Clostridium sordellii Infection in Medical Abortion

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(See the article by Aldape et al. on pages 1436–46)

Doubt is not a pleasant condition, but certainty is absurd.
—Voltaire

A newly described, rare, lethal entity that affects previously healthy young people and has no known prevention or treatment constitutes a true public health nightmare. It also excites public attention and demands for action. The review of Clostridium sordellii infections by Aldape et al. [1] in this issue of Clinical Infectious Diseases tells the beginning of an infectious disease story to which epidemiology and clinical medicine have not yet written an ending.

The organism C. sordellii is an uncommon human pathogen, although it has been more thoroughly described in veterinary medicine. Recently, several dozen cases of human infection have been reported. The number of cases in the literature has accumulated more rapidly in recent years, suggesting that this condition, like other rare diseases, is more likely to be identified when knowledge of the syndrome is more widely disseminated.

Perhaps the most dramatic of the cases described are those that involved previously healthy young women who succumbed to this infection after an obstetric event. Indeed, the cases reported after childbirth, miscarriage, and abortion have been almost uniformly fatal. Furthermore, fatalities due to C. sordellii toxic shock syndrome in conjunction with medical abortion, occurring exclusively in the United States, ensured that the name of this previously unfamiliar pathogen would find a place on the front pages of national newspapers and become a part of the “abortion wars” in the halls of Congress.

Thus, there has been some urgency to have credible scientific wisdom to provide the public with answers about where this infection comes from, why it happens, and what we can do to prevent and/or cure it. Unfortunately, as Aldape et al. [1] make clear, we have few answers to offer. With incomplete knowledge, the field has been wide open to speculation and rumor.

With respect to the occurrence of C. sordellii–related fatalities after abortion using mifepristone and misoprostol, 6 potential theories for understanding causality and for preventing the disease have been put forward: (1) the pills were contaminated; (2) there has been some kind of mutation in the organism that accounts for the occurrence of these cases now and not elsewhere or previously; (3) mifepristone depresses the immune system, thus setting the stage for this infection; (4) the use of vaginal misoprostol allows women with existing vaginal colonization with C. sordellii to develop systemic illness; (5) the vaginal insertion, by women themselves, of misoprostol introduces contamination with C. sordellii into the vagina; and (6) the use of prophylactic antibiotics in surgical abortion procedures may account for the absence of such cases after surgical abortion and may be presumed also to be able to prevent this infection after medical abortion.

As noted by Aldape et al. [1], tests of the lots of pills used by the affected women yielded negative results, putting this hypothesis to rest. A new variant of the organism is possible and is consistent, perhaps, with apparent changes in the virulence of the related organism, Clostridium difficile. Such a change may also be consistent with the geographic specificity of these cases to North America—and, specifically with regard to the United States, to California [2]. But it does not explain any particular relationship to medical abortion.

Studies of animals revealing immune system effects of mifepristone have been cited, along with fairly elaborate hypo-
thetical (but as yet unobserved) clinical pathways by which mifepristone might affect the immune system in humans. On the other hand, there are several larger-picture facts that seem to speak against the importance of this theory. In the first place, the drug is given as a one-time 200-mg dose for abortion. Yet, in experimental long-term use for chronic diseases (e.g., meningioma, fibroids, and ovarian cancer), no such infections have been recorded. Furthermore, in Europe, where the drug has been in use since 1988, the usual dose has been 600 mg (3 times the dose in the United States), but no cases of *C. sordellii* toxic shock have been reported there. In addition, none of the women who died of *C. sordellii* toxic shock after childbirth or spontaneous abortion had received any mifepristone at all. And finally, it is hard to imagine a biological effect in which a drug-induced alteration of the immune system would result in the appearance of only 1 specific infection at a rate of ~0.7 cases per 100,000 users and no other immune effects.

Vaginal use of the misoprostol has also been suggested as a potential causal factor in these events. But with respect to medical abortion, it is not surprising that the 4 women in the United States who developed this condition after medical abortion had used misoprostol vaginally, because almost all use of mifepristone in the United States through mid-2006 involved vaginal misoprostol. If we apply the estimate that 0.1%–0.5% of women may be carriers of this organism [3, 4] to the fact that >600,000 US women have undergone medical abortions, most of which involved vaginal misoprostol, it suggests that somewhere between 600 and 3000 women would have used the medication in the presence of vaginal colonization with *C. sordellii*. However, only 4 infections have occurred in the United States, and because the infections are uniformly fatal, in the context of hypervigilance about abortion events, we can be quite certain that this number is accurate.

Indeed, vaginal use of misoprostol has been standard in the United Kingdom, Sweden, and South Africa, and no cases of *C. sordellii* toxic shock have been reported from those countries. As a matter of fact, a review of all infections after various regimens of medical abortion demonstrated that infection generally occurred very infrequently but was reported more frequently in studies from the United Kingdom than in studies from outside the United Kingdom and in studies from the United States and was unrelated to the route of administration of misoprostol [5].

If women were introducing contamination into the vagina by self-application of the misoprostol in the United States, we would expect to see many more of the common infections that result from contamination by skin and fecal bacteria. Yet, such infections are rarely reported in conjunction with medical abortions in the United States, and as noted above, postmedical abortion infection has generally been a less common condition among patients in US studies than among patients in studies from the United Kingdom, where health service providers (and not the women) insert the vaginal misoprostol.

Finally, there is no compelling evidence that prophylactic antibiotics would be effective in preventing these medical disasters. Moreover, the antibiotic treatment would have to be applied (with all the attendant risks of adverse effects) to ~140,000 women who did not need treatment, to prevent 1 case of infection. Indeed, even considering the costs and risks of such mass treatment and the problems caused by overuse of antibiotic therapy generally, there are some clinicians who would be ready to proceed with such prophylaxis. But other voices have been raised in alarm about this idea. As for clinical studies of the value of this approach, these appear to be out of the question logistically and financially. With such a rare event, estimates of the number of patients required for an adequate clinical trial have ranged from 80,000 to well over 100,000, depending on the assumptions made.

A large natural experiment is now occurring in this country that may provide the best chance of learning more (although probably not definitive) information about some of these causal hypotheses. Until mid-2006, when almost all mifepristone abortions were accompanied by use of vaginal misoprostol, the rate of *C. sordellii* infection after medical abortion appeared to be ~0.7 cases per 100,000 procedures. In 2006, with a great deal of public attention to these deaths, some large clinic systems—including, notably, Planned Parenthood clinics—and many independent providers decided to stop using misoprostol vaginally and to advise oral or buccal use of this medication after use of mifepristone. We will have to wait, perhaps many months or years, but eventually we may see whether this change in practice is accompanied by any measurable change in the rate of these tragic deaths. And even if, with passage of time, there is a suggestion of some impact, we still will not have a complete explanation of this complex epidemiological and clinical situation. In the mean time, we will need to learn to live with our uncertainties and avoid the mistakes so easily caused by acting on assumptions and guesses rather than facts.

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References


