CASE REPORT

MRSA bacteraemia complicating amphotericin B treatment of cryptococcal meningitis

J Scriven,[1,2] MB ChB, MRCP, MRes, DTM&H; **J Cirota**,[3] MB ChB; **C Viljoen**,[3] MB ChB; **J Black**,[4] MB ChB, FCP (SA), Dip HIV Man (SA); **G Meintjes**,[1,4,5] MB ChB, FCP (SA), MRCP, Dip HIV Man (SA), MPH, PhD

[1] *Clinical Infectious Diseases Research Initiative, Institute of Infectious Disease and Molecular Medicine, Faculty of Health Sciences, University of Cape Town, South Africa*
[2] *Liverpool School of Tropical Medicine, Liverpool, United Kingdom*
[3] *Department of Medicine, Faculty of Health Sciences, University of Cape Town, South Africa*
[4] *Division of Infectious Diseases and HIV Medicine, Department of Medicine, Faculty of Health Sciences, University of Cape Town, South Africa*
[5] *Department of Medicine, Imperial College London, United Kingdom*

Corresponding author: *J Scriven (james.scriven@liverpool.ac.uk)*

Intravenous amphotericin B is a key component of the antifungal therapy for cryptococcal meningitis recommended in South African and international guidelines. Unfortunately, its use is associated with significant toxicity including deterioration in renal function, electrolyte disturbance, anaemia and infusion reactions. Chemical phlebitis is common following administration via peripheral cannulae. This can be complicated by bacterial infection, resulting in localised cellulitis or bacterial sepsis. Here we describe two patients with cryptococcal meningitis who developed methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia during, or shortly after treatment with amphotericin B. These cases illustrate the dangers of line-related sepsis in hospitalised individuals and some of the difficulties encountered during treatment of this condition.

S Afr J HIV Med 2013;14(3):144-146. DOI:10.7196/SAJHIVMED.979

Intravenous (IV) amphotericin B is a key component of the antifungal therapy for cryptococcal meningitis (CM) recommended in both South African (SA) and international guidelines.[1,2] Unfortunately, its use is associated with significant toxicity including deterioration in renal function, electrolyte disturbance, anaemia and infusion reactions.[3] Chemical phlebitis is commonly seen following its administration via peripheral cannulae. This can be complicated by bacterial infection, resulting either in localised cellulitis or bacterial sepsis.

Here we describe two patients with CM who developed methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia during, or shortly after treatment with amphotericin B. These cases illustrate the dangers of line-related sepsis in hospitalised individuals and some of the difficulties encountered during treatment of this condition.

Case 1

A 42-year-old, HIV-positive man presented to hospital with a one-week history of headache and vomiting. He was not receiving antiretroviral therapy (ART) and had a $CD4^+$ count of 23×10^6 cells/l.

CM was diagnosed following lumbar puncture (positive India ink, cryptococcal antigen test and culture) and he was treated with 1 mg/kg/day amphotericin B (IV) and 800 mg/day fluconazole (oral) for 14 days. During this time he had frequent episodes of phlebitis at peripheral cannula sites. On day 13 following admission, the patient deteriorated, developing fever and tachycardia. His right forearm was markedly swollen with frank pus discharging from an old cannula site. A diagnosis of bacterial sepsis secondary to drip-site infection was made, a blood culture was performed and IV vancomycin was administered. Within one day, *S. aureus* was identified from a blood culture. Resistance testing confirmed this to be methicillin-resistant, but vancomycin susceptible (minimum inhibitory concentration (MIC) 0.5 µg/ml). Vancomycin was continued with regular monitoring of trough levels. The patient's fever gradually settled, and a repeat blood culture after 7 days of therapy was negative. There were no clinical signs suggestive of complicated bacteraemia and the patient was discharged after 14 days of vancomycin therapy. He has since started ART and remains well 6 months later.

Case 2

A 50-year-old HIV-positive man receiving first-line ART (tenofovir, lamivudine and efavirenz) presented to hospital with a 3-week history of headache, vomiting and blurred vision. He was diagnosed with CM following lumbar puncture

Fig. 1. Cross-sectional computed tomography (CT) of the anterior chest (case 2). A lytic lesion in the sternum and overlying soft tissue mass is marked by the red oval. A needle aspirate of the collection grew methicillin-resistant Staphylococcus aureus *(MRSA), as did 3 blood cultures. Limited views of the lungs showed multiple lesions highly suggestive of septic pulmonary emboli (not shown here).*

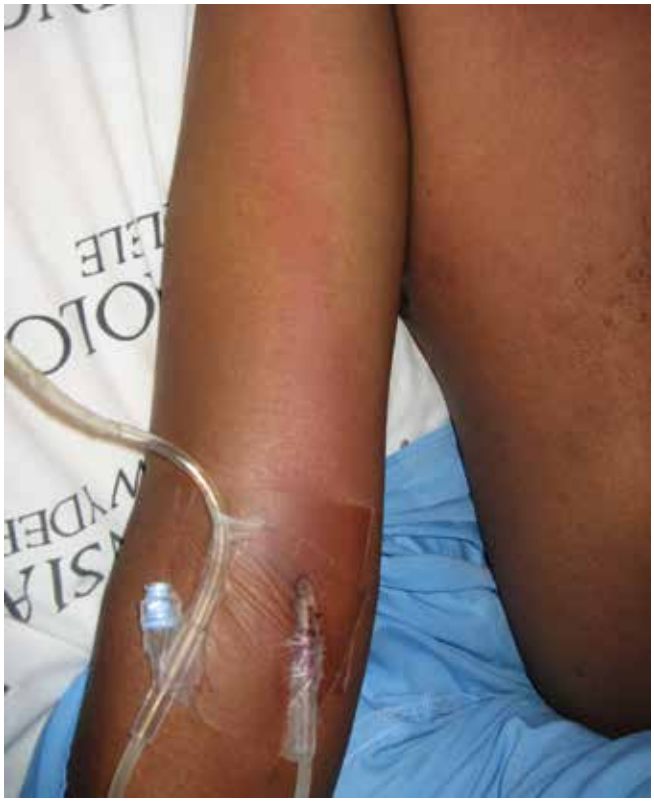

Fig. 2. 'Chemical' phlebitis complicating amphotericin B infusion (photograph courtesy of Dr T A Bicanic). This inflammation occurred during the 4-hour amphotericin B infusion and presented as redness and tenderness tracking up the cannulated vein. In such cases, the cannula should be removed once the infusion is completed and the site monitored closely for infection and the patient for fever. This is not an indication for immediate antibiotics.

(positive India ink, cryptococcal antigen test and culture) and treated with 1 mg/kg/day amphotericin B (IV) and 800 mg/day fluconazole (oral). Two weeks after discharge, he was seen in the infectious diseases clinic. Deemed to have failed first-line ART ($CD4^+$ count 2×10^6 cells/l, HIV viral load 60 414 copies/ml), he was switched to zidovudine, lamivudine and ritonavir-boosted lopinavir. He re-presented a further 3 weeks later with a recurrence of meningeal symptoms. Lumbar puncture was performed and raised intracranial pressure was noted (opening pressure 33 cmH_2O). Amphotericin B was re-started, but discontinued after 7 days when cerebrospinal fluid fungal cultures showed no growth. The patient was diagnosed with CM immune reconstitution inflammatory syndrome (CM-IRIS) and treated with 90 mg/day prednisone, with good resolution of symptoms. During both admissions, phlebitis was noted at amphotericin infusion sites, but this settled following removal of the cannula.

When seen in the outpatient clinic 2 weeks after his admission for IRIS, he complained of a 5-day history of fever and rigors. On examination, there was a tender, fluctuant mass over the inferior part of his sternum, but no signs of infection around any of his previous cannula sites. *S. aureus* was identified from a blood culture and needle aspirate of the mass; IV vancomycin was commenced pending sensitivities. A computed tomography (CT) scan of his chest revealed lytic destruction of the caudal end of the sternum with an adjacent soft-tissue collection (34 × 28 × 15 mm) (Fig. 1). Lung lesions suggestive of multiple septic emboli were also noted. A transthoracic echocardiogram showed no evidence of endocarditis, and a bone scan revealed no other areas of bone involvement. Antibiotic susceptibility testing demonstrated methicillin resistance, but susceptibility to vancomycin (MIC 1 µg/ml).

Incision and drainage of the chest wall abscess was performed and vancomycin was continued, but with little clinical improvement. Repeat blood cultures after 7 days of therapy remained positive for MRSA, and despite treatment, he deteriorated with ongoing fevers and worsening renal and respiratory failure. He died a week thereafter.

Discussion

S. aureus bacteraemia is a serious infection with significant associated mortality. The organism is highly pathogenic and should never be assumed to be a blood culture contaminant, even in a patient who appears systemically well. The infection seeds haematogenously to distant organs in approximately 40% of cases, leading to endocarditis, septic arthritis, osteomyelitis and other deep-tissue abscesses.[4] The second case presented here is an illustration of this.

In the cases described, both patients developed MRSA bacteraemia during, or shortly after treatment for CM; the likely portal of entry being peripheral venous cannulae used to administer amphotericin B and IV fluids. In the first case, the bacteraemia was accompanied by obvious signs of infection at a cannula site. In the second, no evidence of localised infection was found at the time of bacteraemia, but phlebitis (attributed to amphotericin B) had been noted during the recent admission.

Although studies from North America report the risk of blood-stream infection (BSI) associated with peripheral IV devices to be low (0.5 BSI/1 000 IVD days),[5] the risk could be higher in the SA setting, especially in this vulnerable group of patients, with advanced HIV infection receiving prolonged IV amphotericin B therapy.

Diagnosing bacterial infection at IV cannula sites in patients with CM can be difficult, especially given the frequent chemical phlebitis

seen following amphotericin B administration (Fig. 2). Both chemical and infective phlebitis result in erythema and pain, and in our experience, infective phlebitis may occur as a complication at the site of chemical phlebitis. Fever and systemic upset, or the presence of pus at the cannula site, are very suggestive of bacterial infection and should be investigated further. Blood cultures should be taken prior to the use of any antibiotics, and swabs sent for investigation if any exudate or pus is present.[6] In the absence of these features, it is reasonable to remove the cannula, elevate the limb, apply ice and observe. Bacterial infection should be considered if there is no significant improvement in 24 hours, or it there is an expanding area of cellulitis.

If signs of systemic infection are present, then once blood cultures are taken, empirical IV antibiotic therapy should be commenced. Antibiotic choice should ensure adequate coverage of *S. aureus*.[6] Given the high rates of methicillin resistance among nosocomially acquired isolates in SA (30 - 60%),[7,8] IV vancomycin should be used until microbiology results are available. If blood cultures are negative, antibiotics can be stopped after 5 days.

If blood cultures are positive for *S. aureus,* then more prolonged antibiotic treatment is required. The Infectious Diseases Society of America (IDSA) recommends treating *uncomplicated* MRSA bacteraemia for at least 2 weeks with IV vancomycin, with target trough levels of 15 - 20 µg/ml. Due to high rates of unrecognised endocarditis, the IDSA recommends echocardiography in all patients – an impractical option in many SA settings.

A pragmatic approach is to risk stratify patients by taking repeat blood cultures after 2 - 4 days of antibiotic therapy. Patients with no implantable prostheses, no clinical evidence of endocarditis or metastatic infection, who have a negative repeat blood culture and resolution of fever within 72 hours of initiating effective therapy, can be treated for 2 weeks with IV vancomycin (monitoring trough levels and creatinine). Patients at high risk of complicated infection, such as those with prosthetic cardiac material, should be investigated with echocardiography (transoesophageal is preferred over transthoracic). If neither is available, high-risk patients should be treated as having complicated bacteraemia, with careful clinical follow-up to exclude a relapse of infection or complications of prosthetic-valve endocarditis.

Patients with persistent fevers, positive repeat blood cultures or clinical features suggestive of metastatic infection, should be considered as complicated cases and investigated for endocarditis, osteomyelitis and deep-tissue abscesses.[4,9,10] The management of *complicated* MRSA bacteraemia should be discussed with an expert wherever possible. Surgery may be required to drain an abscess or remove a focus of infection, and antibiotic therapy should continue for approximately 4 - 6 weeks depending on the extent of the infection and response to treatment.[10]

With regard to patients with CM, it is important that clinicians are aware of this additional complication of amphotericin B treatment. Cannula sites should be monitored regularly and any patient who develops a new fever should be evaluated carefully for signs of drip-site-related infection.

Finally, efforts should be made to reduce the incidence of nosocomial infections as a whole, through increased emphasis on infection-control practices such as handwashing and aseptic technique. Although it is now more than 100 years since the pioneering work of Semmelweis, his lessons remain pertinent today.

Acknowledgement. We are grateful to Prof. G Maartens for critical review of the manuscript and Dr T A Bicanic for the photograph in Fig. 2.

References

1. Perfect JR, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the infectious diseases society of america. Clin Infect Dis 2010;50(3):291-322.
2. Govender N, Meintjes G, Bicanic T, et al. Guideline for the prevention, diagnosis and management of cryptococcal meningitis among HIV-infected persons: 2013 update. Southern African Journal of HIV Medicine 2013;14(2):76-86.
3. Sawaya BP, Briggs JP, Schnermann J. Amphotericin B nephrotoxicity: The adverse consequences of altered membrane properties. J Am Soc Nephrol 1995;6(2):154-164.
4. Fowler VG, Olsen MK, Corey GR, et al. Clinical identifiers of complicated Staphylococcus aureus bacteremia. Arch Intern Med 2003;163(17):2066-2072.
5. Maki DG, Kluger DM, Crnich CJ. The risk of bloodstream infection in adults with different intravascular devices: A systematic review of 200 published prospective studies. Mayo Clin Proc 2006;81(9):1-13.
6. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis;49(1):1-45.
7. Bamford C, Bonorchis K, Elliott E, et al. Antimicrobial susceptibility patterns of selected bacteraemic isolates from South African public sector hospitals, 2010. Southern African Journal of Epidemiology and Infection 2011;26(4):243-250.
8. Shittu AO, Lin J. Antimicrobial susceptibility patterns and characterization of clinical isolates of Staphylococcus aureus in KwaZulu-Natal province, South Africa. BMC Infect Dis 2006;6(1):125.
9. Kaasch AJ, Fowler VG, Rieg S, et al. Use of a simple criteria set for guiding echocardiography in nosocomial *Staphylococcus aureus* bacteremia. Clin Infect Dis 2011;53(1):1-9.
10. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. Clin Infect Dis 2011;52(3):e18-e55.