The Many Faces of Human-to-Human Transmission of Brucellosis: Congenital Infection and Outbreak of Nosocomial Disease Related to an Unrecognized Clinical Case

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Background. Because person-to-person transmission of brucellosis is exceptional, physicians who care for patients with this disease are not considered to be at increased risk. A woman in her 24th week of pregnancy who had received a diagnosis of placenta previa presented to the hospital with massive vaginal bleeding and hypovolemic shock, requiring performance of an emergency Cesarean delivery. Two physicians who assisted the surgical delivery developed culture-proven Brucella melitensis infection. The organism was also recovered from cultures of blood samples obtained from the mother and the premature newborn. The mother had been observed since early pregnancy because of an undiagnosed febrile hepatitis, but no specific tests for brucellosis had been performed. Retrospective testing of serum samples obtained at the onset of disease were positive for Brucella antibodies, indicating that the disease could have been diagnosed earlier.

Methods. Hospital records of the obstetric, intensive care, and surgical departments were examined to identify all staff members who took care of the mother and her offspring. The identified personnel were interrogated about exposure to potentially infective blood and fomites and were screened by blood cultures and serologic tests for Brucella species.

Results. An additional physician who assisted in the resuscitation of the newborn had a blood culture positive for B. melitensis and a positive result of a diagnostic serological test. Ninety-five other members of the hospital staff, who were potentially exposed to the organism, were found to be uninfected.

Conclusions. Although rare, transmission of B. melitensis from patients to medical personnel may occur. Strict adherence to universal precautions, especially during performance of medical procedures characterized by massive blood exposure, should be reinforced.

Brucellosis is a bacterial zoonotic disease that is still prevalent in the eastern Mediterranean basin and in countries in the Middle East [1]. Several Brucella species are pathogenic to humans, and Brucella melitensis, which is the prevalent organism in southern Israel, appears to be the most virulent [2]. Brucellae are highly contagious to humans exposed to infected animals and contaminated animal products. In areas of endemicity, disease is usually acquired through the enteric route by consumption of unpasteurized dairy products [1]. Additional portals of entry of the organism are the conjunctival and respiratory mucosae and abraded skin.

Brucellosis is considered a professional hazard among laboratory technicians and veterinarians who work in areas where it is endemic [3]. Physicians who treat patients with brucellosis, however, are not regarded as having an increased risk, because person-to-person transmission of the disease is extremely uncommon. In the few proven cases of acquisition of the infection from human sources, mother-to-offspring transmission through the placental circulation, exposure to mother’s fomites during delivery, breast-feeding [4–10], blood transfusion [11], bone marrow trans-
plantation [12], and sexual contact [13] have been implicated.

The purpose of our article is to report the occurrence of an outbreak of *B. melitensis* infection among physicians involved in the delivery of a congenitally infected premature newborn, to describe the investigation of the event, and to emphasize the importance of early recognition of the disease.

**MATERIALS AND METHODS**

**Description of the Outbreak of Infection**

**Patient 1.** A 32-year-old Bedouin woman consulted her family physician on 17 May 2006 on the 11th week of her 10th pregnancy because of fever that had lasted 10 days (figure 1). Her past health history was notable for a previous Cesarean delivery. Physical examination disclosed an enlarged liver, and blood testing revealed elevated hepatic enzyme levels. Tests of serum samples obtained on 21 May and 4 July were negative for hepatitis A and B viruses, Epstein-Barr virus, and cytomegalovirus antibodies. From the end of June until mid-July, the patient experienced multiple episodes of mild vaginal bleeding, and an ultrasound examination revealed placenta previa. A test of a blood sample obtained while the patient was afebrile revealed that the liver enzyme level was still mildly elevated, and she was hospitalized for observation on 19 July. In the course of her hospital stay, she developed mild hyperthermia. Blood and urine cultures were sterile, and the patient was administered empirical ampicillin-clavulanate therapy and experienced defervescence. A third virologic evaluation for hepatitis was performed, with negative results.

On 7 August, the patient experienced sudden massive vaginal bleeding and developed severe hypotension. Abruptio placentae was diagnosed, and an emergency Cesarean delivery was performed under general anesthesia. In the course of the surgical procedure, uncontrollable bleeding occurred, requiring administration of 4 U of packed RBCs, 8 U of fresh frozen plasma, and 10 U of cryoprecipitate and platelets, in addition to 5200 mL of intravenous Hartmann’s solution. Because of technical difficulties in extracting the placenta and stopping the bleeding, total hysterectomy and ligation of the internal iliac artery were performed. After surgery, the patient was transferred to the intensive care unit. Her clinical course was stormy and characterized by hyperthermia (temperature, 40.0°C), hypovolemic shock, acute respiratory distress syndrome, acute adrenal insufficiency, and jaundice. She underwent artificially ventilation for 5 days and was administered 4 additional U of packed RBCs, 2 U of fresh frozen plasma, vasopressor drugs, hydrocortisone, and intravenous fluid solutions. After obtaining blood samples for culture, ampicillin-clavulanate and ofloxacin were administered by the intravenous route.

Four days later, brucellae were isolated from 3 of 4 blood cultures, and a standard agglutination test (SAT) for *Brucella* antigens yielded positive results, with an IgG titer of 1:20 and an IgM titer of 1:60. Antibiotic therapy was shifted to a combination of intravenous ciprofloxacin and doxycycline. Because of the patient’s serious clinical condition, ciprofloxacin, which is considered to be a more potent drug than ofloxacin [14], was preferred. The empirical antimicrobial coverage was broad-
ened with the addition of meropenem for 1 week. The patient completed a 6-week course of specific antibiotic treatment and recovered. Three serum samples, which had originally been submitted for viral serologic tests 12, 4, and 3 weeks before surgery and which had been kept frozen in the laboratory, were retrospectively examined for the presence of Brucella antibodies. All 3 specimens yielded positive results, with SAT titers of 1:320, 1:160, and 1:160, respectively.

**Patient 2.** The premature offspring of patient 1 was delivered at the gestational age of 24 weeks. The Apgar score was 2 at 1 min. The infant was bradycardic and showed no spontaneous breathing effort. Intubation was immediately performed, and the infant was transported to the neonatal intensive care unit (NICU), where he underwent mechanical ventilation. His clinical course was significant for progressive respiratory insufficiency complicated by interstitial emphysema, pulmonary hypertension, shock, and a patent ductus arteriosus, requiring high oxygen concentration and use of nitric oxide, vasopressor drugs, and multiple doses of indomethacin. Culture of a blood sample obtained on the day of delivery yielded a *Brucella* species after 4 days of incubation. The results of a Rose-Bengal screening test were negative for anti-Brucella antibodies. The patient was given intravenous ampicillin, gentamicin, and rifampicin, and the blood culture results became negative. This regimen was administered instead of the traditional trimethoprim-sulfamethoxazole (TMP-SMZ)-based therapy recommended for older children, because sulfa drugs increase the risk of kernicterus and, therefore, are contraindicated in premature babies [15]. On day 14, the patient developed systemic candidiasis and anuria, and intravenous amphotericin B was added to the treatment regimen. The child died at the age of 20 days.

**Patient 3.** A 33-year-old obstetrician was part of the surgical team that performed the emergency Cesarean delivery for patient 1. He could not recall any direct contact with the patient’s blood or amniotic fluid or tear of the surgical gloves. After the patient presented to his family physician at the beginning of October 2006 with a 4-day history of febrile illness accompanied by chills, the findings of a physical examination were unremarkable, and the initial blood tests revealed mild anemia, thrombocytopenia, and elevated liver enzyme levels. Fever continued for an additional week, and arthralgia of the left hip developed. The neonatologist recalled repeatedly taking care of patient 2 during his hospital stay, including performance of brucellar SAT test was diagnostic at a titer of 1:160 (IgG antibody titer, 1:1:40; IgM antibody titer, 1:120).

The patient was initially treated with intramuscular streptomycin for 2 weeks and oral doxycycline for 6 weeks. Because of persistent malaise and development of right knee arthralgia, the duration of the aminoglycoside therapy was extended to a full 3 weeks. With the exception of intermittent episodes of fatigue, her clinical condition improved. Additional blood cultures yielded negative results, and a progressive decrease in the antibody titer was observed over time.

**Patient 4.** This 29-year-old female pediatric resident was called to the infant resuscitation room, which is located beside the obstetric operating room, to assist in the delivery of patient 2. She wore a sterile gown, head and shoe covers, and latex gloves but no facial mask. The infant was brought to the infant resuscitation room by a midwife, and the resident dried the infant with a towel and performed a successful endotracheal intubation in the first attempt. She provided Ambu bag ventilation to the child while in transit to the contiguous NICU. In the NICU, she performed catheterization of the umbilical artery and vein using a sterile technique that included wearing gloves, a cap, and a surgical face mask. She has no recollection of any direct contact with the infant’s blood. Five weeks after the event, she started to experience fatigue, malaise, dizziness, headache, myalgia, and night sweating, as well as intermittent febrile episodes. Complete blood count revealed mild leukopenia and slightly elevated liver enzyme levels. Three months after the infant’s birth, she was approached by the hospital’s infection-control team in the course of the investigation of the outbreak. A blood culture was positive for *Brucella*, and the SAT test was diagnostic at a titer of 1:160 (IgG antibody titer, 1:1:40; IgM antibody titer, 1:120).

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**Patient 5.** This 39-year-old, otherwise healthy male neonatologist presented to his family physician at the beginning of October 2006 with a 4-day history of febrile illness accompanied by chills. The findings of a physical examination were unremarkable, and the initial blood tests revealed mild anemia, thrombocytopenia, and elevated liver enzyme levels. Fever continued for an additional week, and arthralgia of the left hip developed. The neonatologist recalled repeatedly taking care of patient 2 during his hospital stay, including performance of several endotracheal intubations. Although all contact with the newborn involved the use of examination latex gloves, the physician was not protected with either a face mask or goggles. The neonatologist did not recall any tear of the gloves resulting in direct contact with the newborn’s blood. After the patient provided this recollection, samples were obtained for blood culture and specific serological tests for brucellosis. *Brucella* organisms were isolated from the blood culture, and the serum brucellar SAT titer was diagnostic (>1:160). The patient was
administered intramuscular streptomycin for 2 weeks and oral doxycycline for 6 weeks and made an uneventful recovery.

Investigation of the Outbreak
Once the nosocomial outbreak of brucellosis was recognized, the infection-control team conducted an extensive investigation to determine the circumstances of the exposure and to detect possible additional cases of disease among hospital workers. The medical charts for patients 1 and 2 and hospital records for the Obstetric Surgery Room were thoroughly examined to identify all members of the hospital staff who could have been exposed to potentially infective fomites, such as the mother’s blood, amniotic fluid, and urine and the newborn’s respiratory secretions. In addition, the 2 obstetric surgeons who performed the Cesarean delivery and the 3 anesthesiologists and the 4 nurses and midwives who were present at the surgical theater were exhaustively interrogated about potential accidents that may have occurred during the course of the operation and resulted in exposure (e.g., spills of blood or amniotic fluid, tears of gloves, and removal of masks). The identified workers were personally contacted and interrogated about the occurrence of symptoms of disease that are compatible with clinical brucellosis in the previous weeks and were asked for permission to perform a blood culture and a serological test for Brucella antibodies. Patients who received a diagnosis of brucellosis were interrogated about the specific exposure to potentially infected fluids, safe medical practices, and other potential exposures to brucellosis, such as consumption of unpasteurized dairy products or traveling to countries where brucellosis is endemic.

Blood cultures were processed with the Bactec 9240 instrument (Becton Dickinson) and incubated for 7 days. Isolates were presumptively identified as members of the genus Brucella on the basis of typical Gram stain findings (i.e., the presence of small gram-negative coccobacilli; positive oxidase, catalase, and urease test results; CO₂ requirement for growth; and a lack of fermentation of sugars), and results were confirmed by a positive agglutination test result with specific antiserum (Welcome Diagnostics). Speciation was performed at the brucellosis referral center of the Kimron Veterinary Institute of Bet Dagan, Israel. Serum samples were screened for antibodies to Brucella antigens by the Rose-Bengal test. Specimens that yielded positive results were subjected to the SAT test, and a titer of ≥1:160 was considered to be diagnostic of the disease. Separate IgG and IgM antibody titers were determined by the 2-mercaptoethanol method.

RESULTS
Of a total of 114 hospital workers at potential risk for acquiring the disease who were identified, 96 (84.2%) could be contacted and tested. Only 1 previously unrecognized infected individual (patient 4) was identified by the survey. All other 56 members of the Divisions of Anesthesiology and of Obstetrics and Gynecology, 23 members of the NICU, 15 members of the intensive care unit who provided postoperative care to patient 1, and the pathologist who performed the postmortem examination of the newborn had negative results of cultures and serological tests.

No potential exposures to Brucella organisms other than contact with patients 1 and 2 were identified among the 3 affected physicians. The 5 isolates from the infected patients were identified as B. melitensis biotype 1.

DISCUSSION
Brucellosis continues to be a serious public health issue in southern Israel, especially among the semi-nomadic Bedouin population that maintains herds of unvaccinated sheep and goats and consumes unpasteurized dairy products. The incidence of the disease reached a peak of 52 cases per 100,000 inhabitants of the region in 1988 [16] and has remained at a high, endemic level ever since. Awareness about the disease among physicians, however, is low, and in a substantial fraction of patients, diagnosis of brucellosis is only made after the causative organism is unexpectedly detected in cultures of blood or exudate specimens [17].

Despite the fact that the clinical course of the disease in the herein described pregnant Bedouin woman was characterized by prolonged fever and hepatic involvement—2 common manifestations of brucellar infections in humans [1, 18]—the true etiology of her illness was not suspected, and the laboratory investigation did not include either blood cultures or Brucella serologic tests. Moreover, the patient was regularly checked during the course of her pregnancy and was even hospitalized for a prolonged period, but the opportunity to correctly diagnose the disease and administer her specific antibiotic therapy was repeatedly missed. The fact that the antibody tests performed retrospectively on the serum samples collected many weeks before delivery were consistent with an active Brucella infection indicates that the diagnosis of the disease could have been made at an early stage, and the congenital infection (as well as the nosocomial outbreak) could have been avoided by timely administration of appropriate antimicrobial therapy. Because of the serious associated obstetric pathology and premature delivery, it is unknown whether the death of the neonate could have also been prevented. The borderline anti-Brucella screening test result obtained for the mother shortly after delivery is explained by dilution of the antibody concentration by profuse bleeding and replacement of blood loss by blood products devoid of specific antibodies, whereas serum samples collected a few weeks earlier and 1 month after delivery exhibited titers that were consistent with an active infection.

Infected pregnant animals, such as cattle, sheep, goats, swine, and dogs, frequently transmit the organism to the fetus by the
transplacental route, resulting in contagious abortion [19]. The issue of whether brucellosis can also cause abortion and premature delivery in humans has been a subject of controversy. Brucella species have been isolated from human fetal or placental tissues, but it is currently accepted that brucellosis causes fewer spontaneous abortions in humans than it does in animals because of the absence of erythritol in human tissues [20]. Erythritol is a constituent of normal ungulate tissues, and in cases of bovine infection, it promotes overwhelming invasion of the placenta and fetus. A study by Khan et al. [19] demonstrated an excess of spontaneous abortions during the first and second trimesters among pregnant women with active brucellosis. Occurrence of abortion was not associated with either the magnitude of the serum agglutinin titer or the presence of Brucella bacteremia. Antimicrobial therapy with TMP-SMZ or TMP-SMZ plus rifampicin had a strong protective effect against abortion in this context.

Premature delivery of a congenitally infected newborn presenting with disseminated brucellar disease and nonspecific signs of septicemia that were similar to those observed in patient 2 has also been repeatedly documented [21–24]. The negative Rose-Bengal screening test result observed in the neonate (patient 2) is consistent with the fact that IgG antibodies begin to be transferred from mother to fetus by an active transport mechanism after the 17th week of gestation, and IgM does not normally cross the placental barrier [25].

 Deliveries and abortions of infected animals also play an important role in the dissemination of brucellae within the herd through contamination of pastures by infected blood, lochia, and genital secretions, and the organism can survive in the soil for several weeks [26]. Because of the high concentration of virulent brucellae in placental and fetal tissues, veterinarians who assist in the birth of infected animals are at substantial risk of acquiring the disease [27, 28]. Occupational transmission of brucellosis to other health care workers has been previously reported among laboratory workers exposed to contaminated aerosols and, more rarely, by autoinoculation of the organism by contaminated needles [3]. To the best of our knowledge, transmission of brucellosis from patients to medical personnel has been documented only in the single case of an obstetrician who assisted the vaginal delivery of a congenitally infected premature newborn [29]. In that case, transmission was believed to have been caused by ingestion of infectious secretions during clearance of the newborn’s respiratory tract.

In the outbreak of brucellosis that we describe, the pediatric resident and the surgical staff in the operating theater were protected by gloves and face masks, and no mouth-to-mouth suction was performed. On the other hand, performance of the emergency Cesarean delivery, which was complicated by difficult placental extraction, massive uterine bleeding, and a spill of amniotic fluid, probably resulted in gross environmental contamination and massive exposure to brucellae. Under these circumstances, entry of the organism through the conjunctivae may have occurred, although penetration through abraded skin or aspiration of infective aerosols cannot be definitely excluded. The mechanism of transmission of the infection to the neonatologist who assisted the delivery and resuscitation of the newborn is unclear and remains a subject of speculation.

Despite the fact that brucellosis continues to be a major public health problem in many countries, awareness about the disease is frequently inadequate, even in regions where it is endemic, and it can easily go undiagnosed. Untreated brucellosis in pregnant women carries the risk of transplacental transmission that may result in a lethal congenital infection. Although exceptional, patient-to-physician contagion of brucellosis may occur in circumstances characterized by massive bleeding and gross contact with infective fomites. Awareness about the disease and strict observation of universal precautions is recommended to reduce exposure and prevent nosocomial acquisition of bloodborne pathogens.

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References