Pathogenesis, Diagnosis, and Management of Severe Pelvic Inflammatory Disease and Tuboovarian Abscess

CATHERINE A. CHAPPELL, MD and HAROLD C. WIESENFIELD, MD, CM
Magee-Womens Hospital of UPMC, University of Pittsburgh, Pittsburgh, Pennsylvania

Abstract: Severe pelvic inflammatory disease and tuboovarian abscesses (TOAs) are common pelvic infections requiring inpatient admission. There are few large randomized trials guiding appropriate clinical management of TOA, including antibiotic selection and timing of surgical management and drainage. The pathogenesis, diagnosis, and management of severe pelvic inflammatory disease and TOA are summarized and reviewed from the most current literature. Key words: pelvic inflammatory disease, PID, tuboovarian abscess, TOA, management

Introduction
Pelvic inflammatory disease (PID) is a polymicrobial ascending infection that causes inflammation of the upper genital tract, including endometritis, salpingitis, pelvic peritonitis, and occasionally leading to tuboovarian abscess (TOA) formation.1 PID can be classified as acute, subacute, or subclinical. The healthcare burden of PID is generally underestimated because of cases of undiagnosed subclinical PID. Even so, PID accounts for 2.5 million outpatient visits, 200,000 hospitalizations, and 100,000 surgical procedures.2 Annually over 1 billion dollars was spent on the treatment of PID. Another 1 billion dollars was spent on care for the sequelae of PID such as...
chronic pelvic pain, infertility, and ectopic pregnancy. This review will focus on acute and severe cases of PID, including those complicated by TOA.

**Epidemiology and Risk Factors**

The incidence of PID correlates with the incidence of sexually transmitted diseases, which increased in the 1970s and peaked in 1982 with an estimated 1 million cases and 14.2% prevalence of PID treatment among reproductive-aged women in the United States. However, generally the incidence and prevalence of PID is difficult to assess because of the lack of reporting requirement for PID, high rates of subclinical PID, increasing rates of outpatient management, and inaccuracies in diagnosis.

Several risk factors for the development of PID have been identified, while others remain controversial. PID is highly associated with younger age of coitarche, multiple sexual partners, nonuse of barrier contraception, and infection with chlamydia or gonorrhea. The Dalkon Shield, an intrauterine device (IUD) that is no longer available, increased users’ risk of PID by a wicking effect of its multifilament string that allowed microbes to ascend into the upper genital tract from the vagina. Modern IUDs do not seem to increase the risk of development of PID beyond the risk associated with insertion of the device. Case-controlled studies have shown an association between vaginal douching and PID. Hypothesized mechanisms for this association have included the introduction of vaginal microbes into the upper genital tract by the force of the douche fluid or the shift of protective microbiological flora.

It is unclear why some women with PID develop TOA, whereas the majority of women do not. Formation of TOA may be related to prior PID infection, delay in treatment, or virulence factors of the pathogens. Among hospitalized patients with PID approximately one third have TOA. An increase in the prevalence of TOAs among women hospitalized for PID might be related to increasing frequency and acceptability of outpatient treatment of PID, thus leading to hospitalization in only severe cases of PID and those with TOAs. The risk factors for TOA are similar to those of PID, including multiple sex partners, age between 15 and 25 years, and a prior history of PID. Women with human immunodeficiency virus infection may be more likely to develop TOA compared with women negative for human immunodeficiency virus.

**Pathogenesis**

PID is caused by an ascending infection of lower genital tract organisms from the vagina or cervix into the upper tract, including the uterus, fallopian tubes, and peritoneal cavity. Up to 75% of cases occur during the follicular phase of the menstrual cycle. Similarly, a high estrogen environment along with the presence of cervical ectopy found in adolescence facilitates the attachment of Chlamydia trachomatis and Neisseria gonorrhoeae, which may contribute to the higher rates of PID among young women.

TOAs are also caused by an ascending infection to the fallopian tube causing endothelial damage and edema of the infundibulum resulting in tubal blockage. The ovary may become involved presumably by invasion of organisms through the ovulation site. Eventually the separation between the ovary and fallopian tube is lost. Necrosis inside this complex mass may result in 1 or more abscess cavities and an anaerobic growth environment. A TOA may also form from local spread of infection associated with uncontrolled inflammatory disease of the bowel, appendicitis, or adnexal surgery. It is important to note that TOAs, unlike other types of abscesses, occur between organs rather than confined inside an organ. The
adherence of adjacent pelvic structures, such as the omentum and bowel, might serve a host defense mechanism to contain the inflammatory process within the pelvis. This could be a reason that some women with TOA are not overtly sick with an elevated white cell count or fever.

Microbiological Etiology

The organisms associated with upper genital tract infection have been identified using endometrial biopsy, culdocentesis, and laparoscopy. PID has been determined to be polymicrobial in nature, because multiple different bacteria have been isolated from the upper genital tract in women with PID. These bacteria can be artificially divided into 2 categories: sexually transmitted pathogens and lower genital tract flora. Sexually transmitted infections, such as *N. gonorrhoeae*, *Chlamydia trichomatis*, and *Mycoplasma genitalium*, have all been identified from the cervix, endometrium, and fallopian tubes from women with acute salpingitis diagnosed by laparoscopy. However, endogenous, bacterial vaginosis-associated lower genital tract organisms, such as *Prevotella* species, Peptostreptococcus sp., *Gardnerella vaginalis*, *Escherichia coli*, *Haemophilus influenza*, and aerobic streptococci are found in a high percentage of PID cases.

Like PID, TOAs are also polymicrobial infections with a mixture of anaerobic, aerobic, and facultative organisms. Sexually transmitted pathogens are infrequently isolated from TOAs. Gonorrhea was isolated from only 3.8% of 53 TOA aspirates, despite an overall recovery rate of 31% from the cervix. There are no published reports isolating *C. trichomatis* from an abscess cavity. The role of gonorrhea and chlamydia may be limited to antecedent infections such as cervicitis or PID; and gonorrhea may facilitate invasion of the upper genital tract by lower genital tract flora. Alternatively, the inflammatory environment of the abscess cavity may make it difficult to isolate these organisms by culture if they are present. The most common organisms isolated for TOAs are *E. coli*, *Bacteroides fragilis*, *Bacteroides* species, *Peptostreptococcus*, *Peptococcus*, and aerobic streptococci. Importantly, *E. coli* is a common isolate in women with ruptured TOAs and a frequent cause of Gram-negative sepsis. TOAs that occur in women with long-term use of an IUD are often associated with *Actinomyces israelii*.

Diagnosis of PID and TOA

Acute PID is difficult to diagnose because of the wide variation of signs and symptoms. There is no single subjective complaint, physical examination finding, or laboratory finding that is highly sensitive or specific for the diagnosis of PID. The diagnosis of PID is imprecise because clinicians must consider a combination of factors to make the diagnosis. The clinical diagnosis of PID has a positive predictive value of only 65% to 90% even in the most experienced hands. However, delay in diagnosis and treatment can lead to the postinflammatory sequelae of the upper genital tract, such as infertility, ectopic pregnancy, and chronic pelvic pain. Therefore, empiric treatment should be initiated in women at risk for sexually transmitted diseases if they are experiencing pelvic or lower abdominal pain, if other illnesses have been ruled out and if they have cervical motion tenderness, uterine tenderness, or adnexal tenderness. In addition, 1 or more of the following criteria enhances the specificity of the diagnosis: fever, abnormal cervical or vaginal mucopurulent discharge, presence of abundant white blood cells on saline microscopy, elevated erythrocyte sedimentation rate, elevated C-reactive protein, and cervical infection with *N. gonorrhoeae* or *C. trichomatis*.1
The most common clinical manifestations of surgically confirmed TOA are abdominal or pelvic pain (>90%), fever (50%), vaginal discharge (28%), nausea (26%), and abnormal vaginal bleeding (21%). Of these cases, 23% of patients had normal white blood cell counts. It is very important to realize that the absence of fever and an elevated white count does not preclude the diagnosis of TOA. The diagnosis of TOA requires the recognition of an inflammatory mass. However, these masses can be missed on physical examination because pain precludes an adequate examination. Therefore, clinicians should have a low threshold for obtaining imaging in a woman with PID, especially when the woman is acutely ill, when there is exquisite tenderness on examination, when palpation of the adnexa bimanual examination is suboptimal, or when the patient lacks clinical response to antibiotic therapy.

**Imaging of TOA**
Transvaginal ultrasound and pelvic computed tomography (CT) are the most common imaging modalities used to detect TOA. Transvaginal ultrasound is considered the first-line imaging modality because it provides excellent imaging of the upper genital tract, is relatively inexpensive, and does not expose the patient to radiation. Ultrasound findings suggestive of PID include enlarged ovarian volumes or polycystic ovaries, thickened fluid-filled ovaries with incomplete septum or the “cog wheel” sign, and complex free fluid in the cul-de-sac. With more severe or progressive PID, the anatomic distinction between the ovary and the fallopian tube can no longer be identified, forming a TOA. TOAs are characterized by a complex multilocular cystic mass with thick irregular walls, partitions, and internal echoes. Figure 1 shows an ultrasound image of a pyosalpinx where complex fluid inside the fallopian tube and significant tubal wall thickening can be noted. Pelvic CT is preferred for women where the diagnosis is uncertain and there is concern for a coexisting malignancy or gastrointestinal pathology, such as appendicitis or diverticulitis. CT might have slight diagnostic advantages to ultrasound. Specifically it may have increased sensitivity to detect a TOA (78% to 100% vs. 75% to 82%, respectively) and improved specificity (100% to 91%) compared with an ultrasound. In a case series of 22 patients with TOA reported by Hiller and colleagues, the most common CT findings were unilateral location (73%), multilocularity (89%), and thick, uniform, enhancing walls. Less common findings included bowel thickening (59%), uterine sacral ligament thickening (64%), and pyosalpinx (50%). Figure 2 shows a CT image of left pyosalpinx and a right TOA. Magnetic resonance imaging has not been studied greatly in the diagnosis of TOA. It remains unclear if the great cost associated with this imaging modality is worth any additional diagnostic or clinical information provided by it.

**Treatment**
Treatment of PID begins with rapid initiation of broad-spectrum antibiotics.
targeted against the most common patho-
gens, as described in the preceding para-
graphs. The efficacies of these regimens
have been determined by clinical or mi-
crobiological cure in short-term studies,
not by prevention of long-term complica-
tions. Women with mild or moderate PID
achieved clinical outcomes with outpa-
tient oral antibiotics similar to those with
inpatient IV antibiotics.37

The decision for hospitalization should
be based on provider judgment or any of
the following criteria as recommended by
the Centers for Disease Control and Pre-
vention:

- Surgical emergencies cannot be
  excluded;
- Pregnancy;
- Lack of response to oral antibiotics;
- Inability to follow or tolerate an out-
patient oral regimen;
- Severe illness, nausea and vomiting, or
  high fever;
- Presence of TOA.1

Women with TOA should have direct
inpatient observation for 24 hours be-
cause of risk of abscess rupture and sepsis.
Patients with clinically severe PID or
who meet the above criteria should be
admitted to the hospital and receive
parenteral antibiotics. In addition, medi-
cations for symptom relief of pain, nausea
or vomiting, and fever should also be
initiated upon admission. Fluid resusci-
tation should also be considered in patients
that are unable to tolerate oral intake.
The Centers for Disease Control and Pre-
vention recommends the following intra-
venous (IV) antibiotics, which have been
shown to achieve clinical cure in > 90% of
patients with acute PID:

- IV cefotetan or IV cefoxitin plus oral or
  IV doxycycline
- IV clindamycin plus IV gentamicin
- Alternative: ampicillin/sulbactam plus
doxycycline.1

These regimens provide broad coverage
for not only *N. gonorrhoeae, C. trichoma-
tis*, and *M. genitalium*, but also for strep-
tococcus, Gram-negative enteric bacteria
(*E. coli*, *Klebsiella* spp., and *Proteus* spp.),
and bacteria vaginosis-associated anaero-
bic organisms.38–42 The cephalosporin-
based regimen is preferred because of
improved tolerability. In the case of a
severe penicillin allergy, clindamycin plus
gentamicin is recommended.

For the treatment of TOA, when com-
paring the first-line parenteral antibiotic
regimens, none of the regimens have been
shown to be superior.12,24,43 We recom-
pend that antibiotic should be based on
the ability of the antibiotic to penetrate
the abscess cavity, the stability of the
agent in an acidic and hypoxic environ-
ment, and local susceptibility of Gram-
negative aerobic and anaerobic bacteria,
specifically *E. coli*, to the agent. Regimens
including clindamycin, metronidazole,
and cefoxitin should be considered in the
presence of TOA because they have been
shown to have superior abscess wall pen-
etration and activity within the cavity in
animal models.44 Reed et al45 showed in
a series of 232 patients with TOA that
clindamycin plus gentamicin (68%) was
more effective than penicillin and genta-
micin (49%) for reduction of TOA size,
highlighting the importance of anaerobic
coverage with clindamycin. However,
amnioglycosides have reduced activity
in acidic, anaerobic environments with

![FIGURE 2. Computed tomographic image of pyosalpinx and tuboovarian abscess.](image)
purulent debris. McNeeley et al showed that the combination of ampicillin, gentamicin, and clindamycin (87.5%) has an improved cure rate as compared with clindamycin and gentamicin alone (47%). Therefore, for the treatment of TOA, an extended-spectrum cephalosporin for the coverage of Gram-negative organisms (rather than an aminoglycoside) combined with clindamycin or metronidazole is a good option.

Guidelines for the treatment of intra-abdominal infections have recommended that when resistance for a specific antibiotic exceeds >10% to 20% of all isolates, then a change in the recommended antibiotic should occur. For this reason, ampicillin-sulbactam is no longer recommended for treatment of community-acquired intra-abdominal infections because of significant increased resistance in E. coli. As mentioned above, targeted anaerobic antimicrobial therapy should be used in women with a TOA. Clindamycin is generally recommended because this was the agent used in the prior studies and the agent in which clinicians have the most experience. Although resistance to clindamycin has been observed in isolates recovered from the lower genital tract in women with vaginitis, the significance of these findings in women with TOA is uncertain as there are no data suggesting higher failure rates with clindamycin-based regimens.

Antibiotic therapy can be switched from parenteral to oral route of administration after 24 hours of clinical improvement, resolution of nausea and vomiting and severe pain. Patients should complete an entire 14-day course of antibiotics with oral doxycycline. When a TOA is present or when the illness was preceded by gynecologic procedure greater anaerobic coverage is required, thus we recommend the addition of clindamycin or metronidazole to doxycycline. We prefer to use metronidazole because of the increased risk of Clostridium difficile colitis with clindamycin.

**Intrauterine Contraceptive Device (IUCD) In Situ**

When PID occurs with an IUCD in place removal of the IUCD is not required. However, a randomized study showed that removal of the IUCD before the initiation of antibiotic increased the rate of clinical recovery. The availability of alternative methods of contraception and IUCD replacement should be considered in the decision to remove the IUCD. Women with PID and an IUCD in place should have close clinical follow-up. When the IUCD is removed, it should not be replaced until 3 months after the PID has resolved.

**Surgical Management and Drainage of TOAs**

In general, the decision to combine antimicrobial therapy with drainage or surgical excision of the TOA depends on the status of the patient and the size of the abscess. Antibiotics should be initiated as soon as the diagnosis of TOA is determined. When rupture of a TOA is suspected prompt surgical intervention is required because of the morbidity and mortality associated with a ruptured TOA. Signs of sepsis, such as hypotension, tachycardia, and tachypnea, and an acute abdomen are indicative of rupture, and such patients should immediately proceed to the operating room for surgical exploration.

TOAs usually present without evidence of rupture and in these cases the role for drainage or operative management of TOA is less clear. Large case series have shown that antimicrobial therapy alone is usually effective in 70% of all TOAs and in a few of these studies abscess size has been shown to be predictive of treatment success with antibiotics alone. Reed et al in 1991 showed that 35% of abscesses 7 to 9 cm in size required surgery as compared to almost

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60% of abscesses > 9 cm. DeWitt et al\textsuperscript{57} showed that abscesses > 8 cm more often required drainage or surgery and were associated with longer length of hospitalization. Thus, it is reasonable to initiate antibiotics alone in women who are hemodynamically stable and when the abscess is 8 cm or less in diameter. When clinical response is not achieved within 48 hours after initiation of antibiotics, then surgical management or drainage should be considered. In addition, in women with an abscess 8 cm or greater immediate drainage rather awaiting clinical response may decrease duration of hospitalization. In addition, aggressive surgical management should be considered in postmenopausal women, because malignancy is a concern in any postmenopausal woman who presents with an abscess.\textsuperscript{58–60} Papas et al\textsuperscript{59} reported that 8 of 17 (47%) postmenopausal women had an underlying malignancy as compared with 1 of 76 premenopausal women (1.3%). Thus, postmenopausal women with TOA should be counseled on their risk of malignancy and potential need for complete surgical staging. Although the diagnostic yield could be lower in these cases due to the significant necrosis of the tissue, a frozen section of the abscess should be sent from the operating room.

Surgical management options for TOAs range from only drainage to unilateral salpingo-oopherectomy to total abdominal hysterectomy and bilateral salpingo-oopherectomy. Historically, most women with TOA were managed aggressively with a total abdominal hysterectomy and bilateral salpingo-oopherectomy. Although this approach offered high cure rates, it was at the cost of high rates of surgical complications, infertility, and hormone deficiency.\textsuperscript{61} With the advent of effective antimicrobial therapy, operative management has become much more conservative moving toward procedures that allow for sparing of ovarian function and if possible can even be considered in cases of rupture.\textsuperscript{24} Options for approach can range from imaging-guided drainage to laparoscopy to laparotomy. Most gynecologists continue to use the laparotomy as the preferred surgical approach for debridement of TOA. However, the laparoscopic approach seems to be safe in cases where there is no evidence of TOA rupture and may have improved outcomes of laparotomy, including decreased length of hospitalization, decreased rates of wound infections, and more rapid rate of fever defervesce.\textsuperscript{62} However, the surgical approach should depend on the skill and comfort of the surgeon. Surgeries for TOAs can be very complicated because of the extensive adhesions from the abscess to the surrounding structures and the necrotic and inflamed tissues surrounding the abscess. For this reason, the laparoscopic experience and expertise of the surgeon cannot be understated. We recommend the removal of the abscess cavity and the associated necrotic tissue and then irrigation of the peritoneum. We offer hysterectomy with bilateral salpingo-oopherectomy to patients who are acutely ill and have completed child bearing. This approach may hasten recovery compared with fertility-sparing surgery. In addition, this eliminates the need for repeat surgery that is required in 10% to 20% of women who have more conservative approaches.\textsuperscript{24,55}

Since the 1970s, several imaging modalities and approaches have been used to successfully drain intra-abdominal abscess collections eliminating the need for surgery.\textsuperscript{12,63,64} Pelvic abscess have been drained using ultrasound or CT guidance with a transabdominal, transgluteal, transrectal, or transvaginal approach. The approach depends on the location of the collection, with most commonly a transabdominal approach for abscesses in the upper pelvis or abdomen and a transvaginal approach for deeper pelvic abscesses.\textsuperscript{65} Abscesses can be drained with a catheter placement or aspiration alone with a success rate ranging between

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In a prospective randomized trial comparing treatment of TOA with antibiotics alone or antibiotics with aspiration of the abscess, 17 of 20 women responded in the aspiration group, whereas only 10 of 20 responded in the antibiotics alone group. In addition, time to discharge was much shorter in the aspiration group when compared with the antibiotics alone group, 3.9 versus 9.1 days, respectively. Gjelland and colleagues reported a cohort of 302 women with TOAs treated with antibiotics combined with ultrasound-guided transvaginal aspiration of the abscess with a success rate of 93.4%. They repeated the aspiration if abscess material was still seen on ultrasound 2 to 4 days after initial aspiration. They reported complete pain relief in 62.3% of the women within 48 hours of the first aspiration and no procedure-related complications. Only 6% of this cohort of women ultimately required surgery. The optimal approach for management of TOA is still debatable. However, in institutions where there are radiologists trained to do these procedures, it seems advantageous to consider transvaginal aspiration of the abscess in combination with standard antibiotics, particularly with larger abscesses, as this may increase the response rate, decrease the length of hospitalization, and improve pain control.

Long-term Complications

Although prompt diagnosis and treatment decreases the risk of long-term complications of PID, many women, despite adequate treatment, still suffer from recurrent PID, infertility, ectopic pregnancy, and chronic pelvic pain. These complications are attributable to scarring and adhesion formation that accompany the healing of tissues that were damaged initially at the time of acute infection. One study reported that 15% of women had a recurrence within 35 months and 21% of women had a recurrence within 84 months. Westrom and colleagues followed a cohort of 415 women with visually confirmed PID and found that on average 21% of the women had infertility. The most important predictor of infertility was reinfection: 12.8% with a single episode, 35.5% with 2 episodes, and 75% with ≥3 episodes. In addition, they noted that the severity of the initial PID case was a predictor of fertility outcome: with infertility rates of 2.6%, 13.1%, and 28.6% for mild, moderate, and severe disease, respectively. Chlamydial infection and delay in seeking care are also known risk factors for infertility in women with PID. The incidence of ectopic pregnancy in the first pregnancy after PID was 7.8% as compared with 1.3% of women without a history of PID. In addition to complications related to pregnancy outcomes, the scarring and adhesions caused by PID may also lead to chronic pelvic pain in women with a prior history of PID. Up to one third of women with a history of PID go on to develop chronic pelvic pain. Similar to the risks of infertility, the number of PID recurrences was the strongest predictor for the development of chronic pelvic pain.

Conclusions

Severe PID and PID associated with TOA contribute significantly to the number of patients with pelvic infections admitted to the hospital. These diagnoses are associated with significant long-term morbidity, including poor reproductive outcomes and chronic pain. A high level of suspicion for TOAs in women with PID is required, as many women with TOAs do not have fever or an elevated white cell count. Women with TOAs should be admitted to the hospital and immediately started in IV antibiotics that cover enteric Gram-negative rods (a virulent cause of sepsis) and anaerobic bacteria (especially in the cases of TOAs). Percutaneous
radiologic-guided drainage plays an important role in the management of TOAs, particularly if the abscess is large. Immediate surgical management should always be performed in cases suspected of rupture.

References

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