Frequently Asked Questions

Frequently Asked Questions about Fatal Infection and Mifepristone Medical Abortion

TECHNICAL VERSION

BACKGROUND

Since 2000, when Mifeprex® (mifepristone, Danco Laboratories, New York, New York) was approved by the United States Food and Drug Administration (FDA) for use with misoprostol to chemically terminate early pregnancy, five fatal infections in the U.S. have been reported following the procedure, as well as one in Canada during a clinical trial.[1] In the Dec. 1, 2005 issue of the *New England Journal of Medicine*,[2] the U.S. Centers for Disease Control and Prevention (CDC) along with California state and local health agencies reported on four confirmed deaths due to *Clostridium sordellii,* all in California. Since then, enhanced surveillance[3] has identified one other death following mifepristone medical abortion, which has since been attributed to infection by a different Clostridial organism, *C. perfringens.* The broad community of researchers, clinicians and advocates supportive of medical abortion lacks concrete answers about how and why these deaths occurred, which has led to widespread speculation. The uncertainty surrounding these deaths and the general response to them underscores the need for better information and broad dissemination of accurate scientific fact.

This compilation of FAQs and their answers is aimed at giving medical abortion providers and women's health advocates the language to discuss the occurrence of severe infections following mifepristone-misoprostol medical abortion, presenting the science in an informed and responsible manner. The FAQs pertain to general inquiries about the causes of death in these cases, the risk of fatal infection with *C. sordellii* following medical abortion, and the overall safety of mifepristone-misoprostol medical abortion.

GENERAL QUESTIONS

What caused the fatal infection cases in California and in Canada?

Four of the five fatal infection cases in the U.S. and the one in Canada have been attributed to *Clostridium sordellii* bacteria.

C. sordellii are anaerobic bacteria (i.e. can live without oxygen) that, in very rare cases, produce rapidly fatal toxins. More is known about *C. sordellii* in veterinary medicine than in human medicine. They are found in the soil and are a known cause of death in sheep. *C. sordellii* have been isolated from the intestines and vaginas of healthy individuals, not causing symptoms or producing a toxic effect. This asymptomatic state is known as "colonization" and is not known to be a health problem for women. Approximately 4-18% of normal, healthy, non-pregnant women's vaginas are colonized with clostridium species,[4] and an estimated 1% of these colonizations are *C. sordellii.*[5] It is unclear what factors or conditions cause the bacteria to multiply and produce toxins. These toxins cause a clinical picture with some of the characteristics of overwhelming systemic infections. The bacteria can be treated with antibiotics, but the effect of the toxins—exotoxic shock—is not reversible with antibiotics alone. *C. sordellii* has resulted in death in most reported cases of infection and in all but one[6] of the reported obstetric and gynecological cases.

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[1] Mifepristone is not available on the market in Canada. The Canadian woman who died had been enrolled in a clinical trial.

[2] Fischer M, et al. Fatal toxic shock syndrome associated with *Clostridium sordellii* after medical abortion. N Engl J Med 2005;353:2352-60.

[3] Surveillance methods include monitoring of adverse event reports by the FDA, state health departments, academic partners, and Division of Reproductive Health Pregnancy Mortality Surveillance System.

[4] Hammill HA. Normal vaginal flora in relation to vaginitis. Obstet Gynecol Clin N Am 1989;16:329-336.

[5] Hatheway CL. Toxigenic clostridia. Clin Microbial Rev 1990;1:66.

[6] The one known woman to survive *C. sordellii* became ill following a miscarriage (spontaneous abortion).

What is sepsis and what is exotoxic shock?

Sepsis is a condition in which bacteria are present in the bloodstream. The body mounts systemic responses to the presence of pathogens and the toxins they release in the blood. With severe sepsis, the body is overwhelmed by the bacteria and their toxins, which initiate physiological reactions that can result in inflammation and blood clotting throughout the body. Septic shock occurs when the cardiovascular system begins to fail so that blood pressure drops, depriving vital organs of an adequate oxygenated blood supply. Most cases of sepsis do not result in death; however, 50% of septic shock cases are fatal.

The fatalities due to infection after mifepristone medical abortion were not technically caused by "sepsis," (*bacteria* in the blood), as has been commonly described, but rather by *exotoxic shock*. Exotoxic shock results from the presence of exotoxins, *toxins* (poisons) released by bacteria into the bloodstream. Only certain rare strains of bacteria produce these poisons. Bacterial toxins are released into the bloodstream, hyperstimulating the body's immune system and causing exotoxic shock. The patients with exotoxic shock after mifepristone typically did *not* develop high fever; they did experience rapid pulse, low blood pressure, abdominal pain, and failure of multiple organ systems in the body.

Is there anything unusual about the cases in California or the case in Canada?

Yes, the presentation of *C. sordellii* infection differs from the clinical presentation of serious infections resulting in sepsis. Typically, women with serious infections and sepsis after abortion, miscarriage, or childbirth have high fever and tender uteri. However, the clinical presentation of *C. sordellii* infection is atypical. None of the women who developed *C. sordellii* infection were feverish nor were bacteria found in blood specimens. Their uteri were not tender upon examination. The patients felt ill disproportionately to the clinical findings. Other common findings included:

- tachycardia (rapid pulse)
- leukocytosis (increased number of white blood cells)
- hemoconcentration (increased concentration of red blood cells associated with an abnormally high hematocrit)

The toxins produced by C. sordellii affect blood vessels so that they become more permeable (leaky). This causes fluid to move out of the blood vessels into surrounding tissue. Thus, the fluid component of the blood leaves the blood vessels, and in essence, the blood becomes thicker and more concentrated. This leads to the clinical signs of hemoconcentration, tachycardia, and low blood pressure. In addition, the toxins cause necrosis (tissue death), edema, and hemorrhagic fluid accumulation in the uterus, which cause severe pain. Together, these changes initiate a cascade of events known as exotoxic shock, which ultimately caused the deaths of these women (see above).

Is serious infection common following mifepristone medical abortion?

No, serious infection following medical abortion is rare. Approximately 600,000 women in the U.S. have used mifepristone for medical abortion since the year 2000, when the FDA approved mifepristone. The proportion of *all* reported infections among women during the first 18 months of mifepristone use was low at 0.013%.[7] Overwhelmingly, infections reported following use are not serious and are treated with a single course of oral antibiotics in an outpatient setting.

Were there risk factors common to the women who contracted *C. sordellii* infection following mifepristone medical abortion?

To date, investigators have not been able to identify any common risk factors among these women that would have predisposed them to *C. sordellii* infection over other women undergoing medical abortion. However, a common exposure or condition that is still unknown may have heightened their risk of *C. sordellii* infection. It has surprised some observers that all U.S. cases occurred in California with none in any other state, even though only approximately 20% of medical abortions nationwide occur in California. Investigations into the matter are ongoing.

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[7] Hausknecht R. Mifepristone and misoprostol for early medical abortion: 18 months experience in the United States. *Contraception.* 2003;67:463-465.

Are other women, besides those undergoing medical abortion, at risk for this kind of infection?

C. sordellii is not limited to users of mifepristone and misoprostol and infections have occurred following childbirth (vaginal delivery and caesarean section), miscarriage (spontaneous abortion), and pelvic/abdominal surgery. All but one recent case (following miscarriage) have been fatal. *C. sordellii* infection is not restricted to women of reproductive age, however. Other known cases of *C. sordellii* have occurred in males and females of varying ages and under non-obstetric conditions, including umbilical infection, deep skin infection, tendon transplant surgery, orthopedic surgery, and following motor vehicle accidents. Some, but not all, of these latter cases resulted in death.

Do we know how to prevent such incidents following medical abortion?

Ongoing investigations into the factors that came together to cause the known and suspected cases of *C. sordellii* infection following medical abortion have so far proven inconclusive. Without a clearer scientific understanding of the cause, we cannot advise definitively on how to prevent future cases. For example, because this type of infection is observed so rarely and is not well understood, it is not known if antibiotics would prevent the *C. sordellii* from producing toxins and developing into exotoxic shock. For this reason, the FDA recommends *against* prophylactic antibiotics following use of mifepristone. Preventive antibiotic use presents other risks of serious adverse events, such as severe or fatal allergic reactions, and can produce drug-resistant strains of bacteria.[8]

Information about *C. sordellii*, as well as information regarding the clinical circumstances and symptoms of the women who died, are included in the boxed warning and warnings sections of the Mifeprex Prescribing Information. The Medication Guide and Patient Agreement also inform patients to immediately contact their health care provider if they develop abdominal pain or discomfort, or are "feeling sick," including weakness, nausea, vomiting, or diarrhea, with or without fever, more than 24 hours after taking misoprostol.

The Mifeprex label urges that medical personnel be alert to the fact that *C. sordellii* infection appears to present differently than other types of infection, resulting in delayed diagnosis and treatment. Since patients with *C. sordellii* infections can present without fever, bacteremia, or significant findings on pelvic examination following a medical abortion, medical providers should err on the side of caution before ruling out serious infection and sepsis as a concern, particularly if a patient reports abdominal pain, discomfort or general malaise (including weakness, nausea, vomiting or diarrhea) more than 24 hours after taking misoprostol.

Do we know how to treat *C. sordellii* infection, exotoxic shock, and sepsis?

Exotoxic shock and sepsis are serious conditions associated with a risk of death, regardless of the circumstances under which they arise. Patients evaluated in an outpatient setting who are suspected of being septic or having exotoxic shock should be referred immediately to a hospital. Medical personnel are advised to take complete blood counts and aerobic and anaerobic cultures from the cervix, endometrium, and blood. In addition, consideration should be given to conducting an endometrial biopsy for gram stain. A positive gram stain (i.e. positive for gram positive rods) along with other clinical findings consistent with *C. sordellii* should lead to immediate aggressive treatment with IV antibiotics that provide coverage against *C. sordellii* (e.g. penicillins, clindamycin, gentamicin). There is no evidence, however, that antibiotic treatment is effective once the toxin has spread. The effectiveness of hysterectomy to treat *C. sordellii* infection following mifepristone medical abortion is unknown.

For more detailed information on the clinical signs, symptoms, and management of *C. sordellii* infection, consult: Fjerstad M. Infection and medication abortion. *Mife Matters* 2005; 12:1-4 at www.gynuity.org.

[8] "FDA Public Health Advisory," FDA. July 22, 2005, www.fda.gov/cder/drug/advisory/mifeprex.htm.

Are the known cases of C. sordellii infection following medical abortion likely to be an underestimate of what is really happening?

No, the total number of cases of infection reported is very close to the true occurrence of *C. sordellii* following medical abortion and is not the tip of the iceberg. The report of adverse events following Mifeprex use—through MedWatch, the FDA Safety Information and Adverse Event Reporting Program—is thought to be more complete and accurate than with other drugs because of the restricted distribution of the drug and the mandated reporting system. That is, all physicians who prescribe Mifeprex must sign a Prescriber's Agreement stating that they will report all serious adverse events to Danco. In contrast, there is no comparable central reporting system for pregnancy-related adverse events or surgical abortion. In addition, any death is more likely to be reported than other adverse events and more likely to be known publicly. Since *C. sordellii* infections following medical abortion have had a 100% mortality to date, their occurrence is most likely to be reported, investigated, and written about.

Is medical abortion with mifepristone and misoprostol safe?

Yes, medical abortion with mifepristone and misoprostol is safe. Statistical analysis suggests that early medical and early surgical abortion are similarly safe. Medical abortion is associated with the same risks as a natural miscarriage and is many times safer than carrying a pregnancy to term. Although fatal cases of *C. sordellii* infection have occurred, this type of infection is rare, occurring in approximately 1 out of 120,000 uses of mifepristone medical abortion, far less often than the incidence of fatal penicillin-induced anaphylaxis (0.002% or 1 in 50,000 uses).[9] In spite of widespread use of medical abortion in Europe (1.5-2.0 million women), there have been no reports of infectious deaths from any pathogen. The FDA has determined that the pills used—mifepristone and misoprostol—in these fatal cases were not contaminated with the bacteria. FDA statements reiterate that a causal relationship between the deaths of the four Californian women and mifepristone and misoprostol has not been found and that it is premature to conclude anything different. The pills were used in different clinics, administered by different providers and came from different lots.[10] Various organizations, including the CDC and FDA, are conducting investigations into these rare but troubling events.[11] On May 11, 2006, the CDC, FDA, and National Institute of Allergies and Infectious Disease held a workshop to review the existing evidence, identify research needs and priorities to improve understanding within the scientific community, and improve detection of cases.

CAUSES AND MECHANISMS

Could immunologic changes after mifepristone administration explain the risk of *C. sordellii* infection following medical abortion?

It is very unlikely that immunologic changes following use of mifepristone could make a person susceptible to only one type of bacterial infection, and there is no scientific evidence of clinical systemic immunodeficiency induced by mifepristone. If there were systemic immunological compromise, it is likely that there would be a proliferation of all types of infection, rather than the disproportionate number of rare *C. sordellii* infections reported thus far. In Europe, the most common regimen for mifepristone-misoprostol medical abortion uses three times the amount of mifepristone that is commonly used in the U.S. (600 mg compared to 200 mg). There have been no known reports of death due to infection or exotoxic shock in Europe. If mifepristone caused immunologic changes leading to higher susceptibility to infection, it stands to reason that more women would have died from infection in Europe than in the U.S., yet no women have died from this cause in Europe. Furthermore, mifepristone has been prescribed in higher doses for women with chronic conditions like Cushing's Syndrome and meningioma, and subsequent deaths due to infection and/or exotoxic shock have not been reported in those populations.

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[9] Neugut AI, Ghatak AT, Miller RL. Anaphylaxis in the United States: An investigation into its epidemiology. *Arch Intern Med*. 2001;161:15-21.

[10] Fischer, et al, 2005.

[11] "Questions and Answers on Mifeprex (mifepristone)," FDA. July 19, 2005, www.fda.gov/cder/drug/infopage/mifepristone/mifepristone-qa20050719.htm.

Could vaginal administration of misoprostol explain the risk of *C. sordellii* infection following medical abortion?

- ***Could the misoprostol pills used by the women infected have been contaminated?***
  The FDA tested both mifepristone and misoprostol and no contamination was detected.

- ***Could vaginal insertion introduce contaminants into the vagina?***
  The CDC investigated the assertion that vaginal insertion of misoprostol facilitates infection and has found no evidence that the vaginal route of insertion of misoprostol was a factor in the deaths. Given the frequency with which women use vaginal products or have sexual intercourse, if vaginal insertion were likely to increase a woman's risk of infection, we would observe this serious and rare infection much more often.

- ***Could misoprostol induce changes to the vaginal environment?***
  Insertion of misoprostol certainly changes the vaginal pH and also induces cervical changes. Each of these changes could be a risk factor for infection. However, there is currently no scientific evidence or causal mechanism by which these changes would predispose women undergoing medical abortion to *C. sordellii* infection specifically. Further, vaginal misoprostol is commonly used for induction of labor and before surgical abortion to ripen the cervix. No similar infections have been reported following those procedures, although the vaginal environment and flora in post partum women is different than in pre- and post-abortal women.

Could the process of medical abortion explain the risk of *C. sordellii* infection?

Any bleeding or dilation of the cervix could increase the risk of infection that ascends from the vagina to the uterus, but there is no special reason that *C. sordellii* would be implicated.

Could the use of a non-FDA approved regimen (vaginal misoprostol) explain the risk of *C. sordellii* infection?

Although oral use of misoprostol is specified in the FDA-approved regimen, in the U.S., vaginal use of misoprostol in association with mifepristone is the norm. It is therefore expected that most deaths would be recorded among users of vaginal misoprostol, since there is almost no oral use. Consequently, it is almost impossible to draw conclusions about oral versus vaginal use. Indeed, hundreds of thousands of women in Europe and other places have used misoprostol vaginally, and no similar infections have been recorded in those women.

Are there other risk factors that could explain the risk of *C. sordellii* infection following mifepristone medical abortion?

To date, investigators have not been able to identify other risk factors to explain why some women may be at greater risk of *C. sordellii* infection following mifepristone medical abortion than others. Investigations into the matter are ongoing.

What can I say if I am asked why these deaths happened in this country?

The best response is that no adequate explanation that makes scientific and epidemiologic sense has yet been proposed. It is better to accept uncertainty for the moment than to spread false rumors or jump to unreliable conclusions.

Frequently Asked Questions

For More Information

- Danco Laboratories, Mifeprex website. www.earlyoptionpill.com
- FDA, Center for Drug Evaluation and Research, Mifepristone Information. www.fda.gov/cder/drug/infopage/mifepristone/default.htm
- Richard Hausknecht, "Mifepristone and Misoprostol for Early Medical Abortion: 18 Months Experience in the United States," Contraception 67:463-65 (2003).
- National Abortion Federation, Facts About Mifepristone. www.prochoice.org/about_abortion/facts/facts_mifepristone.html

This material was made possible with support from the Richard and Rhoda Goldman Fund.

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