Leukemia Research Reports 15 (2021) 100254

Contents lists available at ScienceDirect

Leukemia Research Reports

journal homepage: www.elsevier.com/locate/lrr

Fatal infection with enterocolitis from methicillin-resistant *Staphylococcus aureus* and the continued value of culture in the era of molecular diagnostics

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ARTICLE INFO

Keywords:
Staphylococcus aureus
Enterocolitis
Immunocompromised
Stool cultures

ABSTRACT

MRSA enterocolitis is under-recognized in the setting of PCR testing. In this case report, we describe risk factors, the importance of stool culture, and the third published case of MRSA enterocolitis in a patient with leukemia. In addition, we performed a retrospective analysis of all stool cultures at our institution that have grown *Staphylococcus aureus*, and we describe an additional five cases. We also report the diagnostic yield of organisms detected by culture, but not on the FilmArray panel. While rare, these cases demonstrate that MRSA in stool may indicate a severe and potentially life-threatening infection, particularly in immunocompromised persons.

1. Introduction

Confirmed fatal infection with enterocolitis from methicillin resistant *Staphylococcus aureus* (MRSA) has rarely been reported in the US. The present case demonstrates the importance of recognizing MRSA as a potential pathogen in the setting of neutropenic enterocolitis during induction chemotherapy and the continued importance of stool culture in the era of molecular diagnostics.

2. Case report

A 72-year-old man with a history of clinically quiescent Crohn's disease presented to the emergency department with fever, fatigue, altered mental status, and nausea/vomiting four days after a new diagnosis of acute myelogenous leukemia (AML) (Fig. 1**A**). He had tumor lysis syndrome with acute kidney injury (AKI) and hyperleukocytosis and required intensive care unit (ICU) admission. Given the initial diagnostic uncertainty regarding whether his multi-organ failure was related to tumor lysis or infection, he was also treated empirically with ceftazidime and vancomycin for possible septic shock. Antibiotic infusions were separated by over 12 h so that co-mixing was avoided [1]. Blood and urine cultures were sterile. Computed tomography (CT) of the chest, abdomen, and pelvis was unremarkable. He became neutropenic after cytoreductive therapy with hydroxyurea and cytarabine, and defervesced after receiving dose-reduced G-CLAM (filgrastim, cladribine, cytarabine, and mitoxantrone). Ceftazidime was continued for neutropenic prophylaxis, and vancomycin was stopped given the lack of evidence for active infection. Five days later, he again fevered. The following day, he reported mild abdominal pain and new diarrhea. In the setting of febrile neutropenia, an enteric pathogen panel was obtained. This panel consisted of a rapid PCR using the Biofire FilmArray GI panel for 13 bacteria, 4 parasites, and 5 viruses, plus a blood agar plate, primarily for the detection of *Aeromonas* spp. Reflexive susceptibility testing for *Salmonella, Campylobacter, Shigella,* and *Vibrio* species is performed if these organisms are detected on the PCR panel. No pathogens were detected by PCR, and loperamide was started. Two days later, the blood agar plate showed 4+ MRSA with reduced normal fecal flora (Fig. 1**B and C**). Due to his profound immunocompromised status,

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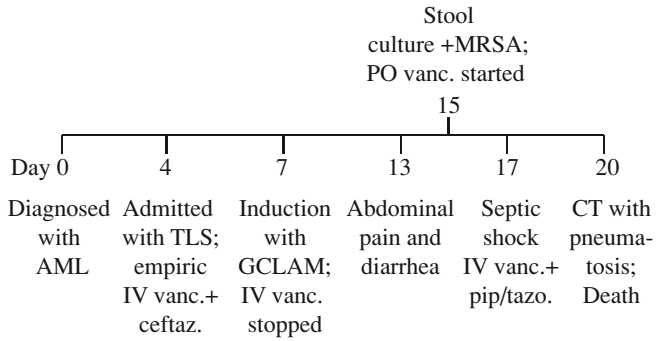
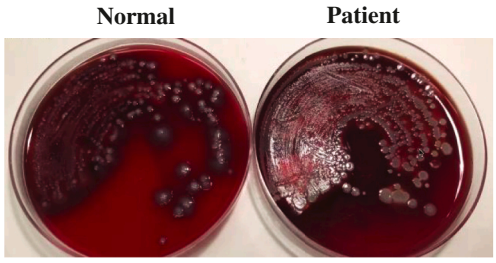
https://doi.org/10.1016/j.lrr.2021.100254
Received 4 January 2021; Received in revised form 15 April 2021; Accepted 23 May 2021
Available online 24 May 2021

A.



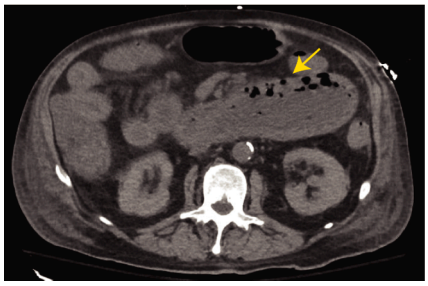
B.



C.

Antibiotic	Microtiter MIC Interpretation	Microtiter MIC Value (mcg/mL)
Clindamycin	S	<=0.5
Daptomycin	S	<=0.5
Erythromycin	R	>4
Levofloxacin	R	>4
Moxifloxacin	R	4
Oxacillin	R	>2
Tetracycline	S	<=2
Trimethoprim - Sulfamethoxazole	S	<=2
Vancomycin	S	1

D.



E.

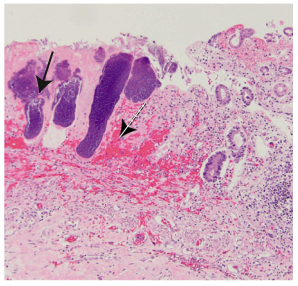


Fig. 1. Clinical, microbiologic, radiographic, and histopathologic findings in a case of MRSA enterocolitis. (A) Timeline of the clinical course from diagnosis to death. (B) Stool cultures from a healthy individual (left) and from the patient (right) showing yellow colonies surrounded by hemolysis. (C) Antibiotic susceptibility testing of the *Staphylococcus aureus* isolate. (D) CT scan of the abdomen with the yellow arrow indicating an area of pneumatosis. (E) Postmortem histopathology of small bowel mucosa. The black arrow points to an area of Gram-positive cocci. The dotted arrow points to an area of submucosal necrosis and hemorrhage. Abbreviations: IV, intravenous; PO, oral; Vanc, vancomycin; Pip/tazo, piperacillin/tazobactam; MIC, minimum inhibitory concentration; AML, acute myeloid leukemia; CT, computed tomography; GCLAM, filgrastim, cladribine, cytarabine, and mitoxantrone; MIC, minimum inhibitory concentration; MRSA, methicillin resistant *Staphylococcus aureus*; TLS, tumor lysis syndrome.

oral vancomycin was started for possible MRSA enterocolitis. Gram-negative and anaerobic coverage was also broadened to piperacillin-tazobactam. The following day, he developed respiratory distress, was intubated, and had recurrence of AKI and shock. Vancomycin IV was added. CT of the abdomen and pelvis showed diffuse small bowel wall edema, thickening, dilatation measuring up to 6.2 cm, and pneumatosis without pneumoperitoneum (**Fig. 1D**). No surgical interventions were available, and the patient was transitioned to comfort care, expiring that same day. Postmortem evaluation revealed gross dilatation of the duodenum and jejunum with dusky discoloration, mucosal erythema and congestion, and Gram positive cocci (**Fig. 1E**). Focal mucosal erosions were noted in the stomach and cecum. No pseudomembranes were found. Cause of death was attributed to septic shock with multiorgan failure, secondary to MRSA enterocolitis.

3. Discussion

Staphylococcus aureus enterocolitis has been recognized as a cause of antibiotic associated colitis since the mid-20th century[2]. However, when attention shifted to *Clostridioides difficile* as the major infectious cause for antibiotic-associated diarrhea, reports of *Staphylococcus aureus* enterocolitis in English scientific literature declined, and awareness diminished. *Staphylococcus aureus* is now often disregarded when isolated from stool culture [3]. Most recent reports published on *Staphylococcus aureus* enterocolitis have been from Japan [2–4]. These and other reports identified gastric resection, older age, longer hospitalization, intestinal carriage, and prior antibiotic exposure as risk factors for *Staphylococcus aureus* enterocolitis [5–7].

Table 1
Organisms recovered from blood agar, not detected by Biofire FilmArray (7/2018–6/2020).

Organism group	N (%)*	Comments
Aeromonas spp.	30 (0.42%)	*A. caviae* ($N = 7$) *A. hydrophila* ($N = 8$) *A. veronii* ($N = 10$) Not determined ($N = 5$)
Bacillus spp.	7 (0.10%)	
Beta hemolytic streptococci	4 (0.06%)	
Pseudomonas spp.	38 (0.53%)	
Staphylococcus aureus	4 (0.06%)	
Grimontia hollisae	1 (0.01%)	
Fungi	112 (1.56%)	*Aspergillus fumigatus* ($N = 2$) *Mucorales* ($N = 3$) Yeast ($N = 107$)

* Percent is out of $N = 7179$ total enteric panels performed.

Patients with hematologic malignancies are also at risk for neutropenic enterocolitis and *Clostridioides difficile* infection (CDI) due to cytotoxic chemotherapy and antibiotic exposure, but reports of MRSA enterocolitis are rare [8,9]. Although targeted and less cytotoxic therapies against AML are being increasingly studied, intestinal complications, including neutropenic enterocolitis, remain problematic [10–13]. To our knowledge, there are only three cases of MRSA enterocolitis in the setting of acute leukemia reported in the literature. This is possibly due to underdiagnosis as stool cultures are not often obtained and now supplanted by PCR testing [14,15]. While our laboratory utilizes a blood

Table 2
Review of *Staphylococcus aureus* positive stool cultures from 1/2014–10/2020*.

Age group (years)	Biofire	Discharge diagnosis by clinician	Comorbidities during diagnosis	Imaging	Antibiotics	Outcome
5–10	Norovirus	Norovirus	none	none	none	Outpatient
20–29	Negative	Laxative-induced	none	none	none	Outpatient
30–39	Negative	Neutropenic enterocolitis (*S. aureus* not contributory)	Relapsed metastatic neuroblastoma status-post autologous hematopoietic stem cell transplant complicated by febrile neutropenia	CT: small bowel thickening	Vancomycin IV, cefepime IV, metronidazole IV	Discharged home with resolution
30–39	*Campylobacter*	*Campylobacter*	none	none	Azithromycin	Outpatient
30–39	Negative	Laxative-induced	Diabetic ketoacidosis, Staphylococcus aureus bacteremia complicated by epidural abscess and sepsis	none	Vancomycin IV	Discharged home with resolution
50–59	Negative	Neutropenic enterocolitis (*S. aureus* not contributory)	Myelodysplastic syndrome status-post allogeneic hematopoietic stem cell transplant complicated by febrile neutropenia	CT: small bowel thickening	Vancomycin IV, cefepime IV, metronidazole IV	Discharged home with resolution
70–79	Negative	Neutropenic enterocolitis (attributed to *S. aureus*)	Acute myelogenous leukemia status-post induction chemotherapy complicated by febrile neutropenia, clinically quiescent Crohn's disease	CT: small bowel thickening and dilatation, pneumatosis	Piperacillin-tazobactam, vancomycin IV, vancomycin PO	Died of septic shock secondary to MRSA enterocolitis with severe neutropenia

* Cultures obtained at the University of Washington Medical Center and Seattle Cancer Care Alliance.

agar plate primarily for the detection of *Aeromonas* species, we report the presence of other organisms of unclear pathogenic potential if they are predominant in the culture (Table 1). Interdisciplinary discussion between the microbiology lab and clinical teams can be helpful in determining if MRSA enterocolitis, in the absence of other more common enteric pathogens, fits with the clinical presentation.

Inflammatory bowel disease and other gastrointestinal disorders have been associated with *Staphylococcus aureus* intestinal carriage [16]. In this case, Crohn's disease may have played a role in the development of MRSA enterocolitis [17]. This, coupled with chemotherapy, neutropenia, and antibiotic exposure may have predisposed to mucosal damage and dysbiosis allowing for MRSA overgrowth and enterotoxin susceptibility [4,18,19]. Although MRSA enterocolitis can present similarly to CDI, it more frequently affects the small bowel, is associated with fever and vomiting, results in more profuse diarrhea, and mucosal invasion is often observed on histopathology [4,20]. It can be difficult to clinically discern whether a positive stool culture for MRSA is due to colonization or disease, but, in this case, a postmortem examination confirmed the histopathologic diagnosis of MRSA enterocolitis, demonstrating the continued importance of autopsy to understand infectious diseases.

Gut microbiome analyses have shown that molecular signatures of baseline microbial diversity might be predictive of infectious risk following induction therapy for AML [21]. Although a comprehensive 16 s rRNA analysis of the gut microbiome was not performed prior to induction chemotherapy, data from the stool culture, which is an assay widely available to clinicians, showed overgrowth of MRSA that was likely a risk factor for invasive disease and sepsis. MRSA enterocolitis is underrecognized and should be considered in patients with hematologic malignancies, particularly those with severe or prolonged antibiotic associated diarrhea, neutropenic enterocolitis, and negative CDI testing [5,20]. Stool cultures can be used to diagnose this rare entity since many commercially available enteric PCR panels do not detect *S. aureus*. In reviewing stool cultures accompanying the Biofire enteric panel at our institution from January 2014 to October 2020, only seven were positive for *S. aureus*, including the case described (Table 2). Three cases involved immunocompromised hosts with malignancies. At the time of the stool cultures, only one patient (this case) was thought to have *S. aureus* enterocolitis, but in retrospect, it is possible that this entity may have contributed to febrile neutropenia in the other two immunocompromised patients. *S. aureus* was likely a colonizer in the other cases. All patients except for the case described recovered. Together, these results demonstrate that *S. aureus* is rarely found in the stool as the predominant organism. However, its presence can indicate either colonization or infection, with immunocompromised hosts being more likely to suffer from severe disease.

In a review of the literature on MRSA enterocolitis, therapy with oral vancomycin is recommended [3,4,20,22]. In our case, at the time of diagnosis and initiation of oral vancomycin, disease was already severe with evidence of pneumatosis. MRSA enterocolitis has been most frequently described in immunocompetent patients [22], and further studies of its role in hematologic malignancy patients with antibiotic associated diarrhea or neutropenic enterocolitis is needed. Non-classic stool pathogens, particularly MRSA, should not be universally disregarded as colonization. These cases demonstrate that MRSA can be a rare cause of neutropenic enterocolitis in patients with hematologic malignancies after induction chemotherapy and demonstrates the continued utility of stool culture in the era of molecular diagnostics.

Funding

This work was supported by the Fred Hutchinson Joel Meyer's Endowment (J.B.), a new investigator award from the American Society for Transplantation and Cell Therapy (J.B.), and the Host Defense Training in Allergy and Infectious Diseases 5T32AI007044–45 (V.A.).

CRediT authorship contribution statement

Pooja Bhattacharyya: Data curation, Writing – original draft. **Andrew Bryan:** Data curation, Writing – original draft, Formal analysis. **Vidya Atluri:** Writing – original draft. **Jimmy Ma:** Writing – original draft. **Lindsey Durowoju:** Formal analysis. **Anshu Bandhlish:** Formal analysis. **Jim Boonyaratanakornkit:** Data curation, Writing – original draft.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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