BRIEF REPORT

# Fatal Toxic Shock Syndrome Associated with *Clostridium sordellii* after Medical Abortion

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## SUMMARY

Endometritis and toxic shock syndrome associated with *Clostridium sordellii* have previously been reported after childbirth and, in one case, after medical abortion. We describe four deaths due to endometritis and toxic shock syndrome associated with *C. sordellii* that occurred within one week after medically induced abortions. Clinical findings included tachycardia, hypotension, edema, hemoconcentration, profound leukocytosis, and absence of fever. These cases indicate the need for physician awareness of this syndrome and for further study of its association with medical abortion.

*Clostridium sordellii* is a gram-positive anaerobic bacillus that has been reported as a cause of infection in the female genital tract and fatal toxic shock syndrome. Of 10 cases identified in the literature, 8 occurred after delivery of live-born infants,[1-6] 1 occurred after a medical abortion,[7] and 1 was not associated with pregnancy.[8] We report four additional deaths due to *C. sordellii* toxic shock syndrome that occurred among previously healthy women after abortions that were medically induced with 200 mg of oral mifepristone and 800 μg of vaginal misoprostol.

## CASE REPORTS

### PATIENT 1

Patient 1 was a previously healthy 18-year-old woman who underwent a medically induced abortion at 47 days of gestation by means of 200 mg of oral mifepristone followed by 800 μg of vaginal misoprostol. Four days after receiving mifepristone, the patient presented to an emergency department with reports of abdominal cramping and dysuria. She had taken acetaminophen with codeine after the abortion. On physical examination, she was afebrile with normal vital signs and no abdominal tenderness. Pelvic examination revealed no uterine tenderness or adnexal mass. No laboratory studies or cultures were performed. She received hydromorphone and promethazine and was discharged taking acetaminophen and codeine.

The patient returned three days later and reported nausea, vomiting, and weakness. On admission, she was afebrile (temperature, 36.3°C), tachycardic (heart rate, 147 beats per minute), and hypotensive (blood pressure, 78/53 mm Hg) and had dry mucous membranes but unremarkable findings on abdominal and pelvic examinations. Laboratory studies showed an elevated white-cell count of 45,600 cells per microliter, a platelet count of 387,000 cells per microliter, and a hematocrit of 52 percent. Creatinine and liver-function studies were normal. Blood cultures obtained before antibacterial thera-

py were later found to be negative for bacteria; vaginal cultures grew gardnerella species. Ultrasonographic examination of the pelvis showed a residual gestational sac in the uterus and a large amount of free peritoneal fluid. A chest radiograph showed bilateral interstitial infiltrates.

Initial treatment included supplemental oxygen, intravenous fluids, and antibacterial therapy with vancomycin and piperacillin–tazobactam. During the next few hours, the patient had respiratory distress and hypotension requiring mechanical ventilation and vasopressor support. Initial arterial blood gas measurements revealed severe metabolic acidosis, with a pH of 7.15, a partial pressure of carbon dioxide of 36 mm Hg, and a bicarbonate concentration of 13 mmol per liter. Within seven hours after admission, the white-cell count increased to 107,000 cells per microliter, with a hematocrit of 58 percent and a platelet count of 158,000 cells per microliter. Urine output and the serum albumin concentration decreased markedly, but concentrations of hepatic enzymes, bilirubin, and creatinine remained normal. Refractory bradycardia, hypotension, and hypoxemia developed, and the patient died approximately 10 hours after admission.

#### PATIENT 2

Patient 2 was a previously healthy 21-year-old woman who underwent a medically induced abortion at 43 days of gestation by means of 200 mg of oral mifepristone followed by 800 μg of vaginal misoprostol. Five days after receiving mifepristone, she reported abdominal pain and vomiting. The following morning she became unresponsive. When paramedics arrived, she had no spontaneous respirations or cardiac activity. She was transported to a local emergency department while receiving ongoing cardiopulmonary resuscitation. Physical examination showed a rectal temperature of 38.9°C, fixed and dilated pupils, and mild abdominal distention. The serum glucose concentration was 108 mg per deciliter. Toxicologic evaluation was negative. No other laboratory studies or cultures were performed. The patient was intubated and received intravenous fluids, epinephrine, and atropine. Resuscitation efforts were discontinued 40 minutes after her arrival at the emergency department.

#### PATIENT 3

Patient 3 was a previously healthy 22-year-old woman who underwent a medically induced abortion at 53 days of gestation by means of 200 mg of oral mifepristone followed by 800 μg of vaginal misoprostol. Five days after receiving mifepristone, she presented to a local emergency department reporting nausea, vomiting, diarrhea, and severe abdominal pain. The patient was afebrile (temperature, 36.2°C), with a heart rate of 104 beats per minute and blood pressure of 115/76 mm Hg. Physical examination was unremarkable except for moderate abdominal tenderness. Laboratory findings included a white-cell count of 21,800 cells per microliter, a platelet count of 256,000 cells per microliter, and a hematocrit of 40 percent. Ultrasonographic examination of the pelvis showed a left adnexal mass and fluid in the cul-de-sac. The patient received intravenous fluids, promethazine, and morphine and was admitted to the hospital to rule out an ectopic pregnancy.

The following day, persistent tachycardia (heart rate, 130 to 140 beats per minute), hypotension (blood pressure, 80/40 mm Hg), lethargy, decreased urine output, and diffuse abdominal tenderness developed, and the patient was transferred to the intensive care unit. Laboratory findings included a white-cell count of 120,200 cells per microliter, a platelet count of 91,000 cells per microliter, a hematocrit of 45 percent, a creatinine concentration of 1.9 mg per deciliter (168 μmol per liter), an albumin concentration of 1.0 g per deciliter, and a prothrombin time of 18.3 seconds with normal levels of aminotransferases and bilirubin. Arterial blood gas measurements showed severe metabolic acidosis, with a pH of 7.15, a partial pressure of carbon dioxide of 29 mm Hg, and a bicarbonate concentration of 10 mmol per liter. Antibacterial therapy was initiated with piperacillin–tazobactam and metronidazole; blood cultures obtained before antibacterial therapy were subsequently found to be negative for bacteria. Within three hours after being transferred to the intensive care unit, the patient had a cardiopulmonary arrest requiring mechanical ventilation and vasopressor support. Emergency laparotomy showed generalized edema of the abdominal and pelvic organs and 1000 ml of serous peritoneal fluid. Gram's stain and aerobic and anaerobic cultures of peritoneal fluid obtained intraoperatively were negative for bacteria. The patient died during the surgical procedure, approximately 23 hours after her initial presentation to the hospital.

#### PATIENT 4

Patient 4 was a previously healthy 34-year-old woman who underwent a medically induced abortion at

45 days of gestation by means of 200 mg of oral mifepristone followed by 800 μg of vaginal misoprostol. Four days after receiving mifepristone, she presented to a local emergency department reporting nausea, vomiting, and severe abdominal pain. She had taken ondansetron and acetaminophen with hydrocodone after the abortion. The patient was afebrile (temperature, 36.3°C), with a heart rate of 89 beats per minute and blood pressure of 99/63 mm Hg. Physical examination was unremarkable except for moderate abdominal tenderness. Laboratory findings included a white-cell count of 55,400 cells per microliter, a platelet count of 149,000 cells per microliter, and a hematocrit of 59 percent. Ultrasonographic examination of the pelvis showed an empty uterus. Initial treatment included intravenous fluids, ondansetron, and hydromorphone.

After the patient received 2 liters of normal saline, a repeated blood count showed a white-cell count of 87,600 cells per microliter, a platelet count of 63,000 cells per microliter, and a hematocrit of 61 percent. Serum chemical analyses including liver-function tests were unremarkable. Aerobic and anaerobic blood cultures and a urine culture were obtained but were subsequently negative for bacteria; antibacterial therapy was initiated with piperacillin–tazobactam and metronidazole. A chest radiograph was normal. Computed tomography of the abdomen showed only a moderate volume of free fluid. Although the patient received 5 liters of intravenous fluids, worsening tachycardia and hypotension with minimal urine output developed. Arterial blood gas measurements showed severe metabolic acidosis, with a pH of 7.07, a partial pressure of carbon dioxide of 10 mm Hg, and a bicarbonate concentration of 3 mmol per liter. Further therapy included sodium bicarbonate and vasopressor support, but refractory hypotension developed and the patient died approximately 12 hours after presentation.

## METHODS

We reviewed medical and autopsy records for each patient. Formalin-fixed tissues were evaluated at the Centers for Disease Control and Prevention. Immunohistochemical assays were performed for clostridium species, *Staphylococcus aureus*, group A streptococcus, and neisseria species by means of a two-step indirect staining technique with immunoalkaline phosphatase. The polyclonal anti-clostridium antibody used in the immunohistochemical assay cross-reacts with multiple clostridium species.[9] DNA was extracted from formalin-fixed uterine tissue with the use of the QIAamp DNA Mini Kit (Qiagen) and was evaluated with broad-range and *C. sordellii*–specific polymerase-chain-reaction (PCR) assays targeting the 16S ribosomal RNA (rRNA) gene and with PCR assays targeting the *C. sordellii* cytotoxin L and phospholipase C genes (Table 1).[10-14] Amplified PCR products were directly sequenced and, with the use of the Basic Local

**Table 1. Primers Used in PCR Assays on Formalin-Fixed Tissues.**

| Gene Target | Primer | Sequence (5' to 3') | Product Size (bp) | Reference |
|---|---|---|---|---|
| 16S rRNA* | F8 | AGT TTG ATC CTG GCT CAG | 330 | Daly et al.[10] and Stackebrandt and Charfreitag[11] |
| | 357R | CTG CTG CCT CCC GTA | | |
| 16S rRNA† | C1SOR-F | TCG AGC GAC CTT CGG | 944 | Kikuchi et al.[12] |
| | C1SOR-R | CAC CAC CTG TCA CCA T | | |
| CytL‡ | CLS-F1 | ATG AAC TTA GTT AAC AAA GCC CAA | 250 | —§ |
| | CLS-R1 | AAT ACT TCC ATA GTT AGA TAT TCT TTA | | |
| Csp¶ | CLS-F2 | TAA AGA TGC AGT AGC TAA TAA GGA TTT | 223 | —‖ |
| | CLS-R2 | TTC CTG AAA TTT GAT CTT CTG AAA CC | | |

* A broad-range PCR assay was used to target the 16S rRNA gene.
† A *C. sordellii*–specific PCR assay was used to target the 16S rRNA gene.
‡ CytL denotes the cytotoxin L–encoding gene of *C. sordellii*.
§ Primers were designed for this investigation from the published sequence of *C. sordellii* (GenBank accession number X82638).[13]
¶ Csp denotes the phospholipase C gene of *C. sordellii*.
‖ Primers were designed for this investigation from the published sequence of *C. sordellii* (GenBank accession number AB061868).[14]

Alignment Search Tool (BLAST), compared with sequences available in the GenBank database.

The National Center for Infectious Diseases determined that this investigation was defined as a public health response. Approval of the institutional review boards and consent of the next of kin were not required to evaluate and publish these case reports.

## RESULTS

Autopsy of Patient 1 revealed marked pleural, pericardial, and peritoneal effusions. Histopathological examination of the uterus showed inflammation of endometrium and myometrium, multiple small abscesses, necrosis, and hemorrhage (Fig. 1A). There was no retained fetal or placental tissue. Other organs were unremarkable. Mixed bacteria, including numerous gram-positive bacilli, were seen in the endometrium (Fig. 1B). Postmortem cultures were not performed. Immunohistochemical testing of uterine tissue was negative for *S. aureus*, group A streptococcus, and neisseria species. Clostridium immunohistochemical analysis showed extensive staining of bacilli and granular antigens associated with areas of inflammation in the endometrium and myometrium (Fig. 1C). Clostridial antigens were noted in blood vessels of the uterus (Fig. 1D) but were not observed in brain, heart, lung, liver, kidney, or adrenal tissues. The 16S rRNA gene sequences amplified from uterine tissue showed 98 percent identity with *C. sordellii*. Cytotoxin L and phospholipase C gene sequences amplified from the uterus showed

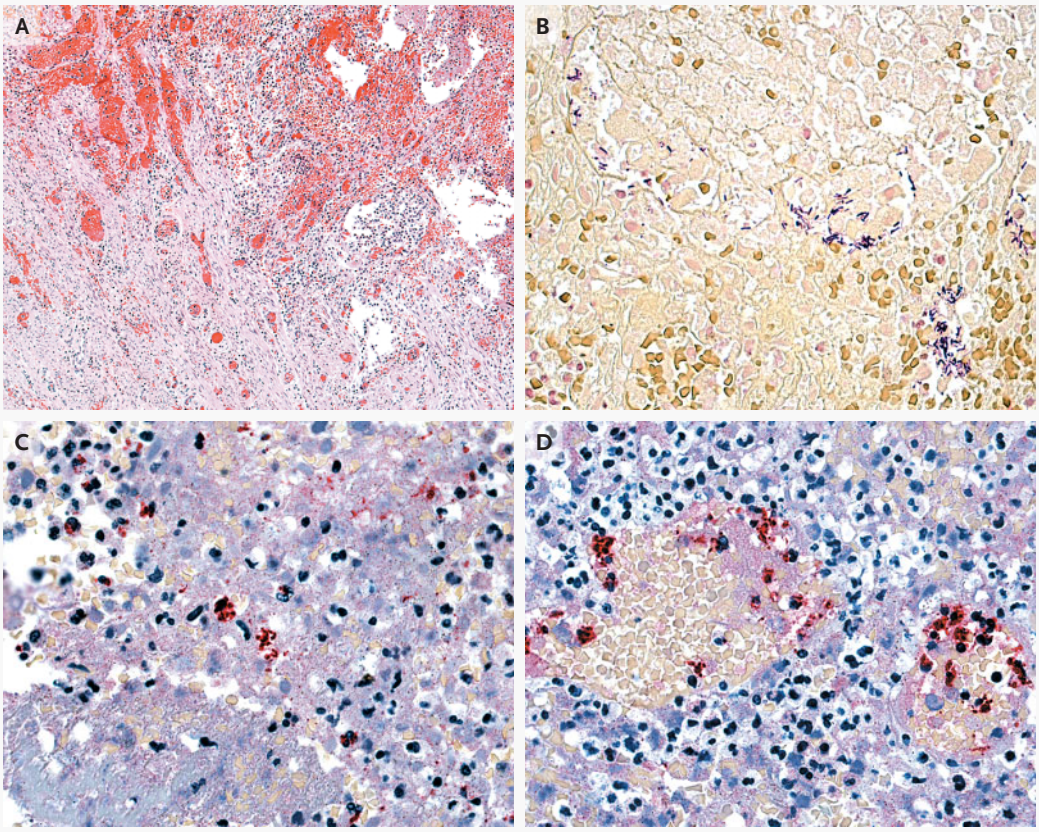


**Figure 1. Photomicrographs of the Uterine Tissue of Patient 1.**

Panel A shows hemorrhage, inflammation, and necrosis of the endometrium (hematoxylin and eosin). Abundant gram-positive bacilli were observed in the necrotic endometrial tissue (Panel B, Gram's stain). Clostridial antigens (red staining) were seen inside inflammatory cells present in the necrotic endometrial tissue (Panel C, immunohistochemical assay with the use of polyclonal anti–clostridium species antibody) and inside myometrial blood vessels closest to the necrotic endometrium (Panel D, immunohistochemical assay with the use of polyclonal anti–clostridium species antibody).

99 percent and 97 percent identity with *C. sordellii*, respectively.

The body of Patient 2 was initially embalmed, and an autopsy was performed one week after death. Histopathological examination of the uterus showed severe inflammation of endometrium and myometrium, necrosis, and hemorrhage with retained necrotic decidual tissue. Mixed bacteria, predominantly gram-positive bacilli, were seen in the endometrium. Immunohistochemical testing of uterine tissue was negative for *S. aureus*, group A streptococcus, and neisseria species. Clostridium immunohistochemical analysis showed extensive staining of bacilli and granular antigens associated with areas of inflammation in the endometrium and myometrium. Clostridial antigens were not observed in brain, heart, lung, liver, kidney, or adrenal tissues. The 16S rRNA gene sequences amplified from uterine tissue showed 98 percent identity with *C. sordellii*. Cytotoxin L and phospholipase C gene sequences amplified from the uterus showed 98 percent and 97 percent identity with *C. sordellii*, respectively.

Autopsy of Patient 3 revealed pleural and peritoneal effusions. Histopathological examination of the uterus showed extensive inflammation, abscess formation, edema, necrosis, and hemorrhage. There was no retained fetal or placental tissue and no evidence of ectopic pregnancy. Mixed bacteria, including numerous gram-positive bacilli, were seen in the endometrium. Postmortem cultures were not obtained. Immunohistochemical testing of uterine tissue was negative for group A streptococcus and neisseria species but showed *S. aureus* antigens on the endometrial surface. Clostridium immunohistochemical analysis showed extensive staining of bacilli and granular antigens associated with areas of inflammation throughout the endometrium and myometrium. Clostridial antigens were not observed in heart, lung, liver, or kidney tissues. The 16S rRNA gene sequences amplified from uterine tissue showed 97 percent identity with *C. sordellii*. Cytotoxin L and phospholipase C gene sequences amplified from the uterus showed 99 percent and 98 percent identity with *C. sordellii*, respectively.

Autopsy of Patient 4 revealed pleural, pericardial, and peritoneal effusions. Histopathological examination of the uterus showed severe inflammation of endometrium and myometrium, necrosis, and hemorrhage, with extensive inflammation and edema. Abundant gram-positive bacilli were seen in the endometrium. Postmortem cultures of the endometrium grew *Escherichia coli* and an anaerobic gram-positive bacillus that was discarded before further identification. Immunohistochemical testing of uterine tissue was negative for *S. aureus*, group A streptococcus, and neisseria species. Clostridium immunohistochemical analysis showed staining of bacilli and abundant granular antigens associated with areas of inflammation throughout the endometrium and myometrium. Clostridial antigens were not observed in heart, lung, liver, spleen, pancreas, kidney, adrenal, or ovarian tissues. The 16S rRNA gene sequences amplified from uterine tissue showed 98 percent identity with *C. sordellii*. Cytotoxin L and phospholipase C gene sequences amplified from the uterus showed 98 percent and 97 percent identity with *C. sordellii*, respectively.

## DISCUSSION

We describe four deaths associated with *C. sordellii* endometritis and toxic shock syndrome that occurred within one week after medically induced abortions. The clinical and pathological findings in these cases are similar to those in 10 other cases of *C. sordellii* infection of the genital tract reported in the literature[1-8] (Table 2). Of the 10 previous cases that we identified, all occurred in previously healthy young women, and 9 occurred within one week after delivery (8 women) or after abortion (1 woman). Notable clinical features included absence of fever and rash, dramatic leukemoid reaction, capillary leak and fluid sequestration with associated hemoconcentration, refractory tachycardia and hypotension, and marked edema of infected tissues without gas production or extensive myonecrosis. All the cases had a fulminant course and fatal outcome. Eight of the previously reported cases had evidence of a polymicrobial infection. Although infections of the female genital tract often include mixed bacteria, the role of other organisms in toxic shock syndrome associated with *C. sordellii* is unclear.

*C. sordellii* is an infrequent human pathogen but has been reported as a cause of pneumonia, endocarditis, arthritis, peritonitis, and myonecrosis.[1,15-17] *C. sordellii* bacteremia and sepsis occur rarely, primarily among patients with serious underlying conditions.[18] Fulminant toxic shock syndrome among previously healthy persons has been described in only a small proportion of cases of *C. sordellii* infection, most often those associated

**Table 2. Characteristics of Women with *C. sordellii* Infections of the Genital Tract and Toxic Shock Syndrome.**

| Characteristic | Currently Reported Patients (N=4) | Previously Reported Patients (N=10)* |
|---|---|---|
| Age — yr | | |
| Median | 22 | 25 |
| Range | 18–34 | 23–40 |
| Fatal outcome — no. (%) | 4 (100) | 10 (100) |
| Underlying medical conditions — no. | 0 | 0 |
| Preceding event — no. (%) | | |
| Childbirth | 0 | 8 (80)† |
| Medical abortion | 4 (100) | 1 (10) |
| None | 0 | 1 (10) |
| Time course (days) | | |
| From event to onset of symptoms | | |
| Median | 5 | 3 |
| Range | 4–5 | 2–5 |
| From hospitalization to death | | |
| Median | 0 | 0 |
| Range | 0–1 | 0–3 |
| Clinical signs and symptoms — no. (%) | | |
| Temperature >38.0°C | 1 (25) | 1 (10) |
| Tachycardia | 4 (100) | 9 (90) |
| Hypotension | 4 (100) | 10 (100) |
| Pleural or peritoneal effusions | 3 (75) | 8 (80) |
| Vomiting or diarrhea | 4 (100) | 5 (50) |
| Abdominal pain | 4 (100) | 5 (50) |
| Rash | 0 | 1 (10)‡ |
| Laboratory findings — no. (%) | | |
| White-cell count >50,000 cells/microliter | 3 (75) | 8 (80) |
| Hematocrit ≥50% | 3 (75) | 7 (70) |
| Microbiologic findings — no. (%) | | |
| Evidence of polymicrobial infection | 4 (100) | 8 (80) |
| *C. sordellii* isolated from blood | 0 | 1 (10) |
| Focus of infection — no. (%) | | |
| Uterus | 4 (100) | 7 (70) |
| Site of episiotomy | 0 | 3 (30) |
| Pathological findings at the focus of infection — no. (%) | | |
| Edema | 3 (75) | 10 (100) |
| Necrosis | 4 (100) | 8 (80) |
| Acute inflammation | 4 (100) | 8 (80) |
| Hemorrhage | 3 (75) | 2 (20) |
| Gas | 0 | 0 |

* This information has been reported elsewhere.[1-8]
† Six deliveries were vaginal, and two were by cesarean section.[1-6]
‡ This rash was described as vesicles on the perineum that enlarged to bullous lesions and spread to the legs and trunk.[6]

with gynecologic infections and neonatal omphalitis.[1-8,17] The distinctive clinical manifestations of *C. sordellii* toxic shock syndrome result from the production of specific exotoxins, as do those of other illnesses caused by clostridium species.[15,16,19] In animal models, *C. sordellii* lethal toxin causes findings similar to those described in these human cases.[15,19] Lethal toxin is expressed variably by different *C. sordellii* strains,[20] and its cytopathic effects are markedly enhanced by a low pH.[21]

Although *C. sordellii* has rarely been identified in the genital tract, other clostridium species colonize the vagina in 4 percent to 18 percent of healthy women and commonly are associated with postpartum endometritis and septic abortion.[22-25] Vaginal flora vary with age, sexual activity, menstrual cycle, pregnancy, medications, and surgery,[22] and the apparent association between *C. sordellii* toxic shock syndrome and gynecologic infections may be attributed to a rare confluence of events. Pregnancy, childbirth, or abortion may predispose a small number of women to acquire *C. sordellii* in the vaginal tract, with dilatation of the cervix allowing for ascending infection of necrotic decidual tissue. Furthermore, the acidic pH of the vaginal tract may enhance the cytopathic effects of *C. sordellii* lethal toxin and further potentiate systemic illness.

The fastidious anaerobic growth, variable staining characteristics, and complex biochemical profiles of clostridium species make them difficult to isolate and identify, and additional cases of *C. sordellii* infection of the genital tract in which the organism was not cultured, speciated, or reported probably exist.[26,27] In the four cases reported here, evidence of *C. sordellii* infection was established with the use of anti–clostridium species immunohistochemical assay and both organism-specific and broad-range PCR assays performed on fixed uterine tissue. Identification of additional cases and application of anaerobic culture techniques or new diagnostic approaches are needed to define the true burden of *C. sordellii* in gynecologic infections.

There are limited data regarding the optimal therapy for *C. sordellii* toxic shock syndrome. As with other severe histotoxic clostridial infections, aggressive surgical wound débridement, removal of infected organs (e.g., by means of hysterectomy), and antibacterial agents with good anaerobic activity are logical first steps to decrease the bacterial load and minimize further production of toxins.[1,23] In vitro susceptibility testing on 24 *C. sordellii* strains showed low minimal inhibitory concentrations for penicillin, ampicillin, erythromycin, rifampin, tetracycline, cefoxitin, clindamycin, and metronidazole[28]; antibiotics that interfere with bacterial protein synthesis (such as clindamycin) may have additional benefit. However, débridement, surgery, and antibacterial therapy will not mitigate the effects of preformed toxin. There are no clinical data on the use of immunoglobulin or anti–lethal toxin antibodies for treatment of *C. sordellii* infections.[16,17]

These cases demonstrate that serious infection can occur after medically induced abortion, much as it can occur after childbirth, spontaneous abortion, and surgical abortion. However, available data suggest that the risk of such infection is low.[29,30] In 2000, 600 mg of oral mifepristone plus 400 μg of oral misoprostol was approved for use in the United States to medically terminate a pregnancy of up to seven weeks' gestation. As of July 2005, five deaths that occurred after medically induced abortions had been reported to the Food and Drug Administration (FDA). These include the four patients described here and one patient whose death was attributed to a ruptured ectopic pregnancy.[31] Since its approval, there have been an estimated 460,000 uses of mifepristone plus misoprostol in the United States.[32] It is not clear how many women this estimate represents. The 460,000 uses may include the regimen approved by the FDA or other dosages, such as 200 mg of oral mifepristone followed by 800 μg of intravaginal misoprostol.

There are no available incidence data for pregnancy-related *C. sordellii* infections or toxic shock syndrome. However, overall rates of infection-related deaths after pregnancy are well described. From 1991 to 1999, 259 maternal deaths due to infection were identified after 35,701,875 live births in the United States.[33,34] From 1981 to 1991, 37 infection-related maternal deaths were associated with 9,279,100 spontaneous abortions at less than 20 weeks' gestation.[35] From 1988 to 1997, 25 maternal deaths attributed to infection were reported after 13,161,608 surgical abortions at any point in gestation.[36] These data must be interpreted with caution, however, because each estimate was obtained with the use of different methods and over different periods. Furthermore, the risk of maternal death after surgical abortion increases with gestational age, and there are no published estimates for the rate of maternal death after surgical abortion performed during the first trimester.

In 2001, one additional death due to *C. sordellii*

infection after medical abortion was reported in Canada.[7] Although all four cases reported in the present study occurred in California, there were no epidemiologic links identified between the patients, and the medications received were from different lots. Some researchers have speculated about the mechanisms by which oral mifepristone or intravaginal misoprostol could potentiate *C. sordellii* infection or toxic shock syndrome.[37] However, additional data are needed to evaluate further the possible association between medical abortion and *C. sordellii* infections, define the spectrum of illness, and identify risk factors for toxic shock syndrome.

The side effects of misoprostol (e.g., vomiting, diarrhea, and abdominal cramping) may be similar to the initial symptoms of toxic shock syndrome associated with *C. sordellii*.[38] To improve diagnosis and therapy, clinicians should be aware of the distinctive features of this potentially fatal entity, including tachycardia, hypotension, edema, hemoconcentration, profound leukocytosis, and absence of fever. Health care providers should report to their state or local health department any cases of toxic shock syndrome occurring after an abortion or associated with pregnancy.

The views expressed are those of the authors and do not necessarily represent the views of the Department of Health and Human Services.

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