassified by these criteria.

In summary, presenting complaints are suggestive but not diagnostic of specific groups of infections. Further research in the family practice setting will be necessary to accurately assess predictive value of symptoms for specific diagnoses.

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VAGINAL INFECTIONS

Vaginitis is the most common lower genitourinary clinical syndrome seen by the primary care practitioner, accounting for two thirds of all visits for genitourinary problems. Recent studies have fundamentally changed the diagnosis and treatment of nonspecific vaginitis and have suggested new ways of evaluating women with yeast and trichomonal infections as well.

Vaginal discharge and vulvar irritation are the usual presenting complaints of vaginal infection. Certain symptoms are associated with particular infections—pruritus with yeast, purulent and copious discharge with trichomonas, and foul-smelling discharge with nonspecific vaginitis. Such symptoms, though characteristic of given infections once the diagnosis is established, may have poor predictive value during the initial evaluation phase. Thus, of all women with vaginal discharge and vulvar pruritus, only one half may be found to have yeast on examination. Recent attempts to correlate groups of symptoms with specific diagnoses have been only marginally successful.

On physical examination, vaginal infections are associated with specific findings. Thick, curdlike discharge and external vulvitis are typical of yeast vaginitis; copious purulent discharge with cervical petechiae and friability are characteristic of trichomonal infections; and a thin, adherent, foul-smelling discharge is the hallmark of nonspecific vaginitis. Again, however, the predictive value of these characteristic physical findings for the three diagnoses is unknown, and a recent Seattle study suggests that additional factors need to be explored.[3,4]

Significant changes in laboratory aids to the diagnosis of vaginal infections have been recently proposed, especially in making the diagnosis of nonspecific vaginitis. Formerly a diagnosis of exclusion, nonspecific vaginitis may now be diagnosed using Amsel's[5] recommendation that at least three of the following four criteria be present: (1) thin, adherent, homogenous discharge, (2) vaginal pH of 4.5 or higher, (3) amine odor upon application of potassium hydroxide to discharge, or (4) clue cells on microscopic examination of saline suspension. Recent microbiologic investigation has strongly implied that the Gardnerella vaginalis organism (formerly Hemophilus vaginalis) may play only a partial role in a mixed infection of several bacteria collectively responsible for symptoms.[6] Finally, at a recent international symposium, nonspecific vaginitis was renamed to be bacterial vaginosis, reflecting the mixed bacterial noninvasive nature of this condition.[7]

The diagnosis of yeast vaginitis has been based upon demonstration of budding yeast and pseudohyphae after application of potassium hydroxide to a bit of the discharge and microscopic examination of the preparation. Additional use of cultures for Candida albicans has been recommended by some.[8] Demonstration of Candida by culture is the gold standard, a standard compared with which the potassium hydroxide preparation performs poorly.[9] Additionally, it is well known that asymptomatic women may harbor yeast organisms.[8] Thus, the physician is left with a dilemma: the potassium hydroxide preparation is insensitive in identifying yeast in symptomatic women, yet use of the culture technique routinely would undoubtedly falsely identify some carriers of Candida as infected. An answer to this dilemma awaits further research testing the efficacy of treatment in symptomatic women who are potassium hydroxide negative but culture positive. In the interim, some have suggested that cultures for Candida be used selectively in symptomatic women with negative potassium hydroxide preparations.[9]

The diagnosis of vaginitis caused by Trichomonas vaginalis has problems similar to those in making the diagnosis of Candida. Traditionally, the diagnosis of trichomonal infection has been based upon direct microscopic observation of the organism in a bit of the discharge mixed with saline. Culture methods are available that detect the organism in a larger proportion of women, however.[10,11] Because women may have asymptomatic Trichomonas infections, the situation is similar to that confronting the physician attempting to make the diagnosis of vaginitis caused by yeast. Again, trichomonal cultures may be used selectively in symptomatic women with negative microscopic examinations.

Treatment protocols for vaginal infections are fairly straightforward. Yeast infections are effectively treated using suppositories or creams containing the polyene (nystatin) or imidazole (clotrimazole, miconazole) antibiotics. Oral ketoconazole for resistant infections is currently under study. Trichomonal vaginitis may be effectively treated using single-dose metronidazole in a 2-g dose. The treatment of bacterial vaginosis formerly included several regimens, including topical sulfa creams and oral ampicillin or amoxicillin. It is now clear that metronidazole is more effective, although exact dosage and duration of treatment are still being studied.[12] Currently recommended is 500 mg of metronidazole twice daily for seven days, longer if symptoms persist (metronidazole is not approved for this application by the Federal Drug Administration).[13] The necessity of treatment of sexual partners for these infections is still being studied. Most yeast infections do not require treatment of the sexual partner, although men with yeast balanitis may occasionally serve as a reservoir for reinfection and should be treated accordingly. Most authorities agree that trichomonas infections should be treated with a similar single 2-g dose of metronidazole

in the partner. Virtually no data are available to support treatment of sexual partners of women who have nonspecific vaginitis, although several studies are currently being conducted.

CYSTITIS AND URETHRITIS

CLINICAL SPECTRUM

Urinary tract infections affect at least 10 to 20 percent of women in the general population during their lifetimes.[14] Though there is some overlap, the clinical spectrum of urinary tract infection includes three primary syndromes. The first is asymptomatic bacteriuria, in which patients have no symptoms but cultures of urine reveal pathogenic organisms. The second syndrome, lower tract infection, is characterized by various combinations of frequency, nocturia, urgency, suprapubic discomfort and tenderness, and sometimes hematuria. This syndrome can be further divided into bacterial infection of the bladder with or without "silent" renal involvement and acute urethral syndrome. Both of these subdivisions have undergone recent redefinition. The third clinical syndrome is acute pyelonephritis, which often presents with costovertebral angle pain and tenderness, fever, rigors, and sometimes with accompanying signs and symptoms of cystitis. As this review is limited to lower genitourinary syndromes, acute pyelonephritis will not be discussed further.

The following problems are included in the clinical categorization of urinary tract infection: (1) History and physical examination do not reliably distinguish between the acute urethral syndrome and other forms of urinary tract infection; (2) it is not possible to distinguish between upper tract infection and lower tract infection on clinical grounds alone[14,15]; and (3) up to 50 percent of all patients with bacteriuria have been shown to have silent renal involvement by localization techniques.[16] Because of these problems, the laboratory has taken on a greater role in the evaluation of urinary tract infections.

LABORATORY FINDINGS

Although the presence in an unspun sample of clean voided urine of leukocytes, erythrocytes, or bacteria is consistent with urinary tract infection, the absence of any or all does not preclude the diagnosis. Leukocyte casts, if present, confirm the presence of renal infection.

In uncomplicated urinary tract infections aerobic gram-negative coliforms are the most common etiologic agents, with Escherichia coli being responsible for 80 to 90 percent of cases. The definition of significant bacteriuria is in the process of radical revision. The traditional criterion of at least 10^5 bacteria per milliliter identifies only one half of symptomatic women with proven coliform infection of the bladder. Among symptomatic women, the criterion of at least 10^2 coliforms per milliliter of clean voided urine has a high sensitivity (.95), specificity (.85), and predictive value (.88) and is preferable to previous criteria.[17] In addition, in many symptomatic women "mixed" culture results (in which one of the isolates is a coliform) have been shown to correlate with true bacterial infection of the bladder. With "mixed" or lower level (fewer than 10^5/mL) culture results, the presence of pyuria increases the likelihood of true infection. Although a reasonable clinical definition of pyuria is at least 10 leukocytes per high-power field of clean, voided, unspun urine, the hemacytometer determination of pyuria has been shown to be simple and highly reproducible and may have a greater role in the future.[18]

The acute urethral syndrome has traditionally been defined as acute dysuria and frequency in women whose clean voided urine has fewer than 10^5 microorganisms per milliliter. More recently,[19] this syndrome has been categorized into three subgroups. The first group is characterized by bladder bacteriuria with less than 10^5 bacteria per milliliter, usually accompanied by pyuria. This disease differs from acute cystitis only in terms of the quantitative bacterial count and in most populations constitutes the largest category of the acute urethral syndrome. The second group is characterized by pyuria and no bacteriuria on culture. Though several studies of young sexually active women have documented a high rate of chlamydia infection,[20] a prospective study of women with genitourinary symptoms presenting to a university-based family practice did not find a high rate of chlamydia infection in women with pyuria and no bacteriuria.[3] Neisseria gonorrhoeae should be considered when evaluating these patients. The third group, without bacteriuria or pyuria, usually has no identifiable etiologic agent.

UPPER VS LOWER TRACT INFECTION

The differentiation of upper from lower tract infection can be accomplished accurately using bladder washout or ureteral catheterization, but these are expensive and time-consuming procedures. A more recent technique, testing for antibody-coated bacteria, has significant numbers of false-positive and false-negative results and should be reserved for research.[18,21] At present, the most practical guide to anatomic site of infection may be the response to single-dose therapy (discussed later).[22] In addition, the failure to seek medical attention within six days of the onset of symptoms or findings consistent with upper tract or "complicated" infection increases the likelihood of upper tract infection.

MANAGEMENT

Many antibiotic regimens will "cure" the majority of acute, uncomplicated urinary tract infections, and, in fact, the high urinary concentration of many antibiotics results in eradication of many organisms with in vitro drug resistance. In discussing cure, it must be remembered that placebo treatment has resulted in sterile urine obtained within five months in 80 percent of nonpregnant women with acutely symptomatic urinary tract infections.[23] Another important aspect of cure is that because of the high rate of recurrence and because of occasional persistence of bacteria in the urinary tract, follow-up urine culture should be obtained several days to a week after the completion of treatment. Failure to respond is generally due to patient noncompliance, reinfection, or more rarely to bacterial persistence. In all aspects of management, health care providers must be aware that women at risk for severe morbidity or renal scarring from urinary tract infections include those with (1) infection with urea-splitting organisms (usually Proteus) that cause struvite renal stones, (2) congenital anomalies of the genitourinary system that become secondarily infected, (3) bacteriuria in the presence of obstruction of the urinary tract (such as by nephrolithiasis), (4) analgesic nephropathy, (5) diabetes, (6) neurogenic bladder, and (7) pregnancy.

In general, asymptomatic bacteriuria in adult women requires treatment only during pregnancy.

The acute urethral syndrome is best treated by single-dose therapy with amoxicillin or trimethoprim-sulfamethoxazole (TMP-SMZ), as described below, when coliforms are the etiologic agent. If contraindications exist or if a coliform infection does not respond to single-dose therapy, a 7- to 14-day course of antibiotic therapy is indicated. When chlamydia is the suspected pathogen, therapy should consist of a ten-day course of doxycycline, 100 mg orally twice daily, or tetracycline, 500 mg orally four times daily. Treatment of sexual partners should be considered. In symptomatic women without pyuria, antibiotic therapy is of no proven benefit.[24]

A major recent advance in the therapy of acute, uncomplicated urinary tract infections in adult women has been the discovery that most such infections can be eradicated with single-dose oral therapy with amoxicillin (3 g), TMP-SMZ (two double-strength tablets), or sulfisoxazole (2 g).[18,22,25-30] This therapy is inappropriate for diabetics, pregnant women, or women who seem unlikely to return for follow-up culture, have had symptoms for over six days, have signs or symptoms suggesting upper tract infection, or have a history of multiple urinary tract infections. However, an important cautionary note has been struck by the recent publication of the largest prospective series to date comparing single- and multiple-dose therapy: women treated with single-dose TMP-SMZ had a higher relapse rate than those treated with a multiple-dose regimen.[31] Clinically stable patients who fail single-dose therapy, as evidenced by a positive urine culture two to three days after treatment, should receive a 10- to 14-day course of a standard antibiotic based on susceptibility testing as described below. If this therapy fails, or if a woman has signs or symptoms of upper tract infection after failed single-dose therapy, a four- to six-week course of antibiotics is indicated. In addition, urologic and radiologic investigations of the urinary tract should be considered.

In acute, uncomplicated urinary tract infection with any of the stated contraindications for single-dose therapy, a seven- to ten-day course of antibiotics is indicated. Choice of antibiotic should be governed by urine culture and sensitivity reports, but pending results, empiric therapy based on symptoms and urinalysis may be started with sulfisoxazole, ampicillin, tetracycline, nitrofurantoin, TMP-SMZ, trimethoprim alone, cephalexin, or various other agents.

In patients with early recurrence of urinary tract infection, many previous episodes that have been difficult to control, underlying anatomic abnormality, or history of renal transplant, a four- to six-week course of antibiotics is indicated. Although many authors recommend a similar regimen for diabetics, an initial seven- to ten-day course is justified for acute, uncomplicated infection.

Therapy of pyelonephritis and catheter-associated urinary tract infection is beyond the scope of this review.

Recent studies have questioned the traditional indications for investigation of the urinary tract in women with urinary tract infections. Procedures such as intravenous pyelography, cystoscopy, and cystography have a very low yield and are cost ineffective for adult women with uncomplicated lower urinary tract infections.[32] These studies appear most useful in women with possible nephrolithiasis, history of multiple childhood infections (if not already evaluated), relapsing infection when repeated lack of response to an effective agent has been documented; in diabetics with relapses; or in women with pyelonephritis that does not respond quickly to treatment, neurogenic bladder, or painless hematuria.

PREVENTION

Prevention of urinary tract infections is cost effective and efficacious in women who have three or more episodes yearly. Effective regimens include daily administration of TMP-SMZ (one-half tablet) or nitrofurantoin (100 mg) or trimethoprim (100 mg). Thrice weekly and postintercourse dosing have also been effective, but as with the daily regimens, the beneficial

effect of the drugs stops when prophylaxis is discontinued. An initial six-month trial to establish tolerance and effectiveness should be followed by individualization of treatment determined by baseline rate of infection. Periodic urine cultures during periods of prophylaxis are needed to confirm efficacy.[33,34]

PREGNANT WOMEN

Because of hormone-induced dilatation of the renal pelvis, calyces, and ureters, there is a high rate of urinary tract infection in pregnancy. Asymptomatic bacteriuria occurs in 4 to 7 percent of pregnant women, and up to 40 percent of these episodes, if untreated, may go on to pyelonephritis.[35] Pyelonephritis in pregnancy has been reported to cause many complications, including septic shock[36] and fetal death.[35] Thus screening all pregnant women for asymptomatic bacteriuria and treating all episodes detected with an initial 10- to 14-day course of antibiotics are essential. Frequent follow-up cultures should be obtained, as the relapse rate is high. If relapse occurs, a four- to six-week antibiotic course is indicated. Tetracyclines are contraindicated in pregnancy. Sulfa preparations are not contraindicated in the first and second trimesters but when used in late pregnancy may contribute to neonatal kernicterus.[37] Drugs in the penicillin family and the cephalosporin family have no known contraindications specifically related to pregnancy.[37,38]

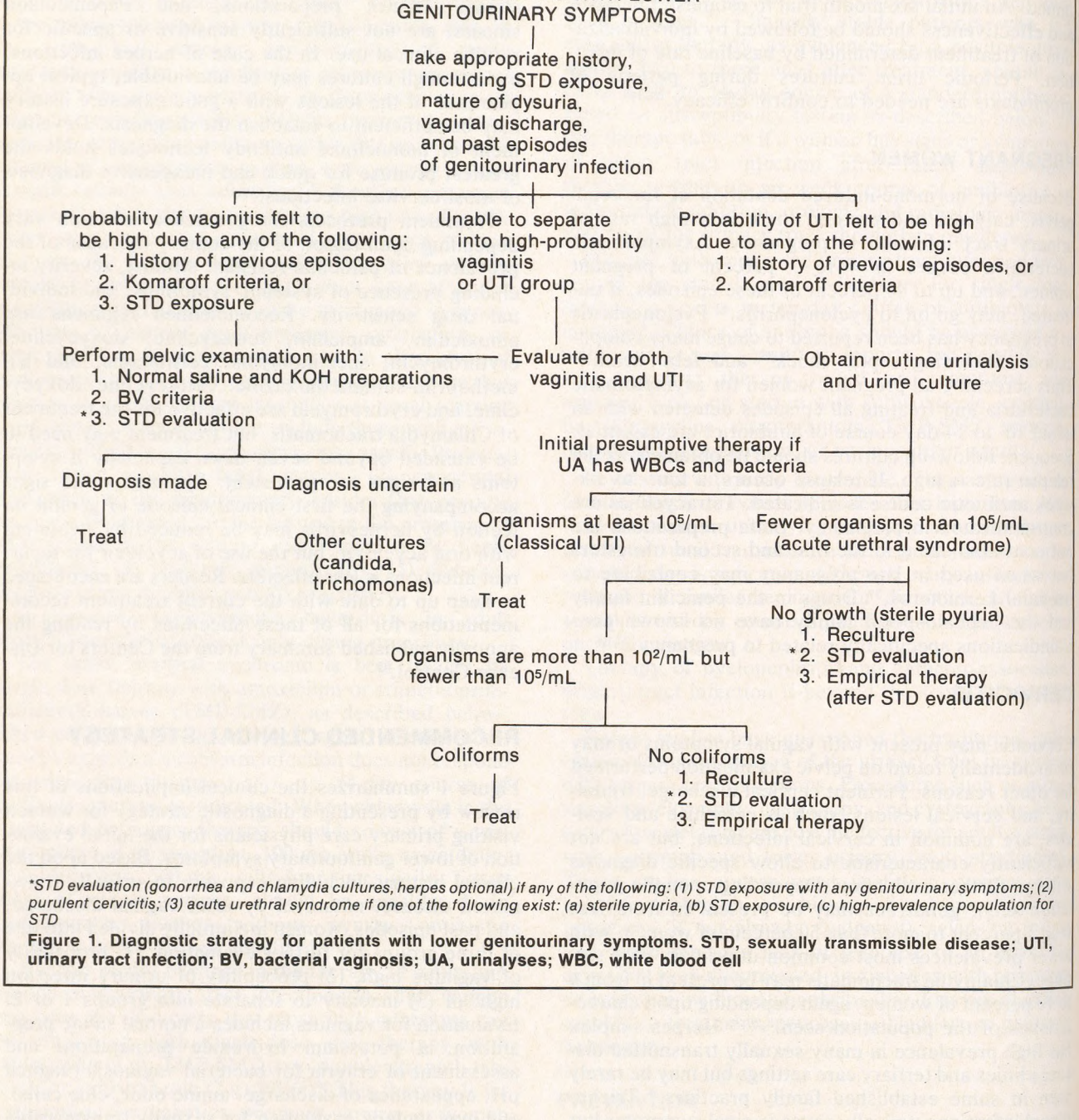
CERVICITIS

Cervicitis may present with vaginal symptoms or may be incidentally found on pelvic examination performed for other reasons. Purulent cervical discharge, friability, and cervical lesions, such as petechiae and vesicles, are common in cervical infections, but are not sufficiently characteristic to allow specific diagnosis without further evaluation. Depending upon the population seen, gonorrhea may be present in from less than 1 percent to more than 50 percent of women, with lower prevalences most common in primary care settings. Chlamydia trachomatis may be present in from 4 to 10 percent of women, again depending upon characteristics of the population seen.[3,20,39] Herpes simplex has high prevalence in many sexually transmitted disease clinics and tertiary care settings but may be rarely seen in some established family practices.[3] Trichomonal infections typically cause vaginal symptoms but may cause isolated cervicitis. Unfortunately, the diagnosis of all cervical infections is dependent upon culture techniques for N gonorrhoeae, Chlamydia trachomatis, and herpesvirus. Although cultures for gonorrhea are widely available, those for chlamydia and herpes are just beginning to penetrate hospital microbiology laboratories and may be unavailable in many communities. Other techniques, such as Gram stains, Tzanck preparations, and Papanicolaou smears, are not sufficiently sensitive or specific for routine clinical use. In the case of herpes infections, even though cultures may be unavailable, typical appearance of the lesions with a good exposure history may be sufficient to establish the diagnosis. Development of monoclonal antibody techniques holds the greatest promise for quick and inexpensive diagnosis of most cervical infections.[40,41]

Treatment protocols for gonorrhea infection vary depending upon region of the country (because of the prevalence of penicillin-resistant strains), severity including presence of systemic symptoms, and individual drug sensitivity. Recommended regimens use amoxicillin, ampicillin, tetracycline, doxycycline, erythromycin, spectinomycin, ceftriaxone, and trimethoprim-sulfamethoxazole. Tetracycline, doxycycline, and erythromycin are effective for the treatment of Chlamydia trachomatis, but treatment may need to be extended beyond seven days, especially if symptoms and signs are persistent. Symptoms and signs accompanying the first clinical episode of genital infection by herpesvirus may be reduced by treatment with oral acyclovir, but the use of acyclovir for recurrent infections is less effective. Readers are encouraged to keep up to date with the current treatment recommendations for all of these infections by reading the annually published summary from the Centers for Disease Control.[42]

RECOMMENDED CLINICAL STRATEGY

Figure 1 summarizes the clinical implications of this review by presenting a diagnostic strategy for women visiting primary care physicians for the initial evaluation of lower genitourinary symptoms. Based upon the clinical history, including exposure to sexually transmitted disease, nature of dysuria, vaginal discharge, and past episodes, women are initially divided into one of three groups for further evaluation: (1) probability of vaginitis high, (2) probability of urinary infection high, or (3) inability to separate into groups 1 or 2. Evaluation for vaginitis includes a normal saline preparation, a potassium hydroxide preparation, and assessment of criteria for bacterial vaginosis (vaginal pH, appearance of discharge, amine odor, clue cells), and may include evaluation for sexually transmissible disease. The evaluation, if initially nondiagnostic, may be followed by further cultures for candida, trichomonas, and others. Evaluation for urinary tract infection includes urinalysis and culture and evaluation for sexually transmissible disease, if appropriate. The workup for sexually transmissible disease in both groups should include cultures for gonorrhea and



*STD evaluation (gonorrhea and chlamydia cultures, herpes optional) if any of the following: (1) STD exposure with any genitourinary symptoms; (2) purulent cervicitis; (3) acute urethral syndrome if one of the following exist: (a) sterile pyuria, (b) STD exposure, (c) high-prevalence population for STD

Figure 1. Diagnostic strategy for patients with lower genitourinary symptoms. STD, sexually transmissible disease; UTI, urinary tract infection; BV, bacterial vaginosis; UA, urinalyses; WBC, white blood cell

chlamydia and possibly herpes. The group of women who are not initially categorized into high-probability vaginitis or urinary tract infection group should be evaluated for both.

Several other points should be emphasized. This proposed clinical strategy differs from those previously published by recommending more rigorous criteria for the diagnosis of bacterial vaginosis, by selective use of cultures for candida and trichomonas, by employing different criteria in the diagnosis of urinary infection, and by recommending the use of gonorrhea and chlamydia cultures in women at risk. Further recommended is that physicians consider the use of empirical therapy in the management of urinary

tract infection when diagnostic tests (including evaluation for sexually transmissible disease) have failed to reach closure.

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