VOLUME - X
ISSUE - LIX
SEP / OCT 2013

The Crux

BIMONTHLY FORUM FOR THE LABORATORIANS

CONTENTS

Editorial

Gonorrhea (colloquially known as **the clap**) is a common human sexually transmitted infection caused by the bacterium *Neisseria gonorrhoeae*. The usual symptoms in men are burning with urination and penile discharge (ALSO KNOWN AS THE MORNING DEW). Women, on the other hand, are asymptomatic half the time or have vaginal discharge and pelvic pain. In both men and women if gonorrhea is left untreated, it may spread locally causing epididymitis or pelvic inflammatory disease or throughout the body, affecting joints and heart valves.

Treatment is commonly with ceftriaxone as antibiotic resistance has developed to many previously used medications. This is typically given in combination with either azithromycin or doxycycline, as gonorrhea infections may occur along with chlamydia, an infection which ceftriaxone does not cover. Some strains of gonorrhea have begun showing resistance to this treatment, which will make infection more difficult to treat.

Half of women with gonorrhea are asymptomatic while others have vaginal discharge, lower abdominal pain or pain with intercourse. Most men who are infected have symptoms such as urethritis associated with burning with urination and discharge from the penis. Either sex may also acquire gonorrhea of the throat from performing oral sex on an infected partner, usually a male partner. Such infection is asymptomatic in 90% of cases, and produces a sore throat in the remaining 10%. The incubation period is 2 to 14 days with most of these symptoms occurring between 4–6 days after being infected. Rarely, gonorrhea may cause skin lesions and joint infection (pain and swelling in the joints) after traveling through the blood stream. Very rarely it may settle in the heart causing endocarditis or in the spinal column causing meningitis (both are more likely among individuals with suppressed immune systems).

Early and accurate diagnosis followed by apt treatment is of utmost importance to avoid lethal complications. This topic has been taken up again as now latest and the best diagnostic platforms are available which can be used by even medium grade to high grade Laboratories. So much so it could become a Point Of Care diagnostic Test too. The **DISEASE DIAGNOSIS** segment delves deep in to the clinical-diagnostic aspects of **GONORRHOEA**.

The overflow of **INTERPRETATION** portion from the previous issue (GI cancer markers) is being concluded here.

The **TROUBLE SHOOTING** section talks about BIOSAFETY aspects as related to diagnostic laboratories.

BOUQUET is lurking somewhere, just peep inside.

DISEASE DIAGNOSIS

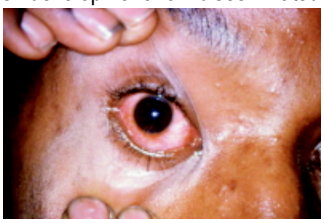
GONORRHEA

Background

Gonorrhea, an important public health problem and is a purulent infection of mucous membrane surfaces caused by the gram-negative diplococcus *Neisseria gonorrhoeae*. Although gonorrhea (known colloquially as the clap and the drip) is most frequently spread during sexual contact, it can also be transmitted from the mother's genital tract to the newborn during birth, causing ophthalmia neonatorum and systemic neonatal infection. In women, the cervix is the most common site of gonorrhea, resulting in endocervicitis and urethritis, which can be complicated by **pelvic inflammatory disease** (PID). In men, gonorrhea causes anterior urethritis. Gonorrhea can also spread throughout the body to cause localized and disseminated disease. Complications also include ectopic pregnancy and increased susceptibility to **human immunodeficiency virus** (HIV) infection. Most commonly, the term gonorrhea refers to urethritis and/or **cervicitis** in a sexually active person. Gonococcal infections following sexual and perinatal transmission are a major source of morbidity worldwide. In the developed world, where prophylaxis for neonatal eye infection is standard, the vast majority of infections follow genitourinary mucosal exposure. In the pediatric population, the importance of gonorrhea is 3-fold, as follows: As a common and preventable sexually transmitted disease (STD) in the sexually active teenage population, As a perinatal infection at childbirth, As a forensic aid in investigating sexual abuse.

Gonococcemia

Gonococcemia is defined as the presence of *N. gonorrhoeae* in the bloodstream, which can lead to the development of disseminated gonococcal infection (DGI). Gonococcemia occurs in about 0.5-3% of patients with gonorrhea (see the image).



This patient presented with gonococcal urethritis, which became systemically disseminated, leading to gonococcal conjunctivitis of the right eye.

The clinical manifestations of this process are biphasic, with an early bacteremic phase consisting of tenosynovitis, arthralgias, and dermatitis, followed by a localized phase consisting of localized septic arthritis. Other potentially severe clinical complications include osteomyelitis, meningitis, endocarditis, adult respiratory distress syndrome (ARDS), and fatal septic shock. Polymyositis is also a rare complication of gonococcemia. Patients who are pregnant or menstruating may be particularly prone to gonococcemia. Other populations at risk of infection include women and individuals with **complement deficiencies, HIV disease,** or **systemic lupus erythematosus** (SLE). DGI is an important, potentially life-threatening, and easily treatable clinical entity that remains the most common cause of acute septic arthritis in young, sexually active adults.

Pathophysiology

The pathophysiology of *N. gonorrhoeae* and the relative virulence of different subtypes depend on the antigenic characteristics of the respective surface proteins. Certain subtypes are able to evade serum immune responses and are more likely to lead to disseminated (systemic) infection. Well-characterized plasmids commonly carry antibiotic-resistance genes, most notably penicillinase. Plasmid and nonplasmid genes are transmitted freely between different subtypes. The ensuing exchange of surface protein genes results in high host susceptibility to reinfection. The exchange of antibiotic resistance genes has led to extremely high levels of resistance to beta-lactam antibiotics. Fluoroquinolone resistance has also been documented on multiple continents and in widespread populations. Infection of the lower genital tract, the most common clinical presentation, primarily manifests as male urethritis and female endocervicitis. Infection of the pharynx, rectum, and female urethra occur frequently but are more likely to be asymptomatic or minimally symptomatic. Retrograde spread of the organisms occurs in as many as 20% of women with cervicitis, often resulting in pelvic inflammatory disease (PID), with salpingitis, endometritis, and/or tubo-ovarian abscess. Retrograde spread can lead to frank abdominal peritonitis and to a perihepatitis known as Fitz-Hugh-Curtis syndrome. Long-term sequelae of PID, such as tubal factor infertility, ectopic pregnancy, and chronic pain, may occur in up to 25% of affected patients. Epididymitis or epididymo-orchitis may occur in men after gonococcal urethritis. Lower genital infection is a risk factor for the presence of other sexually transmitted diseases (STDs), including human immunodeficiency virus (HIV). Conjunctivitis can occur in adults, as well as children, following direct inoculation of organisms (usually as a result of hand-eye inoculation in adults) and can lead to blindness.

Disseminated gonococcal infection: Disseminated gonococcal infection (DGI) occurs following approximately 1% of genital infections. Patients with DGI may present with symptoms of rash, fever, arthralgias, migratory polyarthritis, septic arthritis, tendonitis, tenosynovitis, endocarditis, or meningitis. *N. gonorrhoeae* organisms spread from a primary site, such as the endocervix, the urethra, the pharynx, or the rectum, and disseminate to the blood to infect other end organs. Usually, multiple sites, such as the skin and the joints, are infected. Neisserial organisms disseminate to the blood due to a variety of predisposing factors, such as host physiologic changes, virulence factors of the organism itself, and failures of the host's immune defenses. For example, changes in the vaginal pH that occur during menses and pregnancy and the puerperium period make the vaginal environment more suitable for the growth of the organism and provide increased access to the bloodstream. (Three fourths of the cases of DGI occur in women; susceptibility is increased if the primary mucosal infection occurs during menstruation or pregnancy.) Defects in the host's immune defenses are also involved in the pathophysiology, with certain patients more likely to develop bacteremia. Specifically, patients with deficiency in terminal complement components are less able to combat infection, as complement plays an important role in the killing of neisserial organisms. As many as 13% of patients with DGI have a complement deficiency. A study of 22 patients with DGI revealed that total serum complement activity was greater than 25% below the normal mean. Other causes of immunocompromise (eg, HIV, SLE) also predispose to dissemination of infection. In addition, certain strains of gonorrhea causing asymptomatic genital infections are seen in association with DGI.

Etiology

N. gonorrhoeae is a gram-negative, intracellular, aerobic diplococcus; more specifically, it is a form of diplococcus known as the gonococcus. *N. gonorrhoeae* is spread by sexual contact or through vertical transmission during childbirth. It mainly affects the host's columnar or cuboidal epithelium. Virtually any mucous membrane can be infected by this microorganism. The physiologic ectopy of the squamocolumnar junction onto the ectocervix in the adolescent female is one factor that causes particular susceptibility to this infection. Many factors influence the manner in which gonococci mediate their virulence and pathogenicity. Pili help in attachment of gonococci to mucosal surfaces and contribute to resistance by preventing ingestion and destruction by neutrophils. Opacity-associated (Opa) proteins increase adherence between gonococci and phagocytes, promote invasion into host cells, and possibly down-regulate the immune response. Porin channels (porA, porB) in the outer membrane play key roles in virulence. Gonococcal strains with porA may have inherent resistance to normal human serum and an increased ability to invade epithelial cells, explaining their association with bacteremia. Certain acquired plasmids and genetic mutations enhance virulence. TEM-1–type beta-lactamase (penicillinase) affects penicillin binding and efflux pumps and confers resistance to penicillin. *TetM* protects the ribosome and confers resistance to tetracycline. Alterations in *gyrA* and *parC* genes result in fluoroquinolone resistance by

efflux activation and decreased antibiotic cell permeation. Gonococci attach to the host mucosal cell (pili and Opa proteins play major roles) and, within 24-48 hours, penetrate through and between cells into the subepithelial space. A typical host response is characterized by invasion with neutrophils, followed by epithelial sloughing, formation of submucosal microabscesses, and purulent discharge. If left untreated, macrophage and lymphocyte infiltration replaces the neutrophils. Some gonococcal strains cause an asymptomatic infection, leading to an asymptomatic carrier state in persons of either sex. The ability to grow anaerobically allows gonococci, when mixed with refluxed menstrual blood or attached to sperm, to secondarily invade lower genital structures (vagina and cervix) and progress to upper genital organs (endometrium, salpinx, ovaries). Gonococcal infection usually follows mucosal inoculation during vaginal, anal, or oral sexual contact or perinatally.

Sexually transmitted infection: Gonococcal infection usually follows mucosal inoculation during vaginal, anal, or oral sexual contact. It also may be caused by inoculation of mucosa by contaminated fingers or other objects. Transmission through penile-rectal contact is fairly efficient. The risk of transmission of *N. gonorrhoeae* from an infected woman to the urethra of her male partner is approximately 20% per episode of vaginal intercourse and rises to 60-80% after 4 or more exposures. In contrast, the risk of male-to-female transmission approximates 50-70% per contact, with little evidence of increased risk with more sexual exposures. Persons who have unprotected intercourse with new partners frequently enough to sustain the infection in a community are defined as core transmitters.

Neonatal and pediatric gonococcal infection: Neonatal gonococcal infection may follow conjunctival infection, which is obtained during passage through the birth canal. In addition, direct infection may occur through the scalp at the sites of fetal monitoring electrodes. In children, infection may occur from sexual abuse by an infected individual or possibly nonsexual contact in the child's household or in institutional settings.

Autoinoculation: Autoinoculation can occur when a person touches an infected site (genital organ) and contacts skin or mucosa.

Risk factors: Risk factors for gonorrhea include the following: Sexual exposure to an infected partner without barrier protection (eg, failure to use a condom or condom failure), Multiple sex partners, Male homosexuality, Low socioeconomic status, Minority status - Blacks, Hispanics, and Native Americans have the highest rates in the United States, History of concurrent or past STDs, Exchange of sex for drugs or money, Use of crack cocaine, Early age of onset of sexual activity, Pelvic inflammatory disease (PID) - Use of an intrauterine device (IUD).

Epidemiology

International occurrence: An estimated 200 million new cases of gonorrhea occur annually. In 1999, the number of new cases of gonococcal infection diagnosed in North America was 1.56 million; in Western Europe, 1.11 million; in South and Southeast Asia, 27.2 million; and in Latin America and the Caribbean, 7.27 million. Gonorrhea was the most common STD worldwide for at least most of the 20th century, although since the mid-1970s, public health initiatives in the industrialized world have resulted in declining incidence of the disease. Although the frequency data are unknown in most developing nations, these countries are considered to have the highest rates of gonorrhea and its complications. The incidence of antibiotic-resistant strains has been rising since the late 1940s. Of greatest concern historically has been the high percentage of cases due to penicillinase-producing *N. gonorrhoeae*. However, fluoroquinolone resistance has increased rapidly over the past decade on most continents and within the United States. The CDC reported fluoroquinolone resistance in 6.8% of 2004 isolates, 9.4% of 2005 isolates, and 13.3% of 2006 isolates.

Sex-related demographics: The male-to-female ratio for gonorrhea is approximately 1:1.2; however, females may be asymptomatic, whereas males are rarely asymptomatic. Women younger than 25 years are at the highest risk for gonococcal infection. Men who have sex with men are much more likely to acquire and carry gonorrhea and have far higher rates of antibiotic-resistant bacteria. Serious sequelae are much more common in women, in whom pelvic inflammatory disease (PID) may lead to ectopic pregnancy or infertility and in whom DGI is more likely, owing to menstruation, pregnancy, and a higher incidence in occult infection.

Prognosis

With adequate early therapy, complete cure and return to normal function are the rule. Most gonococcal infections respond quickly to cephalosporin therapy. Late, delayed, or inappropriate therapy may lead to significant morbidity or, on rare occasions, death.

Complications in males: Urethral strictures secondary to gonococcal infection in men are less common than previously thought. Some strictures in the preantibiotic era likely resulted from treatment by urethral irrigation using caustic compounds rather than from the gonorrhea itself. Other complications, such as penile lymphangitis, periurethral abscess, acute prostatitis, seminal vesiculitis, and infection of the Tyson and Cowper glands, are now rare.

Complications in females: Tubal scarring and infertility are the major complications of gonococcal infection in females. The incidence of involuntary infertility is estimated at 15% after one attack of pelvic inflammatory disease (PID) and approximately 50%-80% after 3 attacks. (However, infertility may be more common after chlamydial PID than after gonococcal PID, presumably because the more acute inflammatory signs associated with gonorrhea prompt women to seek diagnosis and treatment sooner.) Failure to diagnose PID can result in acute morbidity, including tuboovarian abscess, endometritis, Fitz-Hugh-Curtis syndrome (perihepatitis), and other chronic sequelae. Perihepatitis secondary to gonorrhea presents as right upper quadrant pain and nausea. The incidence of ectopic pregnancy is increased from 7-fold to 10-fold in women with previous salpingitis, with resultant increased fetal and maternal mortality rates. Gonococcal infections in women may also manifest as gonococcal urethritis or infection of periurethral (Skene) or Bartholin glands.

Pelvic inflammatory disease: PID is generally the most feared complication of gonococcal infection, because it is one of the leading causes of female infertility and often leads to hospitalization. This can be devastating to any woman, especially an adolescent who potentially has many years of childbearing ahead of her. In a 2011 study, female adolescents with PID were more likely than older women to have a rapid recurrence of PID or to become pregnant despite reporting more consistent condom use. Tubo-ovarian abscess and, rarely, tubal perforation with peritonitis and death, can occur, especially if the tubo-ovarian abscess was recurrent. Females with recurrent PID have high rates of ectopic pregnancy and infertility.

Epididymitis and orchitis: Epididymitis and orchitis occur infrequently in males who go untreated. These conditions usually respond well to the same antibiotics used for uncomplicated urethritis, but the drugs are administered for a longer course.

Arthritis: Gonorrhea is the most common cause of arthritis in the adolescent. However, arthritis (septic or reactive) is a rare complication of this disease. Because it mimics septic arthritis, excluding the possibility of gonococcal infection in any adolescent with acute onset of pyogenic arthritis is important. Adequate diagnosis may require culturing extraarticular sites for *N. gonorrhoeae*.

Additional complications: Complications of gonococcal infections also include the following: Corneal scarring after ocular gonococcal infections, Destruction of cardiac valves in gonococcal endocarditis, Death from congestive heart failure related to endocarditis, Central nervous system (CNS) complications of gonococcal meningitis. It has been suggested that a person with a gonococcal infection may be at a 3- to 5-fold increased risk of acquiring HIV infection, if exposed to the virus. DGI is an acute illness that causes fever, asymmetrical polyarthralgias, and skin pustules overlying small joints in patients with gonorrhea. Disseminated infection may also lead to meningitis or endocarditis. In newborns, vertical transmission can cause conjunctivitis, known as ophthalmia neonatorum, and permanent damage

and blindness, if untreated. Oral sex with an infected partner can result in pharyngitis, and, similarly, anal infection can arise from anal sex or local spread from a vaginal source.

Patient Education

Discuss safe sexual practices with all individuals in whom gonorrhea is suspected. Proper education to prevent gonorrhea may be more effective than simplistic instructions to avoid sex, especially in the teenaged population. Teenagers involved with abstinence-only campaigns have unchanged STD rates and disproportionately acquire anal and oral infections, rather than vaginal infections (the perception being that if an activity is not vaginal sex, it is not sex). Stress that oral or anal sex can also transmit disease. Patients should know the method of disease transmission and the adverse impact of recurrent infections on future fertility, they should be counseled about the risks of complications following gonococcal infection and the risk of other STDs, and they should always be instructed to refer any sex partners for prompt evaluation and treatment. In addition, these individuals should be aware that they should avoid sexual contact until medication is finished and until their partners are fully evaluated and treated. Thereafter, they should avoid unprotected contact. The discussion of responsible sexual behavior should not be limited or withheld because of personal religious or moral views, because these may not be shared by the patient, and teenagers are notorious for sexual experimentation; evidence suggests that offering only limited discussion does the teenage population a huge disservice. This advice is especially pertinent in states where sexual education is almost nonexistent in the school system because of abstinence-only teaching, which is misleading and factually inaccurate. In one study in Peru, a bundle of interventions that included extensive public health efforts, including training of local medical personnel, specific and presumptive treatment, outreach to female sex workers, and supply of barrier contraception, may have been effective at reducing the prevalence of several STDs, although the effect did not reach statistical significance overall. The effects were more greatly pronounced (and significant) among female sex workers and young adult women. The study was hampered by several methodologic limitations, such as comparing different cities as controls, which made drawing conclusions from the data difficult.

Abstinence education: Although the most effective STD prevention is abstinence from sex, this is oftentimes an unrealistic expectation, especially in the teenaged population. In fact, 88% of teenagers who pledged abstinence in middle and high school still engaged in premarital sex. Moreover, they tend to have riskier, unprotected sex because of their lack of education. Those who pledge before having sex have been found to have a 33% higher prevalence rate of STDs than have those who had sex and then retrospectively pledged, with nonpledgers falling in between. This is despite a lower number of partners and an older age at first intercourse in pledgers. Moreover, pledgers are less likely to be aware of their STD status and are less likely to seek testing, even if their STD rates are similar overall (again, highlighting a lack of appropriate sexual education). Of course, abstinence should be explained to be the best option, but a more practical expectation is abstinence from sex with someone known or suspected of having an STD until treatment is obtained and completed. In light of the difficulty of knowing a potential partner's sexual history (or honesty), strongly recommend the use of condoms as a reasonable alternative to abstinence.

Risks of unprotected sex: Patients should also be counseled about the additional risks of unprotected sex, including the acquisition of more serious or lifelong infections such as herpes, hepatitis B, and HIV, and, of course, about the risks of pregnancy. The emotional aspect of sexual relationships may also need to be addressed, especially in teenage girls. Teenagers are vulnerable in that they are sexually mature but not yet emotionally mature. For patient education information, see the Sexual Health Center, as well as Sexually Transmitted Diseases, Gonorrhea, and Chlamydia.

CLINICAL

History: The incubation period for gonorrhea is usually 2-7 days after exposure to an infected partner. In all patients who present with a possible STD, the history should include the following: Past history of STDs (including HIV infection and viral hepatitis), Treatment history for known STDs, Known symptoms of STDs in current or past sexual partners, Type of contraception used, Any history of sexual assault. In women, the history should also include the date of the last menstrual period and the details of parity, including any history of ectopic pregnancies.

Female genitourinary tract: The most common site of gonococcal infection in women is the endocervix (80%-90%), followed by the urethra (80%), rectum (40%), and pharynx (10%-20%). If symptoms develop, they often manifest within 10 days of infection. Major symptoms include vaginal discharge, dysuria, intermenstrual bleeding, dyspareunia (painful intercourse), and mild lower abdominal pain. When gonococcal cervicitis is either asymptomatic or unrecognized, the patient may progress to PID, often in proximity to a menstrual period. PID may also be asymptomatic or silent and occurs in 10-20% of infected women. Symptoms of PID include the following: Lower abdominal pain (most consistent symptom of PID), Increased vaginal discharge or mucopurulent urethral discharge, Dysuria (usually without urgency or frequency), Cervical motion tenderness, Adnexal tenderness (usually bilateral) or adnexal mass, Intermenstrual bleeding, Fever, chills, nausea, and vomiting (less common). Acute perihepatitis (Fitz-Hugh-Curtis syndrome) occurs primarily through direct extension of *N gonorrhoeae* or *Chlamydia trachomatis* from the fallopian tube to the liver capsule and overlying peritoneum. Vaginal discharge from endocervicitis is the most common presenting symptom of gonorrhea and is usually described as thin, purulent, and mildly odorous. Many patients have minimal or no symptoms from gonococcal cervicitis. Dysuria or a scant urethral discharge may be due to urethritis accompanying cervicitis. Pelvic or lower abdominal pain suggests ascending infection of the endometrium, fallopian tubes, ovaries, and peritoneum. Pain may be midline, unilateral, or bilateral. Fever, nausea, and vomiting may be present. The possibility of ectopic pregnancy should always be considered in patients with pelvic or lower abdominal pain. Right upper quadrant pain from perihepatitis (Fitz-Hugh-Curtis syndrome) may occur following the spread of organisms upward along peritoneal planes. Rectal infection is often asymptomatic, but rectal pain, pruritus, tenesmus, and rectal discharge may be present if the rectal mucosa is infected. Bloody diarrhea may also occur. Rectal infection may occur from anal intercourse or, in women, by local spread of the organism.

Male genitourinary tract: In men, urethritis is the major manifestation of gonococcal infection. Initial characteristics include burning upon urination and a serous discharge. A few days later, the discharge usually becomes more profuse, purulent, and, at times, blood-tinged. Acute epididymitis may also be caused by *N. gonorrhoeae* or *C. trachomatis*, especially in men younger than 35 years. This is usually unilateral and often occurs in conjunction with a urethral exudate. The classic presentation of epididymitis is of unilateral pain and swelling localized posteriorly within the scrotum. Urethral strictures due to gonococcal infection are now uncommon in the antibiotic era, but they can present with a decreased and abnormal urine stream, as well as with the secondary complications of prostatitis and cystitis. Another manifestation of gonorrhea, rectal infection, may present with pain, pruritus, discharge, or tenesmus.

Sex-independent manifestations: Men and women may exhibit gonococcal infection of the pharynx, rectum, and eye. Gonococcal pharyngitis is most commonly acquired during orogenital contact, with fellatio predisposing to infection more so than cunnilingus. Pharyngitis is often asymptomatic; however, it may present as exudative pharyngitis with cervical lymphadenopathy. Although rectal cultures are positive for gonorrhea in up to 40% of women with cervical gonorrhea (a similar percentage noted in infected homosexual men), symptoms of proctitis are unusual. Eye involvement in adults occurs by autoinoculation of gonococci into the conjunctival sac from a primary site of infection, such as the genitals, and is usually unilateral. The most common form of presentation is a purulent conjunctivitis, which may rapidly progress to panophthalmitis and

loss of the eye unless promptly treated.

Neonates: In neonates, bilateral conjunctivitis (ophthalmia neonatorum) often follows vaginal delivery from an untreated, infected mother. However, transmission to the newborn can also occur in utero or in the postpartum period. Symptoms of gonococcal conjunctivitis include eye pain, redness, and a purulent discharge. Neonates may also acquire pharyngeal, respiratory, or rectal infection or disseminated gonococcal infection (DGI). The organism can cause permanent injury to the eye very quickly. Prompt recognition and treatment are essential to avoid blindness. Blindness due to neonatal gonococcal infection is a serious problem in developing countries but is now uncommon in the United States and in other countries where neonatal conjunctival prophylaxis with antimicrobial therapy is routine. Nevertheless, infants of mothers with untreated infections, poor prenatal care, and unmonitored births continue to be at risk. Direct infection with *N. gonorrhoeae* in neonates may also occur through the scalp at the sites of fetal monitoring electrodes.

Disseminated gonococcal infection: The symptoms of DGI vary greatly from patient to patient. By the time the symptoms of DGI appear, many patients no longer have any localized symptoms of mucosal infection. The classic presentation of DGI is an arthritis dermatitis syndrome. Joint or tendon pain is the most common presenting complaint in the early stage of infection. About 25% of patients with DGI complain of pain in a single joint, but many other patients describe migratory polyarthralgia, especially of the knees, elbows, and more distal joints. Patients may also have tenosynovitis; the early tenosynovitis most commonly affects the flexor tendon sheaths of the wrist or the Achilles tendon ("lovers' heels"). Skin rash is a presenting complaint in approximately 25% of patients, but a careful examination will reveal a rash in most patients with DGI. The rash is usually found below the neck and may also involve the palms and soles. The dermatitis consists of lesions varying from maculopapular to pustular, often with a hemorrhagic component. Lesions usually number 5-40, are peripherally located, and may be painful before they are visible. Fever is common but rarely exceeds 39°C. The second stage of DGI is characterized by septic arthritis, by which time the skin lesions have disappeared and blood culture results are nearly always negative. The knee is the most common site of purulent gonococcal arthritis. Rare complications of DGI include gonococcal meningitis, pericarditis, and endocarditis. Headache, neck pain and stiffness, fever, and decreased sensorium may indicate gonococcal meningitis. This disease may be clinically indistinguishable from meningococcal meningitis on presentation, although the course of gonococcal meningitis is usually less rapid. Gonococcal endocarditis is more common in men than in women. Patients with collagen vascular disease (especially those with systemic lupus erythematosus) may also be more prone to this complication. The aortic valve is affected most commonly. A subacute onset of fever, chills, sweats, and malaise may indicate the presence of gonococcal endocarditis. Patients with endocarditis may develop atypical chest pain, cough, and dyspnea and may also develop the arthralgias and rash typical of DGI. Gonococcal endocarditis can cause severe valvular damage and death if not recognized and treated rapidly.

Physical Examination

N. gonorrhoeae infection may be recognized by the typical signs and symptoms of the disease, but it is important to remember that, by the time disseminated or upper reproductive tract disease is present, the primary site of mucosal infection may be normal in appearance, and the patient may have no localized signs or symptoms. With oropharyngeal infection, pharyngitis (usually mild) may be occur. With rectal infection, mucopurulent or purulent discharge may be present. The physical examination should also always include scrutiny for signs of herpes simplex, syphilis, chancroid, lymphogranuloma venereum, and genital warts.

Neonates: In neonates, look for purulent discharge from the eyes or other infected sites. The discharge from the eyes is usually bilateral in ophthalmia neonatorum, while in older patients, the condition most often is unilateral when secondary to self-inoculation. Also examine neonates for temperature instability (fever, hypothermia), which can result from disseminated sepsis.

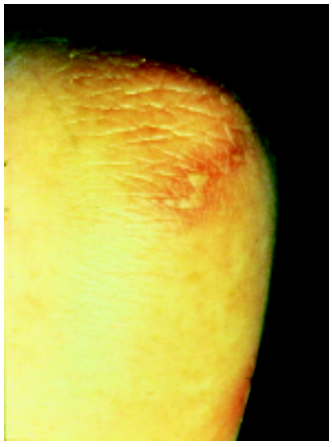
Female genitourinary tract: Look for the following in females: Mucopurulent or purulent vaginal, urethral, or cervical discharge, Vaginal bleeding; vulvovaginitis in children, Cervical friability - Tendency to bleed upon manipulation, Cervical motion tenderness during bimanual pelvic examination, Fullness and/or tenderness of the adnexa, unilateral or bilateral (eg, ovaries, fallopian tubes), Lower abdominal pain/ tenderness, with or without rebound tenderness, Possible low back pain - More common in progression to pelvic inflammatory disease (PID), Upper right abdominal tenderness (with perihepatitis), Fever.

Male genitourinary tract: Look for the following in males: Mucopurulent or purulent urethral discharge - Obtained by milking the urethra along the shaft of the penis, Possible epididymitis - Unilateral epididymal tenderness and edema, with or without penile discharge or dysuria, Penile edema without other overt inflammatory signs, Urethral stricture - Uncommon; more often seen in the preantibiotic era with urethral irrigation using caustic liquids.

Rectal symptoms: Rectal symptoms of gonorrhea include the following: Mucopurulent or purulent discharge with or without rectal bleeding, Mucopurulent exudate and inflammatory in the rectal mucosa, Rectal abscess (less common).

Ocular and periocular symptoms: Ocular and periocular manifestations of gonorrhea include the following: Anterior chamber - Cellular reaction, hypopyon, endophthalmitis, Conjunctiva - Chemosis, acute purulent exudate, hemorrhages. This patient presented with gonococcal urethritis, which became systemically disseminated, leading to gonococcal conjunctivitis of the right eye. Courtesy of the CDC/Joe Miller, VD. Cornea - Punctate epithelial keratitis; marginal, sterile stromal infiltrates; epithelial defects; infectious stromal infiltrates; stromal ulcerations; descemetocele; perforation; opacification, Lids - Erythema, edema.

Disseminated gonococcal infection: DGI may present with any of the following findings: Fever - Usually a temperature of less than 39°C. Skin - Maculopapular, pustular, necrotic, or vesicular rash, typically occurring on the torso, limbs, palms, and soles may be present; the rash usually spares the face, scalp, and mouth; hemorrhagic lesions, erythema nodosum, urticaria, and erythema multiforme occur less frequently; the skin lesions are usually in different stages of development at the time of clinical presentation (see the image) Disseminated gonococcemia, acral pustules. Joints - Most patients may have polyarthralgia with joint tenderness, decreased range of motion, and erythema; less often, purulent arthritis may affect a single joint with severe pain, tenderness, edema, erythema, and decreased range of motion. Tenosynovitis - Presents as erythema and local tenderness along a tendon sheath, with pain on active or passive range of motion; tenosynovitis most often occurs in the hands but may be found in the tendons of the lower extremities as well. Central nervous system - Patients with gonococcal meningitis may present with meningismus or decreased mental status. Cardiac - Patients with gonococcal endocarditis may have a new murmur, tachycardia, and fever; embolic lesions may be present. Muscle - DGI can cause abscess formation within the soft tissues, presenting as localized tenderness, edema, and pain with motion. Certain patient populations, such as patients infected with HIV, can experience involvement of unusual joints, such as the sternoclavicular joint and the hips, and the arthritis may have a more aggressive course, with potential destruction of the joint.



Diagnostic Considerations

When evaluating a female patient with suspected gonococcal infection, also

consider bacterial vaginosis, vaginitis, ectopic pregnancy, pregnancy, tubo-ovarian abscess, endometriosis, and mucopurulent cervicitis. In men, consider epididymitis, orchitis, and testicular torsion. Other conditions that should be considered include the following: Urinary tract infections, Pharyngitis; hepatitis, *Herpes simplex* urethritis, Rat-bite fever, Inflammatory and septic arthritis, Nongonococcal conjunctivitis, endocarditis, meningitis, and urethritis.

Differential diagnosis of DGI: Other causes of arthritis and dermatitis may display a clinical picture similar to that of disseminated gonococcal infection (DGI), with some notable differences. ***Reactive arthritis:*** Reactive arthritis is a human leukocyte antigen B27 (HLA-B27)–associated condition that predominantly occurs in young men and has the clinical triad of urethritis, conjunctivitis, and arthritis. However, the distribution of the arthritis is different, occurring predominantly in the joints of the axial skeleton. The clinical picture is less acute, occurring over the course of weeks rather than days and with less severe fever. This syndrome does not respond to antibiotic therapy, and it does not have the associated dermatitis that occurs in gonococcemia. ***Nongonococcal septic arthritis:*** Nongonococcal septic arthritis can be caused by a variety of organisms, but it presents with an acute onset of joint swelling and pain. Culture of joint fluid commonly reveals organisms. This type of arthritis is a destructive form of arthritis that is usually monoarticular. It most frequently occurs in children and elderly persons. Immediate treatment with antibiotics is indicated. ***Rheumatic fever:*** Rheumatic fever is a rare illness in the modern era and can present with high fever, rash, arthritis, and endocarditis. This condition follows a streptococcal infection and requires long, emergent intravenous (IV) antibiotic therapy for endocarditis; it also responds well to anti-inflammatory medications. ***Syphilis:*** Syphilis, an STD that commonly occurs in sexually active young adults, can also produce a rash, symptoms of arthritis, and genital lesions. However, genital involvement is usually in the form of an ulcer and not urethritis, and the rash can involve the palms and the soles. Laboratory tests, including rapid plasma reagin (RPR) titers, can aid in distinguishing syphilis from gonococcemia. ***Other:*** Other conditions to consider in a patient with arthritis and skin lesions include the following: Meningococcemia, Hepatitis, Bacterial endocarditis, Systemic lupus erythematosus (SLE), Tenosynovitis (eg, de Quervain disease, infectious), Other seronegative arthritides - Eg, ankylosing spondylitis, Sweet syndrome, and related dermal vasculitides.

Additional considerations

Other conditions to consider in the differential diagnosis of *N. gonorrhoeae* infection include the following: Sexual abuse, Enuresis, Sexual assault, Testicular torsion, Trichomoniasis, Endometritis, Vaginitis, Acanthosis nigricans, Cutaneous manifestations of hepatitis C, Lyme disease, Meningococcemia, Psoriatic arthritis, Syphilis.

Approach Considerations

Laboratory diagnosis of gonococcal infection depends on identification of *N. gonorrhoeae* at an infected site. No available serologic test is sufficiently sensitive and specific to merit use for screening or diagnostic purposes. Culture is the most common diagnostic test for gonorrhea, followed by the deoxyribonucleic acid (DNA) probe, and then the polymerase chain reaction (PCR) assay and ligand chain reaction (LCR). The DNA probe is an antigen detection test that uses a probe to detect gonorrhea DNA in specimens. Always obtain a pregnancy test for women of childbearing age who present with gonorrhea or any other sexually transmitted diseases (STD). The diagnosis of DGI should be based on clinical findings and confirmed with laboratory investigations if possible.

Culture and nonculture testing for N. gonorrhoeae: Perform a culture or nonculture detection test for *N. gonorrhoeae* on endocervical, urethral, pharyngeal, or rectal discharge. Because organisms are intracellular, attempt to obtain specimens in a manner that will contain mucosal cells and not merely discharge (similar to a Papanicolaou smear). Nonculture tests are less accurate in the presence of blood or during menses. Use culture instead at these times. Culture is performed on Thayer-Martin plates that must be stored refrigerated but warmed to room temperature before obtaining a sample. The plate is then incubated in a carbon dioxide atmosphere. Poor technique drastically reduces test sensitivity. Medicolegal cases (eg, child abuse, rape) require culture due to the possibility of false-positive results with nonculture methods. However, performing the more sensitive PCR assay-based tests to raise the likelihood of detecting an infection and then following up with culture to produce admissible evidence is appropriate.

Complete blood count: Patients with gonococcemia may have an elevated white blood cell (WBC) count, in the range of 10,000-15,000/µL.

Erythrocyte sedimentation rate: The erythrocyte sedimentation rate (ESR) is usually mildly elevated, with values from 20-50 in most patients. Less than 50% of patients have an ESR of higher than 50.

Serologic tests: These tests include latex agglutination, ELISA, immunoprecipitation, and complement fixation tests. Because of their lower sensitivity and specificity, especially in populations with a low prevalence of disease, these tests are not routinely used for diagnosis, but they can be used as adjuncts to the other laboratory tests and may help in making the diagnosis.

Echocardiography: Because of the potential severity of pericarditis and endocarditis, a cardiologic examination, including echocardiography, is recommended, even though these conditions are rare.

Suspected disseminated gonococcal infection: When DGI is suspected, blood and joint effusions should be sent for Gram stain and culture, although negative Gram stain results and sterile cultures do not rule out disseminated disease. Cerebrospinal fluid should be stained and cultured if signs or symptoms of meningitis are present. Gram stains, cultures, and/or nucleic acid amplification tests (NAATs) of genital, rectal, conjunctival, and pharyngeal secretions should also be obtained when DGI is suspected, even if the patient has no localized symptoms at any of those sites. The highest yield of *N. gonorrhoeae* organisms in gonococcemia is from mucosal sites, including the pharynx, urethra, cervix, or rectum. Urethral and cervical cultures are typically the most revealing. Blood cultures yield positive culture results in 10-30% of patients and joint fluid in 20-30% of patients. Skin lesions yield organisms in only about 10% of patients. Immunofluorescence studies may improve the effectiveness in skin and joint fluid. Gram stain of material from unroofed skin lesions may show typical organisms.

Other STDs: Other tests that may be indicated are those for concurrent STDs. The Preventive Services Task Force recommended that women at increased risk of gonorrhea also be screened for chlamydia, HIV, and syphilis. Patients in whom gonococcal disease is suspected should be evaluated for syphilis infection, as well as for infection with *C. trachomatis* (high rate of asymptomatic carriage), HIV (with counseling), hepatitis B virus, herpes simplex virus, and any STDs that are suggested by the history and physical examination findings. Administer hepatitis B vaccination to these individuals unless they have received the full vaccine series. Rapid HIV test technology makes testing in the emergency department (ED) and referral more practical than enzyme-linked immunosorbent assay (ELISA). The need for additional testing depends on the situation; they are often performed as a battery of tests in suspected rape and child abuse cases. HIV testing in cases of rape or new-onset abuse does not acutely diagnose a new infection but does establish a baseline status of the patient such that subsequent seroconversion might be linked back to the event in question.

Smears With Gram Stain: Urethritis in males: The presence of typical gram-negative intracellular diplococci after Gram stain establishes a diagnosis of gonorrhea. If these organisms are not observed, the patient is said to have nongonococcal urethritis. Results are considered equivocal if typical morphotypes not associated with neutrophils are present or if cell-associated, but morphologically atypical, organisms are observed. A simple Gram stain is probably the method of choice for the detection of gonorrhea in symptomatic males because it is much less expensive and much more rapid than the Gen-Probe method. *Urine:* In men, urethritis can be diagnosed using either of 2 methods of Gram staining. The first is via a urine sample. Preferably, examine the patient at least 2 hours after micturition or before his

first morning void. The patient should provide a first-morning void, with the first 10-15mL of the urine being saved. The urine is centrifuged so that the sediment may be analyzed microscopically under high power or oil immersion. The presence of 10 or more polymorphonuclear leukocytes (PMNs) seen under high power suggests urethritis. *Urethral exudate:* The second method is a Gram stain of urethral exudate. The presence of 4 or more PMNs per oil-immersion field is diagnostic for urethritis. In symptomatic males, Gram staining of urethral exudate yields a sensitivity of 90-98% and a specificity of 95-98%. However, in asymptomatic males, the sensitivity of the Gram stain is only 60%. Therefore, culture studies are recommended if an asymptomatic gonococcal infection is suggested. **Cervicitis in females:** In women with positive cervical culture results, the Gram stain results from the endocervix are 50-60% sensitive and 82-97% specific. In addition, the presence of more than 10 PMNs per high-power field on an endocervical smear is consistent with cervicitis. In women who lack a cervix because of hysterectomy, use urethral culture to make the diagnosis. **Emergency department use:** Gram stain is a rapid and inexpensive test available in many emergency departments (EDs). The positive predictive value is high for urethral infection, but a negative Gram stain does not rule out infection in asymptomatic men. Collect specimens from the urethra, endocervix, pharynx, rectum, conjunctiva, urine, or blood. A Gram stain of urethral or cervical discharge may show gram-negative intracellular diplococci (diagnostic in the male) and PMNs. This is very useful if the physician has easy access to a microscope, because the diagnosis may be made without waiting for culture results. The sensitivity and specificity of the Gram stain are lower for endocervical and rectal specimens. Gram stains from these sites are not recommended for routine use in the ED. In addition, Gram staining is not useful for the diagnosis of pharyngeal infection, because the oropharynx may be colonized by other *Neisseria* species that can lead to false-positive results. **Isolation Through Culture:** Specific culture of a swab from the site of infection is a criterion standard for diagnosis at all potential sites of infection. Cultures are particularly useful when the clinical diagnosis is unclear, when a failure of treatment has occurred, when contact tracing is problematic, and when legal questions arise. However, empiric treatment is often necessary in patients being diagnosed through culture, because culture results are not available for 24-48 hours. A small percentage (approximately 5%) of isolated gram-negative diplococci from genital, rectal, and pharyngeal cultures are actually *Neisseria meningitidis,* which can cause clinical disease that is identical to gonococcal infections of the urethra, cervix, or rectum. Hence, speciation from samples from pharyngeal and rectal sites should be standard, while samples from genital sites are recommended. Antimicrobial susceptibility testing is generally unnecessary except in cases of resistance surveillance testing or cases of disseminated infection. *N. gonorrhoeae* is a fastidious organism that requires a moist carbon dioxide-rich atmosphere and must be grown on enriched media, usually chocolate agar containing lysed blood. **Sensitivity:** A single culture on most selective media yields a sensitivity of 95% or more for urethral specimens from men with symptomatic urethritis. A sensitivity rate of about 80-90% is found for endocervical infections in women. For maximized yield in cervical specimens, simultaneous inoculation on selective and nonselective media is recommended. Culture may take several days to weeks. **Specimen collection:** Although the urethra is commonly infected in women with gonorrhea, culturing urethral specimens does not materially increase the diagnostic yield except in women who lack a cervix because of hysterectomy. Patients with possible disseminated gonococcal infection (DGI) should have culture samples taken from all possible mucosal sites (ie, pharynx, urethra, cervix, rectum) and from blood and synovial fluid. Rectal and pharyngeal specimens are inoculated onto selective medium only. When collecting specimens in males, any discharge present at the meatus can be easily recovered for examination. If no discharge is present at the meatus, urethral material must be recovered by inserting and rotating a small swab 2-3 cm into the urethra. A calcium alginate or Rayon swab on a metal shaft is recommended. When collecting specimens in women, the exocervix is first wiped of exudate. A swab is then placed into the external os and rotated for several seconds. However, take care to avoid contact with vaginal mucosa or secretions, as vaginal fluids are inadequate. **Cultures of the conjunctiva:** Chocolate agar in a carbon dioxide–enriched environment is the best medium. Blood agar, MacConkey medium, and phenylethyl alcohol with 5% sheep blood also are good media. **Isolation through other bodily fluid cultures:** In patients who may have DGI, all possible mucosal sites should be cultured (eg, pharynx, cervix, urethra, rectum), as should blood and synovial fluid (in cases of septic arthritis). Three sets of blood cultures should also be obtained. Specimens from any mucosal site should be inoculated immediately in selective media for gonorrheal organisms, such as modified Thayer-Martin, or on chocolate agar at room temperature, which should be incubated in an enriched carbon dioxide environment. The growth of typical oxidase-positive colonies that consist of gram-negative diplococci strongly suggests gonorrhea. Samples from normally sterile sites (eg, blood, cerebrospinal fluid [CSF], synovial fluid) should be plated on nonselective and broth mediums. On the other hand, rectal and pharyngeal specimens, locations where commensal *Neisseria* may be present, should be inoculated onto selective medium only. Synovial fluid aspirations in patients with septic arthritis usually yield greater than 50,000 leukocytes/µL, while synovial fluid culture is variably positive. Blood cultures, at this point, are often negative. Gram stain and culture of vesicular or pustular skin lesions were found to have a diagnostic yield of less than 5%. Immunofluorescent techniques may be used to achieve better results.

Imaging Studies

Plain radiography: Chest radiography may show hemidiaphragm elevation in Fitz-Hugh-Curtis syndrome. Joint plain films to evaluate septic joints are often unrevealing but may help to rule out fracture or other disease processes.

Ultrasonography or CT scanning: Ultrasonography may be indicated in women to investigate suspected pelvic inflammatory disease (PID) and to visualize the appendix and ovaries as other possible causes of the symptoms. Pelvic ultrasonography or computed tomography (CT) scanning may demonstrate thick, dilated fallopian tubes or abscess formation. PID is uncommon in pregnancy when the cervical mucus plug may provide some protection to the upper tract. Ultrasonography should be used to rule out ectopic pregnancy whenever a pregnant patient has signs and symptoms of possible PID. Abdominal imaging may give indications of peri-hepatic adhesions or abdominal loculated fluid collections or help to exclude other diagnoses.

Nucleic Acid Amplification Tests: NAATs amplify genetic sequences (DNA or ribonucleic acid [RNA]) from a few copies to millions in a short period of time. One of the key benefits of NAATs is that a wide variety of specimen types may be sampled, including swabs from the endocervix, vagina, urethra (men), and urine (men and women). Variations of this process include ligase chain reaction tests and strand displacement amplification. These tests are very sensitive; they are also more rapid than culture, more specific than immunoassays, and do not require viable organisms. However, they are expensive, and results must be interpreted carefully because of false-positive results in certain settings. NAATs may be of particular use when examination and mucosal swab are difficult (in children or extremely apprehensive patients) and urine specimens are more easily obtained. However, although these tests can be used on eye secretions, their performance is less well validated. In addition, NAATs are not all recommended for rectal and pharyngeal specimens at this time. Clinicians should be familiar with specimen collection guidelines and performance parameters of the test available at their own hospitals. NAATs of genital, rectal, conjunctival, and pharyngeal secretions should also be obtained when disseminated gonococcal infection (DGI) is suspected, even if the patient has no localized symptoms at any of those sites. Pharyngeal gonococcal infections can occur in heterosexual men diagnosed with urethritis. Screening for pharyngeal colonization by *N. gonorrhoeae* and *C.*

trachomatis using validated NAATs has been recommended for heterosexual men diagnosed with urethritis.

PCR and LCR: PCR and ligand chain reaction (LCR) are gene amplification techniques that markedly increase the sensitivity of specimen testing. Both techniques amplify the genetic fingerprint of specimens with very few organisms present in order to more easily detect and identify the organisms. These methods have a high sensitivity and a high specificity (78.6% and 96.4%, respectively). They are easily performed on urethral specimens and can even be performed on first-void urine specimens. PCR and LCR are noninvasive, rapid, sensitive, and specific, and they have facilitated the diagnosis of gonococcal infection. However, they cannot report antibiotic sensitivities; therefore, these techniques do not eliminate the need for culture in these patients. In addition, specific molecular tests may produce erroneous results. In certain circumstances, it may be advisable, in consultation with a medical microbiologist, to take a sample for culture or to perform a second molecular test aimed at a different part of the bacterial genome. *N. gonorrhoeae* was identified as the causative agent in a case of culture-negative dermatitis-arthritis syndrome using real-time PCR. This technology can improve the speed and sensitivity of diagnosis and consequent management of patients with this syndrome. Some studies have been shown promise in the use of DNA polymerase chain reaction (PCR) assay for porA pseudogene detection, possibly even in nongenital sites.

Nucleic Acid Probe Signal Amplification: Nucleic acid probe signal amplification (NAPSA) detects DNA sequences using RNA probes. Located sequences are then coated with detection antibodies, which allow detection. One commercial product uses a single test to detect gonorrhea and chlamydia. More study is needed to evaluate the sensitivity of this technique compared with that of NAAT. Consider verifying positive urogenital nucleic acid detection test results (PCR, LCR, strand displacement amplification, ribosomal RNA or DNA sequence amplification tests) when false-positive results are likely. In 2002, the CDC recommended testing a second specimen with a different test to confirm the positive results. Australia and the United Kingdom have proposed guidelines to test the initial specimen with supplementary tests using different target sequences. The recommendations were that a result be reported as positive only if both test results were positive. Be aware that nonculture tests do not provide antimicrobial susceptibility results. Thus, in scenarios in which resistance or treatment failure is considered, culture and antimicrobial susceptibility testing may be warranted.

Antibody-Antigen Testing

The immunochromatographic strip test (IST) combines antibodies from a patient's specimen (secretions or urine) and *N. gonorrhoeae* antigens on a nitrocellulose strip. One study showed that this technique yielded a sensitivity of 70% and specificity of 97%. Optical immunoassay (OIA) also uses antigen-antibody reactions (monoclonal), but on a silicon wafer; a positive reaction is evidenced by a color change. A sensitivity of 60% and specificity of 90% was reported. Both rapid tests yield results within 30 minutes and require minimal training to use. Initial test results show some promise, but additional verification of their utility in appropriate settings is still needed.

Procedures

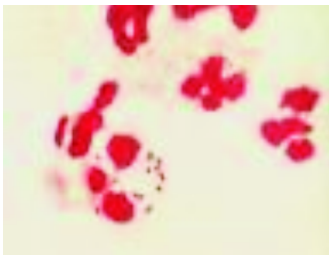
Laparoscopy: In women with symptoms and signs suggestive of pelvic inflammatory disease (PID) who are difficult to diagnose clinically, laparoscopy may be indicated to rule out (and, if need be, to treat) appendicitis, ovarian torsion, ectopic pregnancy, or other surgical emergencies. Imaging studies such as ultrasonography are obviously a less invasive means of obtaining diagnostic information, but potentially emergent cases may require a more definitive examination, which permits rapid intervention if required.

Culdocentesis: In PID, culdocentesis, although rarely indicated, may demonstrate free purulent exudate and provide material for Gram stain and culture.

Arthrocentesis: In septic arthritis cases, arthrocentesis may show purulence and/or causative organisms.

Lumbar puncture: Perform lumbar puncture and joint aspiration, if indicated by clinical findings. Rarely would CSF fluid yield positive results in cases of meningitis secondary to gonorrhea.

Histologic Findings: Exudate of PMNs is typical. Gram-negative intracellular diplococci are seen microscopically (see the image below). In pelvic inflammatory disease (PID), loss of ciliated columnar epithelium from the fallopian tubes may occur. Tubes, pelvic mesentery, and ovaries may be bound together with dense fibrosis and abscess formation.



Cytologic smear of cutaneous acral pustule showing gram-negative, intracellular diplococci.

Approach Considerations

As discussed in the Workup section, females with diagnosed or suspected sexually transmitted diseases (STDs) should have a concomitant pregnancy test. This guides further care and allows treatment with medications that are not approved for use in pregnancy. Identification and treatment of the patient's partner and any partners of the partner are important to prevent reinfection and complications. Prevention of neonatal disease is with the use of silver nitrate, erythromycin, ciprofloxacin, gentamicin, or erythromycin eye drops.

Inpatient versus outpatient treatment: The main decision once a diagnosis of gonorrhea has been made, either definitively or presumptively, is whether to treat the patient as an outpatient or to hospitalize him or her. For males, treatment is always outpatient for genital infection; however, admission may be necessary for complications such as disseminated gonococcal infection (DGI) or gonococcal arthritis. In females, the decision is much more difficult, because the risk of complications is much higher. In light of high rates of noncompliance, reinfection, and poor follow-up, some clinicians advocate admitting a female patient whenever a question of a complication such as pelvic inflammatory disease (PID) is present, particularly in the adolescent population. Many institutions have attempted to quantify abnormalities found on pelvic examination (ie, the PID score) in an attempt to admit those patients with a higher likelihood of complications. In cases in which future fertility is at risk, most physicians are fairly aggressive, especially in situations in which the patient is very young or unfamiliar to them. Many physicians admit patients who have corneal involvement for treatment with IV antibiotics. These patients can be discharged once the infection is under control and the corneal infection is improving.

Surgical care: Septic joints should be aspirated to make the initial diagnosis and to remove inflammatory exudate. Open drainage is rarely indicated, except in infections of the hip in children. Most authorities recommend removal of intrauterine devices in women with PID.

Activity: Patients with uncomplicated gonococcal disease can remain fully active.

Pharmacologic Treatment Regimens: The decision to implement antimicrobial therapy should be made quickly. The choice of which regimen to use should be based on the clinical presentation.

Monitoring: Patients with disseminated gonococcal infection (DGI) or pelvic inflammatory disease (PID) who are treated in an outpatient setting must receive follow-up care within 24 hours. Early follow-up care and culture with antibiotic sensitivities are indicated in patients with unresolved or recurrent symptoms despite therapy. Immediate test of cure is not recommended by the CDC in any patient with uncomplicated gonorrhea treated with recommended or alternative treatments. It may be prudent to evaluate efficacy of therapy in all patients with pharyngitis treated with spectinomycin, because of efficacy rates of less than 60%.

INTERPRETATION

(Continued from Crux 57)

GASTRO-INTESTINAL TUMOUR MARKERS

Indications/Applications

CA 19-9 for pancreatic cancer, as a screening test: CA 19-9 is not recommended for use as a screening test for pancreatic cancer. Its sensitivity (68-93%) and specificity (76-100%) are inadequate for accurate diagnosis. The test may be falsely normal or inappropriately elevated in people who do not have cancer, since increased levels can be seen in healthy individuals, in benign conditions, and in other malignant conditions. Conversely, CA 19-9 levels may not be elevated in patients with small pancreatic tumors or with early-stage tumors. Approximately 5% of the population does not produce the CA 19-9 antigen.

CA 19-9 for pancreatic cancer, to determine surgical resectability and postoperative outcomes: CA 19-9 should not be used alone to determine surgical resectability or outcomes after surgical resection. In the evaluation of patients for surgical intervention, preoperative CA 19-9 levels have been used to predict patient outcomes. When blood levels of CA 19-9 were greater than 1000 U/mL, 96% of tumors were found to be unresectable. However, this preoperative evaluation alone has yet to be widely used to establish inoperability. Furthermore, several studies have shown a correlation between a postoperative decline in CA 19-9 levels and the increased duration of patient survival. Patients whose CA 19-9 normalized postoperatively may live longer, whereas rising CA 19-9 levels may correlate with shorter survival times.

CA 19-9 for pancreatic cancer, to detect recurrence: CA 19-9 may predict recurrence of pancreatic cancer before the clinical examination or radiographic findings. However, CA 19-9 determinations alone cannot provide definitive evidence of disease recurrence and must be confirmed with imaging studies or biopsy. Serial assay measurements may be helpful in the management of patients following surgical resection with adjuvant chemotherapy and/or radiation therapy or surgical resection alone without adjuvant therapy. Elevation of CA 19-9 above certain levels may also correlate with disease recurrence early in the postoperative period.

CA 19-9 for pancreatic cancer, to monitor treatment response: Currently, insufficient data exists to recommend routine use of CA 19-9 alone to monitor treatment response. CA 19-9 can be measured at the start of treatment for locally advanced and metastatic disease and every 1-3 months during active treatment with chemotherapy, radiation therapy, and/or other targeted or biological therapies. A fall in CA 19-9 levels could help confirm the effectiveness of a particular treatment regimen. Conversely, a rise in CA 19-9 levels could indicate a need to change the treatment regimen. If CA 19-9 rises during surveillance, disease progression needs to be confirmed with clinical examination, diagnostic imaging, and/or biopsy. However, no agreement exists regarding the frequency with which the CA 19-9 assay should be performed or the magnitude of change or time period of change of CA 19-9 levels that is considered significant.

CA 19-9 for colon cancer: Currently, insufficient data exists to recommend CA 19-9 for screening, diagnosis, staging, surveillance, or monitoring the treatment of patients with colorectal cancer.

Considerations

Pancreatic cancer is just one of several conditions that may cause elevated levels of CA 19-9. Increased levels can be seen in healthy individuals, in benign conditions, and in other malignant conditions. In particular, cholestasis and jaundice, such as from bile duct disease, cirrhosis, or pancreatitis, can falsely elevate CA 19-9 levels and cause diagnostic uncertainty. CA 19-9 levels correlate with alkaline phosphatase levels, which further associates the 2 mechanisms of CA 19-9 elevation by secretion from pancreatic cancer cells and cholestasis. Serial determination of levels after relief of jaundice and/or the use of higher cut-off levels in patients with jaundice could be necessary to exclude pancreatic cancer in patients with normal imaging and clinical studies. Since this marker cannot be synthesized in approximately 5% of the population (ie, those who lack the Lewis antigen or are Lewis A-B-), CA 19-9 levels may be falsely low even in the presence of pancreatic cancer. Because of the low prevalence of pancreatic cancer in the general population and the possibility of elevated tumor marker levels in conditions other than pancreatic cancer, the CA 19-9 assay is not accurate enough to be used as a screening tool in the asymptomatic population. CA 19-9 levels are increased in only about 40% of stage I pancreatic cancers, and levels may be normal even up to several months prior to clinical signs of pancreatic cancer. However, the higher the levels of CA 19-9, the greater the PPV and specificity in diagnosing pancreatic cancer. When CA 19-9 levels were greater than 1000 U/mL, the PPV and specificity approached 100% and were correlated with unresectable tumors. Studies also show that CA 19-9 levels may correlate with tumor burden, disease recurrence, and response to treatment. Thus, CA 19-9 is a better marker for advanced pancreatic neoplasms than for early-stage disease. Low sensitivity in early-stage pancreatic cancer and low overall specificity are important limitations of CA 19-9 that preclude the use of this assay as a screening tool for pancreatic cancer. Although not yet standardized, CA 19-9 may also be used to determine surgical resectability and predict postoperative outcomes. Future studies are needed to detail the use of this marker in patients with jaundice and/or cholestasis. Cancer antigen 19-9 (CA 19-9) is used to help differentiate between cancer of the pancreas and other conditions, as well as to monitor treatment response and recurrence. The reference range of serum CA 19-9 is less than 37 U/mL.

Interpretation

Elevated levels of CA 19-9 can be seen in healthy individuals. Elevated levels can also be seen in benign conditions, such as the following: Biliary tract obstruction, Cholangitis, Inflammatory bowel disease, Acute or chronic pancreatitis, Liver cirrhosis, Cystic fibrosis, Thyroid disease.

Elevated levels of CA 19-9 can be seen in the following malignant conditions as well: Bile duct cancers, Colorectal cancers, Gastric cancers, Ovarian cancers, Hepatocellular cancers, Esophageal cancers, Pancreatic cancers. Additionally, at least 5% of the population is unable to produce the CA 19-9 antigen. The overall low specificity and sensitivity of this assay precludes its use as a screening tool for pancreatic cancer. An elevated tumor marker level needs to be interpreted within the context of the patient's history, physical examination, diagnostic imaging, and laboratory work-up findings. High CA 19-9 levels (ie, greater than 1000 U/mL) correlate with unresectable or more advanced tumors, although this preoperative evaluation of CA 19-9 has not been widely used to establish inoperability. High marker levels may also be used to predict patient outcomes. A decrease or normalization of CA 19-9 levels postoperatively correlates with a longer duration of survival. Conversely, rising marker levels postoperatively have been correlated with shorter duration of survival and increased disease recurrence. Finally, CA 19-9 levels can be used to monitor tumor response to active treatment with surgery, with or without chemotherapy, radiation therapy, and/or other targeted or biological therapies. A decrease in CA 19-9 levels confirms the effectiveness of the therapeutic regimen, while a stable or rising level may indicate the need to change therapies.

TROUBLESHOOTING

BIOSAFETY

Introduction

The purpose of this article is to be a resource for information, guidelines, policies, and procedures that will enable and encourage those working in the laboratory environment to work safely and reduce or eliminate the potential for exposure to biological, chemical and radioactive materials hazard. The goal of the laboratory safety is to minimize the risk of injury and illness to laboratory workers by ensuring they have the training, information, support and equipment needed. The manual promotes safe and practical laboratory procedures, included laboratory biosafety, laboratory biosecurity, microbiological risk assessment, laboratory biosafety levels, information on the use of personal protective equipment, laboratory animal facilities, laboratories equipment, laboratory techniques, hazard communication and packing of infectious substances, biosafety and biotechnology, the proper use of disinfection and sterilization, the use and storage of chemicals and radioactive materials, biosafety officer and biosafety committee and the proper methods of waste disposal. Finally, emphasis must be placed on the practices and procedures used by trained laboratory staff. Since "no biosafety cabinet or other facility or procedure alone guarantees safety unless the users operate safe techniques based on informed understanding." It is the responsibility of everyone, including managers and laboratory workers, to use the information available in these manual and to perform their work in a safe and secure manner.

Laboratory Biosafety

'Laboratory biosafety' is the term used to describe the containment principles, technologies and practices that are implemented to prevent unintentional exposure to pathogens and toxins, or their accidental release. A laboratory biosafety goal is to ensure that hazardous materials will be handled and disposed of in such a way that people, other living organisms, and the environment are protected from harm. Safety awareness must be a part of everyone's habits, and can only be achieved if all senior and responsible staff has a sincere, visible, and continuing interest in preventing injuries and occupational illnesses.

Manual of Laboratory Safety

Laboratory facilities are designated as: Basic Biosafety Level 1 (BSL-1), Basic Biosafety Level 2 (BSL-2), Containment Biosafety Level 3 (BSL-3) and Maximum containment Biosafety Level 4 (BSL-4).

Biosafety Level 1

Practices, safety equipment, and facility design and construction are appropriate for undergraduate and secondary educational training and teaching laboratories, and for other laboratories in which work is done with defined and characterized strains of viable microorganisms not known to consistently cause disease in healthy adult humans. *Bacillus subtilis, Naegleria gruberi*, infectious canine hepatitis virus, and exempt organisms. BSL-1 represents a basic level of containment that relies on standard microbiological practices with no special primary or secondary barriers recommended, other than a sink for handwashing.

Biosafety Level 2

Practices, equipment, and facility design and construction are applicable to clinical, diagnostic, teaching, and other laboratories in which work is done with the broad spectrum of indigenous moderate-risk agents that are present in the community and associated with human disease of varying severity. With good microbiological techniques, these agents can be used safely in activities conducted on the open bench, provided the potential for producing splashes or aerosols is low. Hepatitis B virus, HIV, the *Salmonella*, and *Toxoplasma* are representative of microorganisms to this containment level. BSL-2 is appropriate when work is done with any human-derived blood, body fluids, tissues, or primary human cell lines where the presence of an infectious agent may be unknown. Primary hazards to personnel working with these agents relate to accidental percutaneous or mucous membrane exposures, or ingestion of infectious materials. Extreme caution should be taken with contaminated needles or sharp instruments. Even though organisms routinely manipulated at BSL-2 are not known to be transmissible by the aerosol route, procedures with aerosol or high splash potential that may increase the risk of such personnel exposure must be conducted in primary containment equipment, or in devices such as a BSC or safety centrifuge cups. Personal protective equipment should be used as appropriate, such as splash shields, face protection, gowns, and gloves. Secondary barriers, such as hand washing sinks and waste decontamination facilities, must be available to reduce potential environmental contamination.

Biosafety Level 3

Practices, safety equipment, and facility design and construction are applicable to clinical, diagnostic, teaching, research, or production facilities in which work is done with indigenous or exotic agents with a potential for respiratory transmission, and which may cause serious and potentially lethal infection. *Mycobacterium tuberculosis*, St. Louis encephalitis virus, and *Coxiella burnetii* are representative of the microorganisms assigned to this level. Primary hazards to personnel working with these agents relate to autoinoculation, ingestion, and exposure to infectious aerosols. At BSL-3, more emphasis is placed on: Primary barriers to protect personnel in contiguous areas, the community, and the environment from exposure to potentially infectious aerosols. For example, all laboratory manipulations should be performed in a BSC or other enclosed equipment, such as a gas-tight aerosol generation chamber. Secondary barriers for this level include controlled access to the laboratory and ventilation requirements that minimize the release of infectious aerosols from the laboratory.

Biosafety Level 4

Practices, safety equipment, and facility design and construction are applicable for work with dangerous and exotic agents that pose a high individual risk of life-threatening disease, which may be transmitted via the aerosol route and for which there is no available vaccine or therapy. Agents with a close or identical antigenic relationship to BSL-4 agents also should be handled at this level. When sufficient data are obtained, work with these agents may continue at this level or at a lower level. Viruses such as Marburg or Congo-Crimean hemorrhagic fever are manipulated at BSL-4. Biosafety level designations are based on a composite of the design features, construction, containment facilities, equipment, practices and operational procedures required for working with agents from the various risk groups. The primary hazards to personnel working with BSL-4 agents are respiratory exposure to infectious aerosols, mucous membrane or broken skin exposure to infectious droplets, and autoinoculation. All manipulations of potentially infectious diagnostic materials, isolates, and naturally or experimentally infected animals, pose a high-risk of exposure and infection to laboratory personnel, the community, and the environment. The assignment of an agent to a biosafety level for laboratory work must be based on a risk assessment. Such an assessment will take the risk group as well as other factors into consideration in establishing the appropriate biosafety level. For example, an agent that is assigned to Risk Group 2 may generally require Biosafety Level 2 facilities, equipment, practices and procedures for safe conduct of work. However, if particular experiments require the generation of highconcentration aerosols, then Biosafety Level 3 may be more appropriate to provide the necessary degree of safety, since it ensures superior containment of aerosols in the laboratory workplace. The biosafety level assigned for the specific work to be done is therefore driven by professional judgment based on a risk assessment, rather than by automatic assignment of a laboratory biosafety level according to the particular risk group designation of the pathogenic agent to be used.

Classification of infective microorganisms by risk group:

Risk Group 1 (no or low individual and community risk): A microorganism that is unlikely to cause human or animal disease.

Risk Group 2 (moderate individual risk, low community risk): A

pathogen that can cause human or animal disease but is unlikely to be a serious hazard to laboratory workers, the community, livestock or the environment. Laboratory exposures may cause serious infection, but effective treatment and preventive measures are available and the risk of spread of infection is limited.

Risk Group 3 (high individual risk, low community risk): A pathogen that usually causes serious human or animal disease but does not ordinarily spread from one infected individual to another. Effective treatment and preventive measures are available.

Risk Group 4 (high individual and community risk): A pathogen that usually causes serious human or animal disease and that can be readily transmitted from one individual to another, directly or indirectly. Effective treatment and preventive measures are not usually available. Effective biosafety practices are the very foundation of "laboratory biosecurity" activities. In the absence of careful implementation, various aspects of biosafety may conflict with laboratory biosecurity. For example, controls that reduce unauthorized access might also hinder an emergency response by fire or rescue personnel. Mechanisms need to be established that allow entry by emergency responders but ensure uninterrupted and constant laboratory biosecurity, control and accountability. Signage may also represent a potential conflict between biosafety and laboratory biosecurity. In the past, biohazard signs placed on laboratory doors identified the biological agents present in the laboratory. However, as a laboratory biosecurity measure to better protection it is recommended certain information on biohazard signs to the laboratory biosafety level, the name and telephone number of the responsible investigator, and emergency contact information.

Microbiological risk-assessment

The backbone of the practice of biosafety is risk-assessment. While there are many tools available to assist in the assessment of risk for a given procedure or experiment, the most important component is professional judgment. Risk assessments should be performed by the individuals most familiar with the specific characteristics of the organisms being considered for use, the equipment and procedures to be employed, animal models that may be used, and the containment equipment and facilities available. The laboratory director or principal investigator is responsible for ensuring that adequate and timely risk assessments are performed, and for working closely with the institution's safety committee and biosafety personnel to ensure that appropriate equipment and facilities are available to support the work being considered. Once performed, risk assessments should be reviewed routinely and revised when necessary, taking into consideration the acquisition of new data having a bearing on the degree of risk and other relevant new information from the scientific literature. One of the most helpful tools available for performing a microbiological risk assessment is the listing of risk groups for microbiological agents. However, simple reference to the risk grouping for a particular agent is insufficient in the conduct of a risk assessment. Other factors that should be considered, as appropriate, include: (1) Pathogenicity of the agent and infectious dose. (2) Natural route of infection. (3) Other routes of infection, resulting from laboratory manipulations (parenteral, airborne, ingestion). (4) Stability of the agent in the environment.

BOUQUET

In Lighter Vein

A blonde, a brunette, a movie star, the Pope, and a pilot were on a plane.
The plane was going down fast, and there were only four parachutes for all five of them.
The pilot took one and jumped, then the movie star took one and jumped, and then the blonde took one and jumped.
The pope told the brunette to take the last one.
The brunette said, "There are still 2 parachutes left! The blonde took my backpack!"

On his first visit to a girl's house, a guy waited in the living room while she prepared a snack in the kitchen.
Left alone, he noticed a small, attractive vase on the mantelpiece.
He picked it up and was looking at it when the girl walked back in.
"What's this?" he asked.
"Oh, my father's ashes are in there," she said.
"Oh! I'm so sorry..."
"Yeah, he's too lazy to go to the kitchen and get an ashtray."

A man was praying to god.
He said, "God?"
God responded, "Yes?"
And the Guy said, "Can I ask a question?"
"Go right ahead", God said.
"God, what is a million years to you?"
God said, "A million years to me is only a second."
The man wondered.
Then he asked, "God, what is a million dollars worth to you?"
God said, "A million dollars to me is a penny."
So the man said, "God can I have a penny?"
And God cheerfully said, "Sure!.....just a second."

Wisdom Whispers

- Only those who dare to fail greately can ever achieve greatly.
- Even if you're in the right track, you'll get run over if you just sit there.
- Every time you subtract negative from your life, you make room for more positive.
- Beautiful things Are not Always Good ~ But Good things are Always Beautiful!
- Never Miss the First Opportunity, Because the Second Opportunity Will be Much More Difficult than First!
- If the Road is Beautiful then, Worry About the Destination, But if the Destination is Beautiful, Then Don't Worry About The Road!
- We Always Feel that GOD Never comes on Time When We Call Him...But the Truth is ~ "He is Always on Time" But "We are Always in Hurry!
- Trust the One Who can See, These Three Things in You ~Sorrow Behind Your SMILE, Love Behind Your ANGER & Reason Behind Your SILENCE!
- Dreams Aren't those That You Have when You are Asleep, Dreams are Those that Don't Let You Sleep till They are Fulfilled!

Brain Teasers

Match the following with the investigations that they attract.

1. Banti's Syndrome	A. Esophageal biopsy
2. Barret Syndrome	B. Anemia
3. Chediak-higashi Syndrome	C. Aldosterone level assay
4. Conn's Syndrome	D. Peripheral smear, neutrophils study
5. Cronkhite-canada Syndrome	E. Serum bilirubin level
6. Dubin-johnson Syndrome	F. Endoscopic colonic biopsy
7. Guillain-barre Syndrome	G. Blood sugar level
8. Kimmelstiel-wilson syndrome	H. Lumbar puncture, CSF study
9. Meigs syndrome	I. Small intestine polyp study
10. Peutz-jeghers Syndrome	J. Ovarian tumour study
11. Plummer-vinson Syndrome	K. Meningococcal infection.
12. Waterhouse-Friderichsen Syndrome	L. Serum Ferritin level

Answers: 1.B, 2.A, 3.D, 4.C, 5.F, 6.E, 7.F, 8.H, 9.J, 10.I, 11.L, 12.K

TULIP NEWS

Tulip Introduces

Verti-kal

Strips for periodic performance testing of ELISA readers

*"Numerous surveys have demonstrated the need for regular checks to assure that instrument meets specifications and that proper techniques are employed".**

Linearity, Sensitivity, Wavelength Calibration, Stray Light and Photometric accuracy should be evaluated periodically.

**Practical Spectrophotometery Standards*

- **VertiKal can be used for monitoring Filter integrity, Linearity, Repeatability and Stray light interference for ELISA readers.**
- **VertiKal simulates true test conditions and is very simple to perform;**
  - **Add Distilled Water to Vertikal strip**
  - **Read**
  - **Compare results with acceptance criteria**

Presentation 6 Strips

• Linearity • Calibration • Repeatability

Printed and published by D.G. Tripathi, Edited by Dr. Ramnik Sood, M.D. (Path.) for and on behalf of Tulip Diagnostics Private Ltd., Gitanjali, Tulip Block, Dr. Antonio Do Rego Bagh, Alto Santacruz, Bambolim Complex Post Office, Goa - 403 202, INDIA.
Fax: (0832) 2458544. E-mail: sales@tulipgroup.com Website: www.tulipgroup.com