



## Case report

Spontaneous *Streptococcus pyogenes* pelvic inflammatory disease; Case report and review of the literatureA Snyder<sup>a,b</sup>, SA Schmalzle<sup>a,c,\*</sup><sup>a</sup> University of Maryland Medical Center, Department of Medicine, Division of Infectious Disease, 22 South Greene St, Baltimore MD 21201, United States<sup>b</sup> University of Maryland Medical Center, Department of Neurology, 110 S Paca St, Baltimore MD 21201, United States<sup>c</sup> Institute of Human Virology, University of Maryland School of Medicine, 725 W Lombard Street, Baltimore, MD 21201, United States

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## ABSTRACT

*Streptococcus pyogenes* gynecological infections generally occur in association with childbirth, intra-uterine devices, and other invasive gynecologic procedures, but rarely cause spontaneous pelvic inflammatory disease. We describe a case of a healthy young woman with spontaneous *S. pyogenes* pelvic inflammatory disease, bacteremia, and shock, and summarize an additional 13 cases found in the literature. The majority were bacteremic and a significant number were also hypotensive. The same proportion had presenting gastrointestinal symptoms as had genitourinary symptoms, masking the diagnosis in many. Many prior case reports postulate a connection with *S. pyogenes* pharyngitis in a close contact, and an oro-genital route of transmission has been proposed given the exceedingly low rates of genital colonization with *S. pyogenes*. A high index of suspicion is needed for an accurate and timely diagnosis of this rare but potentially fatal condition.

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## Introduction

Infections due to *Streptococcus pyogenes* ('Group A Strep' or GAS) were first detailed in 1874 by the German surgeon Christian Billroth in his description of a wound infection. Louis Pasteur later described the first cases of 'childbed fever' or puerperal sepsis in 1879 and by 1884 the organism was isolated and named *Streptococcus pyogenes* [1]. With the advent of universal hand washing and modern hygiene practices, infection rates dropped significantly, but outbreaks of invasive GAS continue to occur [2].

Manifestations of GAS infections range from mild illness (pharyngitis, impetigo, cellulitis) to invasive life threatening toxin-mediated diseases such as necrotizing fasciitis and streptococcal toxic shock syndrome (STSS). Gynecologic GAS infections are well described in peripartum women, in association with intrauterine devices (IUD), and following invasive gynecologic procedures. Gynecologic GAS infections occurring spontaneously outside of these common presentations are rare. We present a case of GAS pelvic inflammatory disease (PID) complicated by bacteremia and shock, and perform a review of the literature of similar spontaneous GAS PID cases.

## Case report

A 23 year-old healthy woman developed sudden onset diffuse sharp abdominal pain, nausea, vomiting, and watery diarrhea approximately twenty minutes after eating sushi at a local shopping mall. She sought medical care two days later because of persistent and progressive abdominal pain, bloody diarrhea, subjective fever and chills, and vaginal discharge.

Her last menstrual period started two weeks before presentation, and the last sexual encounter occurred one to two weeks prior with her monogamous male partner. Condoms were used for vaginal but not oral intercourse and the couple did not engage in anal intercourse. Neither had any known history of sexually transmitted infections and the patient did not have contact with anyone suffering from pharyngitis or other acute illnesses. She had an elective abortion seven months previously and no other recent gynecologic instrumentation and did not currently or previously have an IUD. She reported taking an over the counter medication two weeks previously for self-diagnosed urinary tract infection.

On admission temperature was 38.2 °C, blood pressure was 88/49 mmHg, and pulse was 109 beats per minute. Physical examination revealed a well-nourished woman in mild distress, with dry mucous membranes, and a mildly distended abdomen. The abdomen was diffusely tender to palpation, more prominently in the peri-umbilical region, with rebound tenderness but no guarding. Rovsing's and Murphy's signs were absent. Pelvic

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examination revealed normal external female genitalia and copious purulent malodorous discharge from the cervical os. Cervical motion tenderness was absent on bimanual pelvic examination, but left adnexal tenderness was noted. White blood cell count peaked at 21,700 cells/mcL with 80% polymorphonuclear leukocytes and 17% bands, creatinine 1.21 mg/dL (baseline 0.50 mg/dL), and lactate 3.4 mmol/L. Evidence of coagulopathy included drop in platelet count from 222,000/mcL to 138,000/mcL, international normalized ratio 2.6, and prothrombin time 28.5 s (normal range 12.1–15.0). Despite volume resuscitation with 6.5 liters of intravenous fluids she remained hypotensive; norepinephrine, vasopressin, and high-dose corticosteroids were initiated for septic shock. Vancomycin, ceftriaxone, doxycycline, and metronidazole were given empirically to cover *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Bacteroides* sp., *Streptococcus*

*agalactiae* (Group B Strep, or GBS), and *Enterobacteriaceae* for presumed PID or enteric infection.

Computed tomography of the abdomen and pelvis revealed a well-circumscribed left adnexal hypodensity consistent with an ovarian cyst, a small amount of complex fluid in the pelvis, and irregular enhancement of the endometrial lining. Free fluid in the pelvis and thickened fallopian tubes consistent with salpingitis were seen on transvaginal ultrasound. *C. trachomatis* and *N. gonorrhoeae* were not detected by PCR of cervical discharge, and no trichomonads were identified on wet mount. HIV antibody/antigen screening was negative. GAS grew from one aerobic blood culture bottle out of two sets after 8 h. No GAS was isolated from vaginal swabs, though these were collected several days after initiation of antimicrobials. Vital signs stabilized and patient was discharged seven days after admission without ongoing symptoms or signs of

**Table 1**

Clinical details of individual GAS PID cases. NR = not reported.

Reference	Age	Manifestation of PID	Available Cultures	Abnormal Vital Signs	Genitourinary Findings	Genitourinary Symptoms	Gastrointestinal Findings	Gastrointestinal Symptoms
Monif et al. [11]	29	Endometritis, salpingitis, peritonitis	Cervical (+), Peritoneal (+)	Fever, tachycardia	Cervical motion tenderness, bilateral adnexal tenderness, fluid in cul-de-sac	Vaginal discharge	Abdominal tenderness, guarding, rebound	Diarrhea, abdominal pain
Goepel et al. [8]	15	Salpingitis, peritonitis	Tubal (+)	NR	NR	NR	NR	NR
	69	'erosion of uterine cervix'	Blood (+), Cervical (+), Peritoneal (+)	Hypotension	NR	NR	NR	Abdominal pain
Fikrig et al. [6]	32	Salpingitis, peritonitis	Blood (+), Vaginal (-), Peritoneal (-)	Fever, tachycardia, tachypnea	Adnexal tenderness, fluid in cul-de-sac	Dysuria, vaginal discharge	Abdominal tenderness, rebound	Nausea, vomiting, abdominal pain
Brown-Harrison et al. [4]	3	Salpingitis, peritonitis	Blood (+), Perineal (-), Tubal (+), Peritoneal (+), Pharyngeal (-)	Fever, tachycardia hypotension,	Right pelvic tenderness	NR	Abdominal tenderness, ileus	Vomiting, diarrhea, abdominal pain
Garvey et al. [7]	41	Salpingitis, peritonitis	Blood (+), Cervical (+) Peritoneal (-)	Fever, tachycardia, hypotension	Cervical motion tenderness, fluid in cul-de-sac	Vaginal discharge, dyspareunia	Abdominal tenderness, guarding	Abdominal pain, rectal discharge
Lamb et al. [9]	47	Salpingitis	Blood (-), Cervical (+), Endometrial (+), Tubal (+), Throat (+)	Fever	Cervical motion tenderness, uterine tenderness, bilateral adnexal tenderness, copious cervical discharge, fluid in cul-de-sac	NR	Abdominal tenderness, RLQ fluid collection	Abdominal pain
Borgia et al. [5]	36	'PID' by laparoscopy, peritonitis	Blood (+), Vaginal (+), Peritoneal (+), Pharyngeal (-)	Fever	Cervical motion tenderness, bilateral adnexal tenderness	NR	Abdominal tenderness, guarding, rebound	Nausea, diarrhea, abdominal pain
Manalo et al. [10]	26	Right tuboovarian abscess, left tubo-ovarian abscess perforation, peritonitis	Tubal (+), Peritoneal (+), Throat (-)	Fever, tachypnea	NR	NR	Abdominal tenderness, peritoneal signs	Abdominal pain
Saha et al. [12]	23	Salpingitis, peritonitis	Blood (+), Vaginal (-), Cervical (-), Peritoneal (-), Throat (-)	Fever, tachycardia, hypotension,	Left adnexal mass on imaging, fluid in cul-de-sac	Vaginal discharge	Abdominal tenderness, guarding, rebound	Diarrhea, vomiting, abdominal pain
Verkaeren et al. [13]	64	Endometritis	Blood (+), Urine (+), Vaginal (+)	Fever	Endometritis, adenomyosis	Vaginal discharge	NR	Flank pain
Paulson et al. [15]	55	Necrotizing endometritis & salpingitis, peritonitis	Blood (+), Uterus (+), Cervical (+)	Fever, tachycardia, hypotension	Vaginal edema & erythema, enlarged tender uterus, right adnexal mass, necrotizing infection of bilateral fallopian tubes and uterus	Pelvic pain	Abdominal tenderness	Nausea, vomiting, diarrhea, abdominal pain
Iwata et al. [14]	66		Blood (+), Vaginal (+)	Fever, tachypnea hypotension	Cervical motion tenderness, pelvic abscess	NR	Abdominal tenderness, guarding	Vomiting, diarrhea, abdominal pain
This Case 2014	23	Endometritis and salpingitis	Blood (+), Cervical (-) Pharyngeal (-)	Fever, tachycardia hypotension	Left adnexal tenderness, copious cervical discharge, fluid in cul-de-sac	Vaginal discharge	Abdominal tenderness, rebound	Nausea, vomiting, diarrhea, abdominal pain

infection. A fourteen-day course of intravenous penicillin was given for definitive therapy of GAS PID and bacteremia. Clindamycin was also given briefly to halt GAS toxin production until hemodynamic recovery was apparent.

This patient did have hypotension (systolic blood pressure <90 mm Hg), GAS cultured from a sterile site, and had abnormalities in renal function and coagulation parameters that were close to, but did not meet strict criteria for organ dysfunction per the 2010 STSS definition set by the Centers for Disease Control and Prevention (CDC) [3]. She did not have evidence of liver function abnormalities, acute respiratory distress syndrome, soft tissue necrosis, or a disseminated rash.

## Methods

A systematic review of the medical literature was performed using the PubMed database and the search terms Group A Strep, Group A *Streptococcus*, or *Streptococcus pyogenes* plus either pelvic inflammatory disease, salpingitis, tubo-ovarian abscess, endometritis, gynecologic, or gynecology. All cases reports and case series published in English through December 31, 2019 were reviewed. References cited in these publications were also screened. Cases associated with pregnancy, childbirth, and invasive gynecologic procedures or devices were excluded, as were cases of non-invasive gynecologic infections such as vulvovaginitis. Diagnoses of PID reported here are per each case report author's diagnosis of PID, endometritis, salpingitis, or tubo-ovarian abscess.

## Results

Thirteen additional cases of invasive gynecologic *S. pyogenes* infections were identified (Table 1) [4–13]. Age ranged from 3 to 69 years, with a mean of 38. Seven cases were associated with leukocytosis [4–7,9–11]; one was leukopenic [8]. All had GAS isolated from a normally sterile site, including endometrial, tubal, or peritoneal fluid, or blood. Of 11 cases with blood culture results reported, 10 (91%) were positive. Of those with positive cultures, seven of nine reportedly were hypotensive. One patient died [8]. The majority of cases did not include sufficient information on end organ function to determine if patients met CDC's 2010 criteria for STSS. Only two case reports mentioned presence [10] or absence [4] of rash.

All but one cases with a description of patient symptoms reported abdominal pain. Eight of 13 (62%) had nausea, vomiting, or diarrhea. The same proportion noted genitourinary symptoms. Appendicitis [5,8,9,12], gastroenteritis or enteritis [4,14] and gram negative bacteremia [8] were on the list of presumed etiologies in several cases prior to imaging or operative findings proving a gynecologic cause. Meningitis was also considered and ruled out in one patient [8] (Table 1).

Association with *S. pyogenes* pharyngitis was raised in several cases – one had culture confirmed GAS pharyngitis in the preceding nine months and engaged in oral sex [9]. This patient also had a recurrence of vaginal discharge concurrent with a sore throat. Another three were noted to have family or sexual contacts suffering from pharyngitis [7,10,15]; molecular typing of one patient's genital and her partner's pharyngeal cultures confirmed a linked-transmission. One patient had recurrent vaginal symptoms at two and four months after initial presentation; the patient and her spouse both had positive culture for GAS from nasal and rectal swabs. They were given a prophylactic antimicrobial course to eradicate the colonizing GAS and no further recurrences occurred in a follow up period of two years [13]. Several authors noted the timing between start of last menstrual period and illness onset. In this series, the timing of onset ranged from two days to two weeks following menstruation, but there was no clear association with menses.

## Discussion

Acute PID is most often attributed to sexually transmitted infection (85%; *N. gonorrhoeae*, *C. trachomatis*, *Mycoplasma genitalium*) or lower genital tract colonizers (15%) that are able to ascend and cause infection [16]. Often the causative infectious agent is not identified by nucleic acid amplification testing for *N. gonorrhoea* and *C. trachomatis* or by routine bacterial culture however. 16 s DNA sequencing of 45 women with laparoscopically proven salpingitis identified various organisms, many of which were not readily identifiable at the species level [17], raising the possibility of more complex vaginal microbiota than previously suspected.

GBS is known to colonize the lower genital tract, with colonization being a risk factor for neonatal sepsis and warranting screening and prophylactic antimicrobials during childbirth. GAS is not known to colonize the female urogenital tract. A study of almost seven thousand predominantly Caucasian pregnant women in New England revealed a GBS colonization rate of 20.1%, but only 2 (0.03%) women with GAS colonization [18]. A study of 1600 women in Australia in late pregnancy screened for colonization showed only one patient with vaginal GAS carriage (0.06%) [19]. The authors of the first study note that this rate for GAS may in fact be an overestimate, and not be generalizable to other populations, as Caucasian women engage in orogenital sexual contact more than other races [20]. In a Nigerian study of 100 women with PID, bacterial culture identified one or more potentially causative organisms in 45 women; GAS was identified in only 1 case [21]. GAS was identified in only 1 case of 45 in the 16 s sequencing study also [17]. Thus, GAS appears to rarely be present in vaginal flora. Instrumentation, foreign bodies (IUDs), and vaginal or cesarean delivery are logical modes of entry for GAS or GBS into sterile genitourinary sites. Cases of *S. pyogenes* PID without recent instrumentation or pregnancy are unexpected based on current knowledge of routes of entry. Some authors have suggested that asymptomatic vaginal colonization with GAS, similar to Group B strep (GBS) is a potential precursor to ascending infection, though this appears to be extremely rare.

GAS is commonly considered in the context of pharyngeal infection. The majority of cases reviewed in this series mentioned this connection and specifically investigated recent history of 'strep throat' or upper respiratory infections. In three of the cases, close contacts, including sexual partners and children, recently had upper respiratory infections. None of these patient's pharyngeal cultures were positive and only one family member yielded a positive culture, though this did show an identical electrophoresis pattern as the patients sample [10]. Additional cases of suspected orogenital transfer of GAS in IUD associated GAS PID have been published [22]. The relationship between streptococcal pharyngitis and PID has not been definitively proven, but is plausible and worthy of further investigation.

The rarity of the convergence of PID and invasive GAS infection or TSSS make GAS PID a difficult to recognize entity. Additionally, in this review of cases in the literature the same proportion of patients presented with gastrointestinal (GI) symptoms as presented with genitourinary symptoms. Rates of 24% and 36% of patients in prior series of invasive GAS infections were noted to have vomiting or diarrhea at initial presentation [23,24]. These GI symptoms understandably can lead to incorrect initial diagnosis or delayed diagnosis and care, as occurred in several cases in this series. Fortunately in terms of treatment, GAS is likely covered by most empiric antimicrobial regimens, given its susceptibility to penicillin. Recommended PID antimicrobial regimens cover common causes of PID; as GBS is always covered, GAS also is covered by usual empiric PID treatment. However, regimens that

do not contain a protein synthesis inhibitor to impede toxin production may be insufficient to combat STSS.

## Conclusion

We have presented a case of young previously healthy 23-year-old female who presented with predominantly gastrointestinal complaints including nausea, vomiting and diarrhea, and who quickly developed septic shock due to GAS bacteremia. This case and others found in the literature emphasize several important points. First, it is always important to consider pelvic sources of infection in any female presenting with abdominal complaints. Second, GAS is able to cause spontaneous infection of the female genitourinary system outside of commonly recognized peripartum, IUD associated, and peri-procedural infections. This suggests possible asymptomatic genital colonization that can ascend though available literature does not support this theory. Additionally it is worth noting that as many patients presented with gastrointestinal symptoms as presented with genitourinary complaints.

Possible associations with menstruation, sexual activity, pharyngitis, and close contact with active pharyngitis cases have all been postulated; evidence thus far does not strongly support these associations, though they remain plausible.

Clinicians should be aware of GAS PID as an entity and that regardless of the route of entry, GAS is a potentially fatal infection capable of causing circulatory collapse and death.

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Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

## CRedit authorship contribution statement

**A Snyder:** Data curation, Writing - original draft. **SA Schmalzle:** Conceptualization, Data curation, Methodology, Resources, Supervision, Writing - original draft, Writing - review & editing.

## Declaration of competing interest

None.

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