Prevention of Laboratory-Acquired Brucellosis: Significant Side Effects of Prophylaxis

Sir—We describe our experience in responding to a laboratory exposure to Brucella melitensis—in particular, the high incidence of adverse events associated with antibiotic prophylaxis. This information may be useful to other laboratories with similar exposures.

A 45-year-old man returned to Australia from Iraq. He presented to the hospital with a cerebrovascular accident and was noted to be febrile and to have a systolic murmur. An echocardiogram demonstrated a vegetation on the aortic valve, and blood cultures grew B. melitensis after 2 days. His condition was treated with a combination of rifampicin, doxycycline, and gentamicin, and he had an uneventful recovery.

In the laboratory, the blood cultures were continuously monitored by the BacT/Alert 3D instrument (bioMérieux). When the bottles signaled positive results, they were moved to a class II biological safety cabinet (BSC II), where the bottles were accessed and an aliquot was transferred to a slide and was also placed onto solid agar media. The inoculated media were removed from the cabinet, and plate streaking was performed on an open bench. Initial plate reading and manipulation of the cultures were performed on the open bench, but, within 24 h of the appearance of growth, a presumptive identification of Brucella species was made, after which all further manipulation was performed in the BSC II. The organism was confirmed to be B. melitensis by a reference laboratory. It was thought that staff may have been exposed to the organism during these procedures.

Staff were interviewed about their exposure and were assigned to high-, medium-, and low-risk groups. Seven staff members were assigned to the high-risk group. These staff manipulated or handled open-plate cultures or potentially inhaled material from the liquid or plate cultures outside the BSC II (i.e., they sniffed the plate, streaked the plate with flamed loops, inspected open-plate cultures, or performed subcultures or biochemical tests).

The medium-risk group members were in close proximity while these procedures were being performed (12 staff), and the low-risk group members were working in other areas of the microbiology laboratory (25 staff). We decided our response would be similar to that reported by Robichaud et al. [1]. After counseling, the high-risk group was offered antimicrobial prophylaxis with rifampicin (450 or 600 mg once daily, depending on body weight) and doxycycline (100 mg twice daily) for 3 weeks. In addition, second-weekly serological testing for brucellosis for 12 weeks was recommended for staff in the high- and medium-risk groups.

All 7 staff members in the high-risk group decided to take prophylaxis. Six started treatment within 1 week after potential exposure, and the seventh started it within 4 weeks after potential exposure, after the exclusion of early pregnancy. Of those 7 staff members, 6 experienced significant side effects associated with the medications. All 6 reported nausea, vomiting, and anorexia. One staff member developed fever and mild hepatitis and required admission to the hospital for monitoring. The symptoms resolved promptly with cessation of the course of antibiotics. One staff member developed minor facial swelling, and another described mild depression and anxiety during antibiotic use. Eight and a half working days were lost because of sick leave among 4 of the staff who received prophylactic antibiotics.

Only 4 of the 7 staff completed the treatment course, with 2 staff members missing 2 days of treatment, and 1 missing >5 days. A total of 82% of scheduled serological tests were performed. There were no seroconversions to suggest subclinical infection, and no staff members developed clinical brucellosis during 8 months of follow-up.

No definitive guidelines for the management of potential laboratory exposure to brucellosis are available. Some groups have used postexposure antibiotic prophylaxis, although the effectiveness of this treatment is difficult to measure, and levels of risk are difficult to determine. Robichaud et al. [1] gave prophylaxis with rifampicin and doxycycline to 5 of 6 laboratory technicians, and there were no infections among those 5. The 1 technician who declined prophylaxis developed clinical disease, which suggests that prophylaxis may have been effective. In that study, the regimen was said to be well tolerated, and the adverse effects acceptable. This information was taken into account in our decision to offer prophylaxis to our staff.

We were surprised by the high rate of significant side effects in our treated group and the sick leave that resulted. The lack of infections may indicate that the antibiotic prophylaxis was successful, although it is likely that exposure in our laboratory was limited. The possibility that Brucella species were present was quickly recognized, there was minimal manipulation of the culture, and only 1 staff member reported sniffing the plate. Nevertheless, brucellosis is a potentially fatal illness, and any laboratory exposure should be carefully assessed and managed. There may be a role for antibiotic prophylaxis in managing high-risk exposures, but the need for prophylaxis must be balanced against the possibility of significant side effects. Primarily, laboratory protocols should aim to minimize potential laboratory exposures to dangerous pathogens, and laboratory staff should remain vigilant while performing their duties.

Reference


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Only 4 of the 7 staff completed the treatment course, with 2 staff members missing 2 days of treatment, and 1 missing >5 days. A total of 82% of scheduled serological tests were performed. There were no seroconversions to suggest subclinical infection, and no staff members developed clinical brucellosis during 8 months of follow-up.

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Hyperlactacidemia Potentially Due to Linezolid Overexposure in a Liver Transplant Recipient

Sir—A 59-year-old white liver transplant recipient developed bilateral pneumonia on day 4 after the operation. After performing bronchoscopy with bronchoalveolar lavage, empirical therapy with piperacillin-tazobactam (4.5 g every 6 h) and levofloxacin (500 mg every 12 h) was commenced. During the subsequent 24 h, the patient’s clinical condition worsened until he developed severe sepsis. Drotrecogin-α was administered, but because of the persistence of the patient’s critical condition, and because no bacteria were isolated, antibiotic therapy was shifted 48 h later to meropenem (500 mg every 6 h) plus linezolid (600 mg every 12 h).

Over the subsequent days, the patient’s clinical condition slowly improved. However, despite there being no evidence of graft dysfunction or renal failure, a progressive asymptomatic increase in the plasma lactate level was noted (peak level, 8.4 mmol/L) (figure 1).

On day 10 of the second-line antibiotic regimen, therapy was de-escalated by withdrawing meropenem. In accordance with our institution’s antibiotic policy, which is oriented at optimizing therapy for critically ill patients [1], multiple blood samples were obtained to assess linezolid exposure during a dosing interval and were subsequently analyzed by high-performance liquid chromatography [2]. Pharmacokinetic analysis revealed significant plasma overexposure to linezolid (12-h area under the curve, 412.55 mg·h/L; maximum concentration, 43.32 mg/L; minimum concentration, 26.99 mg/L) because of impaired clearance (1.51 L/h) with a prolonged elimination half-life (16.57 h) [3].

We hypothesized that the patient potentially had drug-induced hyperlactacidemia. On day 12 of hospitalization, linezolid was withdrawn, and blood samples were obtained to determine whether plasma drug levels were decreasing. During the subsequent 2 days, concomitantly with a decrease in the plasma linezolid level, a progressive decrease of the plasma lactate level (until complete normalization occurred) was documented (figure 1).

Hyperlactacidemia during linezolid therapy has been previously reported to be an adverse event that mainly develops after long treatment periods and that slowly resolves after withdrawal of the drug [4–6]. Conversely, in the case we report, lactate levels started increasing just after the first week of treatment, rapidly achieved the maximum level, and returned to a normal level within 48 h after drug withdrawal.

It has been suggested that, on the basis of its mechanism of action, linezolid may cause hyperlactacidemia by inhibiting mitochondrial protein synthesis [6]. Therefore, hyperlactacidemia should be expected to occur earlier in the course of treatment and to be more severe in patients who...