



Case report

Staphylococcus haemolyticus meningitis and bacteremia in an allogenic stem cell transplant patient



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ABSTRACT

Staphylococcus haemolyticus is a rare cause of bacterial meningitis and most commonly occurs as a nosocomial infection in patients' post-neurosurgery. We report a patient post-allogenic stem cell transplant, with no prior history of neurosurgical procedures, who developed *S. haemolyticus* meningitis and bacteremia following central catheter-related bloodstream infection. The patient failed therapy with vancomycin and daptomycin but was successfully treated with a prolonged course of linezolid. We review the pharmacological management of coagulase negative *Staphylococcus* (CoNS) meningitis, with a focus on the pharmacokinetic properties of vancomycin, daptomycin and linezolid within the cerebrospinal fluid (CSF).

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Introduction

Staphylococcus haemolyticus is a coagulase negative Staphylococcus (CoNS) and common skin colonizer. *S. haemolyticus* can cause nosocomial meningitis in association with neurosurgical device implantation or traumatic brain injury [1–3]; however, CoNS are an extremely rare cause of bacterial meningitis in adult patients without history of traumatic or iatrogenic disruption to the blood-brain barrier. Here, we present an immunosuppressed, post-allogenic stem cell transplant patient without significant neurosurgical history, who presented with *S. haemolyticus* meningitis and persistent bacteremia. We review the pharmacological management of *S. haemolyticus* and CoNS meningitis, with a focus on the pharmacokinetic properties of vancomycin, daptomycin and linezolid within the cerebrospinal fluid (CSF).

Case presentation

The patient, a 42-year old woman, presented to the Emergency Department with a one-week history of increasing lethargy and musculoskeletal pains. Her medical history was significant for HLA (Human Leukocyte Antigen) identical sibling donor allogeneic stem

cell transplant 98-days prior to presentation. The patient was febrile to 38 °C with neck stiffness, photophobia and sluggish pupils. She had no intravenous catheters or prosthetic devices and no other focus of infection was identified on clinical examination. Laboratory examination revealed a neutrophil count of $9.5 \times 10^9/L$ and normal creatinine (48 $\mu\text{mol/L}$). A midstream urinalysis and culture did not identify evidence of urine infection. Her chest radiograph was unremarkable. Early hydrocephalus was present on brain computed tomogram (CT). Cerebrospinal fluid parameters were consistent with bacterial meningitis with 1370×10^6 nucleated cells and 94% polymorphs (Table 1). A Gram stain of CSF revealed gram positive cocci; cultures subsequently grew *S. haemolyticus*.

The patient had been diagnosed with poor-risk acute myeloid leukemia (AML) six months previously and had achieved a complete remission following induction treatment with Fludarabine, Cytarabine (Ara-C), Granulocyte-Colony Stimulating Factor and Idarubicin (FLAG-IDA) chemotherapy. Her second cycle of FLAG-IDA was complicated by neutropenic fever with *S. haemolyticus* isolated from multiple peripheral and catheter blood cultures over a 72 h period. The isolate was reported susceptible to vancomycin (Mean Inhibitory Concentration (MIC) = 2 mg/L) and resistant to penicillin, erythromycin and flucloxacillin on disc testing (Table 2). Central venous catheter associated line infection was suspected as the source. The patient's peripherally inserted central catheter (PICC) was removed and she received a 7-day course of intravenous vancomycin. Four days after completing therapy, neutropenic fever

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Table 1
Collated cerebrospinal fluid (CSF) analysis. Day 0 represents the day of presentation. The patient started linezolid on Day 24 and completed 28 days of therapy on Day 52.

Days post-admission	Day 0	Day 22	Day 29	Day 36	Day 57	Day 64
Nucleated Cells ($\times 10^6$)	1370	155	12	1	7	6
RBC ($\times 10^6$)	< 1	3	7	2	< 1	< 1
Polymorphs	94%	95%	75%	13%	34%	3%
Protein (g/L)	2.16	0.58	0.78	0.55	0.42	0.41
Glucose (mmol/L)	0.6	< 0.5	1.6	2.3	2.4	2.5
Culture	<i>S.haemolyticus</i>	<i>S.haemolyticus</i>	No growth	No growth	No growth	No growth

returned and blood cultures again repeatedly isolated *S. haemolyticus*. Investigations including transthoracic echocardiogram, whole-body Magnetic Resonance Imaging (MRI) and CT of the chest, abdomen and pelvis did not reveal a source for bacteremia. She remained bacteremic for 3 days with sterilization of blood cultures following line removal. Vancomycin was continued for 14 days with a good clinical response.

Three weeks later, the patient underwent myeloablative allogeneic peripheral blood stem cell transplant with cells donated from an HLA-identical sibling sister. Prophylactic therapy with valganciclovir, cotrimoxazole and fluconazole was commenced post-transplant in line with local protocols. Successful engraftment was achieved albeit with slow count recovery. The patient had been monitored closely for 2 months in the outpatient setting and appeared to be progressing well until her deterioration and admission with meningitis.

Following the diagnosis of *S. haemolyticus* meningitis, treatment with vancomycin was resumed. Whilst her neurological status improved, symptomatic fevers continued. *S. haemolyticus* was isolated repeatedly from daily blood cultures. The isolate remained susceptible to vancomycin (MIC = 2 mg/L). After 6 days with minimal clinical response, vancomycin was discontinued and intravenous daptomycin 500 mg every 24 h (8 mg/kg) was initiated. The patient remained persistently bacteremic over a 19-day period despite treatment with daptomycin and multiple peripherally inserted central catheter changes. MRI of the brain and spine, CT pulmonary angiogram, CT abdomen and whole-body positron emission tomography showed no focus of infection. Transesophageal echocardiogram did not demonstrate vegetations.

After 17 days of persistent bacteremia, lumbar puncture was repeated (Table 1) demonstrating 155 nucleated cells (95% polymorphs). CSF cultures again grew *S. haemolyticus*. At this point all intravenous catheters were removed. Daptomycin was discontinued and the patient was commenced on oral linezolid 500 mg every 12 h. The patient subjectively improved and fevers ceased after 48 h of linezolid therapy. Five days later, CSF demonstrated improving pleocytosis (Table 1) and was culture negative. The patient was discharged and completed a 28-day course of linezolid with weekly outpatient follow-up for symptomatic review, lumbar puncture and blood cultures. She tolerated the therapy well with no adverse effects reported. Repeat CSF sampling exhibited improving parameters and all subsequent blood cultures remained sterile. One year following discharge, the patient remains well and has returned to full time work.

Discussion

S. haemolyticus is a coagulase negative Staphylococcus and predominately an innocuous skin colonizing organism. CoNS, such as *S. haemolyticus*, may be implicated as nosocomial pathogens in device-related infections and can cause bacteremia in patients with chemotherapy-induced neutropenia [1]. CoNS are an uncommon cause of bacterial meningitis, occurring predominately when there is disruption of protective central nervous system (CNS) structures such as in traumatic brain injury [3,4] or craniotomy. CoNS form biofilms and are often implicated in neurosurgical device associated

meningitis and ventriculitis [2]. *S. haemolyticus* has been described as a causative pathogen in both neonatal meningitis and device related meningitis [2] however, to our knowledge, this is the first reported case of *S. haemolyticus* meningitis in adult patient without history of neurosurgery. The patient's initial bacteremia, prior to transplant, occurred in the context of central line infection and immunosuppression. The subsequent *S. haemolyticus* meningitis presumably occurred secondary to haematogenous spread. It is unusual the patient remained asymptomatic for almost 4 months, particularly whilst extensively immunosuppressed. It was strongly suspected that a persisting nadir of infection, such as an infected thrombus was present however this could not be identified on extensive investigations.

Due to their rarity, the majority of literature pertaining to treatment of CoNS meningitis relates to nosocomial neurosurgical device infection and resultant meningitis or ventriculitis. In this setting, good treatment outcomes have been described with a combination of device removal and intravenous vancomycin (median 12.5 days duration post-device removal) [2]. In patients without a neurosurgical device, and therefore no option for source control, descriptions of treatment are limited to case reports [4]. Successful management of a patient with *Staphylococcus epidermidis* bacteremia and meningitis on a background of AML, and no history of neurosurgery, was achieved with a 39-day course of intravenous vancomycin and oral rifampin [5].

Antimicrobial management of CoNS meningitis is further complicated by a propensity towards intrinsic or acquired beta-lactam resistance. Vancomycin, a glycopeptide antibiotic, is frequently used as a first-line agent in CoNS meningitis [2,6] but was ultimately unsuccessful in curing our patient. The vancomycin MIC for the *S. haemolyticus* isolate was 2 $\mu\text{g}/\text{mL}$, suggestive of susceptibility as per European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria, although close to the 4 $\mu\text{g}/\text{mL}$ breakpoint [7]. The MIC remained stable during subsequent bacteremia suggesting acquisition of drug resistance is unlikely (Table 2). While vancomycin was an appropriate antimicrobial during initial bacteremia, if occult seeding to the CNS had occurred, the target 24 h area under the concentration-time curve (AUC₂₄) may not have been adequate for CSF sterilization. Indeed, IDSA guidelines for Healthcare-Associated Ventriculitis and Meningitis recommend considering an alternative antimicrobial if the vancomycin MIC is $\geq 1 \mu\text{g}/\text{mL}$ [6]. Vancomycin is thought to penetrate poorly across the blood brain barrier due to its large mass and hydrophilic properties. Inflammation of the meninges during acute meningitis may enhance penetration but this appears highly variable between patients with a recent systematic review reporting serum to CSF penetration ratios between 6% and 81% [8].

We utilized therapeutic drug monitoring (TDM) of vancomycin through each treatment course with a target trough level of 15–20 mg/L and intermittent bolus administration. Dosing was calculated using Nextdose software, a web-based Bayesian forecasting dose optimization tool with a target AUC of 400–600 $\mu\text{g}/\text{mL}$. During the second episode of bloodstream infection, a supratherapeutic trough level (27.5 mg/L) was recorded after 48 h of therapy resulting in dose reduction. Persistently subtherapeutic trough levels (4.3–8.7 mg/L) were then subsequently recorded through treatment

Table 2
Susceptibility profiles of *S. haemolyticus* in CSF and blood cultures during recurrent episodes of bacteremia.

	Peripheral blood cultures								CSF	
	1st episode		2nd episode		3rd episode				3rd episode	
	Day 1	Day 3	Day 1	Day 3	Day 5	Day 8	Day 16	Day 24	Day 0	Day 22
Penicillin	R	R	R	R	R	R	R	R	R	R
Erythromycin	R	R	R	R	R	R	R	R	R	R
Doxycycline	S	S	S	S	S	S	S	S	S	S
Vancomycin	S ^a	S	S ^a	S	S	S ^a	S	S	S	S
Daptomycin							S ^b	R		
Linezolid							S			S ^c
Ciprofloxacin							R			
Cotrimoxazole							R			
Gentamicin							R			
Rifampicin							S			

Abbreviations: R = resistant, S = susceptible. S^a = MIC performed = 2 mg/L (Susceptible), S^b = MIC performed = 0.06 mg/L (Susceptible), S^c = MIC performed = 1.0 mg/L (Susceptible).

despite dose modifications. This could have precipitated the development of an occult CNS nadir of infection potentiated by patient immunosuppression. During the 6 days of treatment for meningitis, trough levels ranged from 8.6 to 20.9 mg/L.

Daptomycin, a lipopeptide antibiotic effective against a wide variety of gram-positive bacteria, also failed to achieve *S. haemolyticus* clearance despite a favorable MIC of 0.06 µg/mL. This agent is recommended as a potential second line agent for staphylococcus meningitis at a dose of 6–10 mg/kg when vancomycin cannot be used [6]. There is minimal literature on the effectiveness of daptomycin in meningitis however, its large molecular size and high protein-binding would indicate CSF penetration is likely limited [9]. This was supported in a clinical pharmacokinetic study by Piva et al. which estimated plasma daptomycin to CSF penetration of 0.45% in patients with ventriculostomy associated meningitis [10]. Daptomycin may act synergistically with rifampicin, this combination has been described in case reports of enterococcus and methicillin resistant *Staphylococcus aureus* (MRSA) device-associated meningitis [11]. However, there is minimal literature on the efficacy of this combination and no specific studies in CoNS meningitis [1] or in those without indwelling devices.

Linezolid, a predominately bacteriostatic antimicrobial of the oxazolidinone class, achieves much higher levels of CSF penetration than daptomycin with a CSF to serum penetration of around 66% [12]. A retrospective case series by Sipahi et al. [13] regarding utilization of linezolid in multi-resistant staphylococcus post-neurosurgical meningitis reported microbiological clearance of 8 of 9 patients with multi-resistant CoNS meningitis treated with linezolid twice daily for 18–21 days. Of note, all patients achieving clearance had sterile CSF samples after 5 days of treatment. Linezolid has excellent oral bioavailability making it an attractive choice. Relative success of linezolid therapy has also been reported in a small retrospective analysis of *S. aureus* meningitis by Pintado et al. [14]. The authors conclude no significant difference in mortality from use of linezolid when compared to vancomycin (MRSA) or cloxacillin (methicillin susceptible *S. aureus*) as well as a favorable side effect profile. The duration of treatment for healthcare-associated meningitis as per IDSA is recommended as 10–14 days after the last positive culture [6]. We elected to extend to 28 days due to ongoing concern of an unidentified infected thrombus as a focus.

Conclusion

In conclusion, this is the first reported case of *S. haemolyticus* meningitis in an adult patient without history of neurosurgical device implantation. A number of factors may have resulted in a poor clinical response to vancomycin, the most commonly indicated antimicrobial for CoNS CNS infection. However, it is notable that an extended course of daptomycin also failed to eradicate bloodstream

infection or meningitis despite microbiological evidence of susceptibility. A rapid and sustained bacterial clearance was achieved with 28-days of linezolid treatment which appears to be a promising candidate for the treatment of *S. haemolyticus* meningitis.

Authors statement

AB wrote the initial draft of the case report and performed the literature search. Both RH and RD were involved in the patients care and reviewed and edited the final manuscript.

Declaration of Competing Interest

The authors declare that they have no competing interests. Verbal and written consent has been provided by the patient for publication of this case report.

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