ABSTRACT

Fitz-Hugh-Curtis syndrome—inflammation of the liver capsule associated with genital tract infection—occurs in up to one fourth of patients with pelvic inflammatory disease (PID). Classically presenting as sharp, pleuritic right upper quadrant pain, usually but not always accompanied by signs of salpingitis, it can mimic many other common disorders such as cholecystitis and pyelonephritis.

KEY POINTS

*Neisseria gonorrhoeae* and *Chlamydia trachomatis* are thought to be the primary causative agents of Fitz-Hugh-Curtis syndrome.

The pathogenesis of Fitz-Hugh-Curtis syndrome is incompletely understood. It may result from direct, hematogenous, or lymphatic infection of the liver capsule and related structures, or from an exaggerated immune response to *C trachomatis*.

The incidence ranges from 4% to 14% in women with PID, but is as high as 27% in adolescents with PID, whose less-mature anatomy makes them more susceptible to infection.

The diagnosis is usually made clinically by eliminating other causes of right upper quadrant pain and isolating the pathogen. This can be difficult if salpingitis is absent.

Treatment consists of antibiotics directed against *N gonorrhoeae* and *C trachomatis*; mechanical lysis of adhesions can be performed laparoscopically if conservative treatment fails.
one, based on the history and physical examination plus positive cultures. As the syndrome became better known, it began to be diagnosed more frequently during surgical exploration for other problems such as infertility or presumed cholecystitis. Laparoscopy further improved the ability to detect the syndrome and is an option when lysis of adhesions is necessary to relieve its symptoms.

Chlamydia also implicated

For many years, *N gonorrhoeae* was thought to be the sole causative agent of the syndrome. In 1978, however, Muller-Schoop et al first demonstrated serologic evidence of acute infection with *Chlamydia trachomatis* in 9 of 11 patients who had undergone laparoscopic evaluation for peritonitis, 6 of whom also had perihepatitis. Others have since documented similar findings. C trachomatis has also been cultured from the cervix, the fallopian tubes, and in a few cases from the liver capsule in patients with perihepatitis. Most experts now believe *C trachomatis* is the culprit more often than *N gonorrhoeae* and is the likely explanation for most “culture-negative” cases described before *C trachomatis* infection was recognized as a sexually transmitted disease.

If Fitz-Hugh-Curtis syndrome is present, screen for other STDs, including HIV

Estimates of the incidence of Fitz-Hugh-Curtis syndrome depend on the diagnostic criteria used, as patients with no symptoms sometimes have impressive perihepatic adhesions seen at laparoscopy, while patients with pelvic inflammatory disease (PID) and right upper quadrant pain may have no laparoscopic evidence or other signs of perihepatitis.

Using only clinical criteria, Semchyshyn found perihepatitis in 12% of patients with PID. Onsrud used laparoscopic criteria and found a similar (13.8%) rate of coincident perihepatitis and PID. In this study, which examined all cases of PID seen in the gynecologic department of one hospital in 2 years, 37% of the patients with laparoscopic evidence of both PID and perihepatitis had no right upper quadrant symptoms. The incidence of laparoscopic perihepatitis was higher in women who had undergone placement of an intrauterine contraceptive device (IUD) within the previous 6 weeks than in those who had had such a device for a longer period.

Others have found lower rates of Fitz-Hugh-Curtis syndrome. In a study in Sweden between 1978 and 1982, Paavonen et al found perihepatitis in 4% of 322 women with laparoscopic evidence of PID. Wang et al reported that only 17 (3.8%) of 442 women referred for evaluation of PID had clinical evidence of Fitz-Hugh-Curtis syndrome.

Rates higher in adolescents

In contrast, Litt and Cohen found clinical evidence of perihepatitis (right upper quadrant tenderness or elevated liver enzymes) in 37 (27%) of 137 adolescents with salpingitis. The high rate in this study may be partially explained by anatomical features of the adolescent genitourinary tract that facilitate progression of cervicitis to PID and, presumably, to Fitz-Hugh-Curtis syndrome. For example, the transitional zone between squamous and columnar epithelium of the cervix (the ectropion) is at the outer margin of the cervix in adolescents, vs within the cervix in adults.

PATHOGENESIS IS UNCERTAIN

The pathogenesis of the Fitz-Hugh-Curtis syndrome is still poorly understood. Several mechanisms have been proposed.

Direct infection of the liver?

Traditionally, inflammation of the liver capsule has been attributed to direct bacterial infection. Organisms were thought to travel from the genital area via the fallopian tubes and the paracolic gutters to the liver capsule.

Some evidence supports this: Holm-Nielsen et al demonstrated that peritoneal fluid is propelled from the pelvis to the diaphragm, where it is preferentially absorbed on the right side. The association between recent insertion of an IUD and Fitz-Hugh-Curtis syndrome also supports the hypothesis of intraperitoneal spread of organisms.

While direct spread may occur in some cases, several factors suggest an alternate etiology. Bacteria have only rarely been isolated from the liver surface or surrounding ascites in patients with Fitz-Hugh-Curtis syndrome.
Also, if organisms traveled via the peritoneum, we should see inflammation and infection of structures between the pelvis and the liver, but evidence of this is rare. In addition, Fitz-Hugh-Curtis syndrome has been reported in men, in whom a mechanism other than direct infection must exist.

**Hematogenous spread?**
Could bacteria travel from the pelvis to the liver via the bloodstream? The theory is supported by a case report that found focal lesions in the liver of a patient with Fitz-Hugh-Curtis syndrome, which resolved following antibiotic therapy. However, there is no evidence to support disseminated blood infection in most cases.

**Lymphatic spread?**
It is plausible that bacteria could spread from the pelvis to the liver capsule through the lymphatic system, and this mechanism would explain why most patients with Fitz-Hugh-Curtis syndrome show no evidence of generalized intra-abdominal infection or disseminated blood stream infection. However, most of the lymphatic drainage in the female reproductive tract is retroperitoneal, with no anatomical evidence linking the pelvic and subdiaphragmatic lymphatic systems.

**An exaggerated immune response?**
Perihepatitis and Fitz-Hugh-Curtis syndrome may represent a “hyperimmune” response to *Chlamydia*. Several studies demonstrated higher serum titers of antichlamydial immunoglobulin G (IgG) antibodies in patients with perihepatitis and salpingitis than in patients with salpingitis alone.

There is evidence that variable host factors can affect the inflammatory response to *Chlamydia* infection: for example, postinfectious scarring of the eyelid due to *C. trachomatis* is more common in patients with certain HLA class I antigens. Patton et al produced perihepatitis in a pig-tail macaque after exposing it to one strain of *C. trachomatis* and then challenging it with different strains, suggesting that the vigorous immune response manifested by perihepatitis might be a reinfection phenomenon. Why such a response should be limited to the liver capsule is unknown.

Certain aspects of the organism may also influence the host response. Recent attention has focused on the *Chlamydia* 60-kd heat-shock protein Chsp60, which exhibits considerable homology with human heat-shock proteins. An immune response triggered by *C. trachomatis* might cross-react with human heat-shock proteins in other tissues.

Money et al compared 27 patients with laparoscopically diagnosed perihepatitis and salpingitis and 46 patients with salpingitis alone. Elevated levels of antibody to Chsp60 were found in 67% of the perihepatitis-salpingitis group vs only 28% of the salpingitis-alone group. The median titer of the Chsp60 antibody was also significantly higher in the perihepatitis-salpingitis group. Antichlamydial IgG and IgM levels were not significantly different between the two groups. The authors concluded that the Chsp60 antigen influences the host’s inflammatory response. However, whether Chsp60 is involved in inducing immunopathology or whether it is a byproduct of severe infection remains unclear.

**DIAGNOSIS IS DIFFICULT**
Fitz-Hugh-Curtis syndrome can be difficult to diagnose, as its symptoms and physical findings can mimic those of many other diseases. Most experts now believe *C. trachomatis* is the culprit more often than *N gonorrhoeae*.

**Symptoms**
Symptoms of acute or subacute PID (fever, abdominal pain, vaginal discharge) are almost always present. Right upper quadrant pain. The perihepatic component usually presents as sharp pleuritic pain localized to the right upper quadrant at the lower rib margin, likely relat-
ed to inflammation of the underside of the diaphragm.\textsuperscript{2,17} The pain may be referred to the right shoulder or to the inside of the right arm and may be accompanied by nausea, vomiting, hiccupping, chills, fever, night sweats, headache, and malaise.\textsuperscript{17} Movement often exacerbates the pain.\textsuperscript{2}

The right upper quadrant pain may follow the lower abdominal pain by days, or the two may occur simultaneously. Rarely, the right upper quadrant pain is the presenting symptom without lower abdominal pain.\textsuperscript{7,26,28,30} This occurs in patients who have recovered from an acute episode of PID without appropriate treatment. In this more indolent presentation, the pain may be due to adhesions between the liver capsule and the diaphragm or the abdominal wall.\textsuperscript{17}

Although most patients present with right-sided pain, a few cases of left upper quadrant pain with perisplenitis seen on laparoscopy have also been reported.\textsuperscript{31}

**Physical findings**

On physical examination, patients have moderate to severe tenderness in the right upper quadrant, with some guarding and possibly splinting.

A friction rub may be heard along the right anterior costal margin. (Fitz-Hugh described it as “beautiful ‘new snow’ creaking frictions.”\textsuperscript{2})

A bimanual pelvic examination may detect vaginal discharge, cervical frictions, or adnexal tenderness previously unnoticed by the patient. These findings suggest underlying PID.

**Identifying the pathogen**

The pathogen is most commonly isolated from a cervical specimen, but if clinical suspicion is high, rectal, urethral, and pharyngeal samples should be obtained as well.

There are several tests for *C trachomatis* and *N gonorrhoeae*. Cultures are still widely used, but genetic amplification tests such as the ligase chain reaction (LCR) and nucleic acid amplification test are highly sensitive and specific, making them promising for diagnosing both *N gonorrhoeae* and *C trachomatis*. They can be performed on vaginal, urine, and cervical samples.\textsuperscript{14} Their main limitation is their cost. Serologic tests specific for *C trachomatis* can also be helpful.\textsuperscript{14,32}

**Radiographic studies**

Radiographic studies are most useful to rule out other possible causes.

- **Chest and abdominal radiographs** may exclude pneumonia or free air under the diaphragm.

- **Ultrasoundography** is the study of choice for evaluating the gallbladder and liver, and can exclude cholecystitis, cholelithiasis, and other common causes of right upper quadrant pain. It can also help evaluate the ovaries for abscesses or other findings consistent with PID.

In addition, typical ultrasonographic abnormalities in the perihilar area have been detected in patients with Fitz-Hugh-Curtis syndrome\textsuperscript{19,33–35}:

- Dinerman et al\textsuperscript{33} described an adolescent with PID not responding to usual treatment who had ultrasonographic evidence of ascitic fluid in the hepatorenal space and at the splenic hilus.
- Romo and Clarke\textsuperscript{34} described a patient with Fitz-Hugh-Curtis syndrome who had large amounts of loculated fluid in the abdomen and pelvis, seen by both ultrasonography and computed tomography.

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**TABLE 1**

**Differential diagnosis of Fitz-Hugh-Curtis syndrome**

<table>
<thead>
<tr>
<th>Disorder</th>
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<tbody>
<tr>
<td>Cholelithiasis</td>
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<td>Pleurisy</td>
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<td>Pyelonephritis</td>
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<td>Hepatitis</td>
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<td>Nephrolithiasis</td>
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<td>Perforated ulcer</td>
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<td>Subphrenic abscess</td>
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<td>Pancreatitis</td>
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<td>Appendicitis</td>
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<tr>
<td>Herpes zoster</td>
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<tr>
<td>Enteroviral epidemic pleurodynia (Bornholm disease)</td>
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Van Dongen described two patients in whom ascites and adhesions between the liver capsule and the abdominal wall were clearly seen on ultrasonography.

Schoenfeld et al found that the right anterior extrarenal space (measured by ultrasonography) was wider in 9 patients with Fitz-Hugh-Curtis syndrome than in 72 patients without clinical signs of the syndrome, suggesting that such a finding should prompt a search for genital tract infection.

Further study is needed to confirm these findings and evaluate the usefulness of these tools in diagnosing Fitz-Hugh-Curtis syndrome. Clinically, ultrasonography is most useful in excluding more common causes of right upper quadrant pain (TABLE 1).

Computed tomography. Contrast enhancement of the liver capsule can also support the diagnosis.

Laboratory tests may provide clues
Laboratory tests are only partially helpful with Fitz-Hugh-Curtis syndrome.

Liver enzyme levels are usually normal or only slightly elevated, which can help rule out hepatitis. Litt and Cohen, in a 1978 case series, cited a high rate of nonspecific elevations in transaminase levels in patients with Fitz-Hugh-Curtis syndrome. The enzyme abnormalities responded to antibiotics, suggesting that the perihepatic inflammation was responsible for the abnormal levels.

The erythrocyte sedimentation rate (ESR) has conflicting evidence for its use in the diagnosis of Fitz-Hugh-Curtis syndrome. Some small series and case reports demonstrated elevated ESRs in patients with Fitz-Hugh-Curtis syndrome, but larger studies have found a less robust association.

The white blood cell count may be normal or elevated.

Surgical exploration
Surgical exploration is warranted only if symptoms do not resolve with therapy. Laparoscopy can help confirm the diagnosis of PID in patients with suspected Fitz-Hugh-Curtis syndrome, as well as help exclude other diagnoses.

Counseling and further testing
The diagnosis of Fitz-Hugh-Curtis syndrome provides an opportunity for education and counseling about safer sex, and should prompt the clinician to screen for other sexually transmitted diseases including human immunodeficiency virus (HIV) infection.

TREATMENT SIMILAR TO PID

The management of Fitz-Hugh-Curtis syndrome is similar to that of PID.

Most patients can be treated as outpatients, although hospitalization should be strongly considered if the patient is:

- Adolescent (a group whose anatomy and high rate of noncompliance put them at particularly high risk for reproductive complications)
- Pregnant
- Immunodeficient
- A potential candidate for surgery (eg, if cholecystitis cannot be excluded)
- Unreliable for follow-up
- Having particularly severe symptoms
- Unresponsive to oral therapy or unable to tolerate oral medication.

Antibiotic therapy
Antibiotics should be directed at the most likely pathogens, in particular N gonorrhoeae, C trachomatis, facultative gram-negative rods, and anaerobes, since isolation of all offending agents is unlikely.

The Centers for Disease Control and Prevention has recently issued guidelines for treating PID (TABLE 2). If the patient is on parenteral therapy, it should be continued for 48 hours after she shows clinical improvement; then oral therapy can be started to complete 14-days.

The symptoms of perihepatitis usually resolve quickly once appropriate treatment is started, which in difficult cases may lend support to the diagnosis.

Managing complications
Long-term complications of Fitz-Hugh-Curtis syndrome are rare and can mostly be attrib-
Several regimens are possible

TABLE 2

**CDC guidelines for treating pelvic inflammatory disease**

**Parenteral regimens**

- **Either cefotetan** (Cefotan) 2 g intravenously (IV) every 12 hours or **cefoxitin** (Mefoxin) 2 g IV every 6 hours; plus
- **Doxycycline** (Doryx and others) 100 mg orally (PO; preferred) or IV every 12 hours; followed by
- **Doxycycline** 100 mg PO twice a day to complete 14 days

- **Clindamycin** (Cleocin) 900 mg IV every 8 hours; plus
- **Gentamicin** (Garamycin) in a loading dose of 2 mg/kg of body weight IV or intramuscularly (IM) followed by 1.5 mg/kg every 8 hours (single daily dosing may be used); followed by
- **Either doxycycline** 100 mg PO twice a day or **clindamycin** 450 mg PO four times a day to complete 14 days

**Alternative parenteral regimens**

- **Either ofloxacin** (Floxin) 400 mg IV every 12 hours or **levofloxacin** (Levaquin) 500 mg IV once daily; with or without
- **Metronidazole** (Flagyl and others) 500 mg IV every 8 hours*; followed by
- **Doxycycline** 100 mg PO twice a day to complete 14 days

- **Ampicillin/sulbactam** (Unasyn) 3 g IV every 6 hours; plus
- **Doxycycline** 100 mg PO or IV every 12 hours; followed by
- **Doxycycline** 100 mg PO twice a day to complete 14 days

**Oral regimens**

- **Either ofloxacin** 400 mg PO twice a day for 14 days or **levofloxacin** 500 mg PO once daily for 14 days; with or without
- **Metronidazole** 500 mg PO twice a day for 14 days*

- **Either ceftriaxone** (Rocephin) 250 mg IM in a single dose, **cefoxitin** 2 g IM in a single dose and **probenecid** (Benemid, Probalan) 1 g PO given concurrently in a single dose, or another parenteral third-generation cephalosporin (eg, **cefizoxime** or **cefotaxime**); plus
- **Doxycycline** 100 mg PO twice a day for 14 days; with or without
- **Metronidazole** 500 mg PO twice a day for 14 days

*Ofloxacin alone has been demonstrated to be effective; however, concerns about its effectiveness against anaerobes have led to the addition of metronidazole to fluoroquinolone-alone regimens.

REFERENCES


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