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Chromobacterium Violaceum Sepsis: Rethinking Conventional Therapy to Improve Outcome

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Patient: Male, 11
Final Diagnosis: Chromobacterium violaceum infection
Symptoms: Abscess • fever • rash
Medication: —
Clinical Procedure: ECMO
Specialty: Critical Care Medicine

Objective: Rare disease

Background: *Chromobacterium violaceum* (*C. violaceum*) is a facultative anaerobic gram-negative bacterium found in soil and water, especially in tropical and subtropical areas. Although infection in humans is rare, it is associated with significant morbidity. The bacterium is known for its resistance to multiple antimicrobials, and the possibility of relapse and reinfection. Presence of bacteremia, disseminated infection, and ineffective antimicrobial agents are predictors of mortality.





Case Report: We report the case of a previously healthy 11-year-old male with *C. violaceum* sepsis who was exposed to stagnant water. He presented with severe septic shock and developed multi-organ system failure. Initial presumptive diagnosis was staphylococcal infection secondary to presence of skin abscesses resulting in antibiotic coverage with vancomycin, clindamycin, nafcillin and ceftriaxone. He also had multiple lung and liver abscesses. Once *C. violaceum* was identified, he received meropenem and ciprofloxacin, and was later discharged on ertapenem and trimethoprim-sulfamethoxazole (TMP-SMX) to complete a total of six months of antibiotics. He was diagnosed with chronic granulomatous disease (CGD) and is currently on prophylactic TMP-SMX and itraconazole. He has not had any relapses since his initial presentation.

Conclusions: This case highlights the importance of considering *C. violaceum* as a relevant human pathogen, and considering it early in temperate regions, particularly in cases of fulminant sepsis associated with multi-organ abscesses. Once *C. violaceum* is identified, appropriate antimicrobial therapy should be started promptly, and sufficient duration of treatment is necessary for successful therapy.

MeSH Keywords: Chromobacterium • Pediatrics • Sepsis • Drug Therapy

Abbreviations: *C. violaceum* – *Chromobacterium violaceum*; ECMO – extracorporeal membrane oxygenation; TMP-SMX – Trimethoprim-Sulfamethoxazole; CGD – chronic granulomatous disease; IV – intravenous (intravenously); PICU – pediatric intensive care unit; ARDS – Acute Respiratory Distress Syndrome; PO – oral (per os)

Full-text PDF: <http://www.amjcaserep.com/abstract/index/idArt/894509>

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Background

Chromobacterium violaceum (*C. violaceum*) is a facultative anaerobic bacterium that is prevalent in temperate climates of the United States and worldwide in soil and stagnant water [1–3]. The first case of *C. violaceum* infection in humans was reported in 1927 [1]. Although human infections are still rare, recent interest in the medical virulence of *C. violaceum* has emerged secondary to the severe morbidity and mortality associated with infection [4]. Patients with chronic granulomatous disease (CGD) are at increased risk for infection, because of their innate inability to perform oxygen metabolism [5]. Infection typically occurs during the summer months, and often results from an area of broken skin followed by hematogenous seeding [6–8].

Here, we discuss a case of *C. violaceum* sepsis associated with multiple organ abscesses in a child exposed to stagnant water. Despite rapidly progressive shock and development of multi-organ system failure, he survived his illness. He was successfully treated with use of appropriate antibiotics, and has not had relapse or any reinfection at the time of this case report. He was later diagnosed with CGD, and currently remains on prophylactic treatment.

Case Report

An 11-year-old male presented to a regional community hospital with gluteal abscesses. The only reported past medical history was a submental abscess at age two that was drained, and resolved without further treatment. Prior to this hospitalization, he had no other symptoms, including the absence of fever, rash, myalgia and lethargy. The parents reported that recently the patient had been in areas of stagnant water, during football practices. His lesions were initially small (Figure 1A), but progressed within two days to approximately two centimeters in diameter (Figure 1B) with deep induration of the gluteal tissue. He was placed on *per oral* (PO) clindamycin for outpatient treatment. However, within twenty-four hours, he developed a high fever and was admitted to the local community hospital for surgical drainage of presumed *staphylococcal* soft tissue infection, with clindamycin given intravenously (IV) and IV ceftriaxone added to his antibiotic regimen.

Within thirty-six hours of admission, he began having shortness of breath and hypoxia. At that time, he was transferred directly to our pediatric intensive care unit (PICU) for further care. On arrival to the PICU, he complained of significant dyspnea, with grunting and retractions noted on exam. The patient was urgently intubated for impending respiratory failure and progressive shock. Physical exam revealed two large, indurated abscesses on the buttocks as well as multiple small

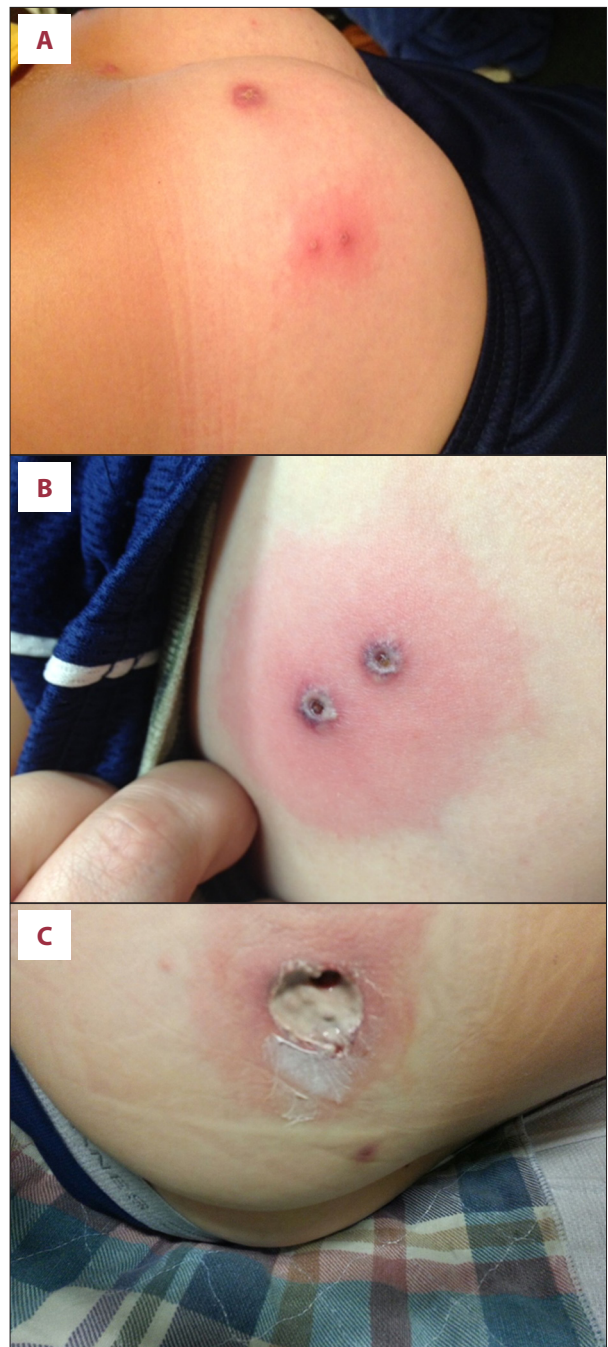


Figure 1. (A) Small gluteal lesions 2 days after exposure to stagnant water. (B) On his initial presentation to the community hospital, the lesions were approximately 2 centimeters in diameter, with a larger surrounding area of erythema. (C) Lesions were deep and indurated upon his presentation to the PICU, and were approximately 24 hours post-drainage.

pustules on his chest, abdomen, and extremities concerning for *staphylococcal* infection or for ecthyma (Figure 1C). Initial laboratory examination revealed elevated lactate of 5.5 mg/dL

and a white blood cell count of $2.12 \times 10^3/\mu\text{L}$. Within 12 hours, the lactate increased precipitously to 12.2 mg/dL and leukopenia progressed to $0.85 \times 10^3/\mu\text{L}$, with an absolute neutrophil count nadir of 100.

After intubation, the patient briefly stabilized, but quickly developed severe acute respiratory distress syndrome (ARDS) requiring oscillatory ventilation. By eighteen hours post-transfer, his oxygenation index was consistently greater than 50 despite maximal oscillatory support, and he remained hypotensive despite aggressive fluid resuscitation and infusions of dopamine, milrinone, norepinephrine, epinephrine, and vasopressin. Due to the patient's refractory ARDS and overwhelming septic shock, he was placed on veno-arterial extracorporeal membrane oxygenation (ECMO) in an attempt to maximize cardiac output. The patient was also oliguric on arrival and quickly progressed to anuria, requiring continuous renal replacement therapy within twelve hours of arrival.

Given the patient's presentation with gluteal abscesses, the initial antibiotics were based on a presumptive *staphylococcal* infection (vancomycin, clindamycin and nafcillin). A report of trace gram-negative rods in the wound gram stain also led to the continuation of ceftriaxone. However, because of his significant clinical decompensation, meropenem was added empirically in place of ceftriaxone within two hours of his admission to the PICU. With the identification of *C. violaceum* from the wound and blood cultures, IV TMP-SMX and ciprofloxacin were added to his antibiotic regimen given the known variable antimicrobial resistance characteristic of this pathogen. Susceptibilities from the outside hospital cultures later revealed a susceptibility to piperacillin/tazobactam, cefepime, meropenem, ciprofloxacin, levofloxacin, gentamicin, tobramycin and TMP-SMX, with intermediate susceptibility to amikacin. Once the sensitivities were known, the antibiotics were paired down to meropenem and ciprofloxacin.

In total, he required fourteen days of ECMO support, and an additional five days of mechanical ventilation. He was ultimately in the PICU for a total of five weeks, and was discharged home on hospital day forty. During his hospitalization, imaging revealed multiple septic emboli and abscesses involving his lungs and liver. However, none were large enough to warrant surgical intervention. The patient was sent home on IV ertapenem (instead of meropenem due to ease of once daily dosing) and PO TMP-SMX to continue therapy for *C. violaceum*.

After approximately four months of therapy, a computed tomography was obtained which showed resolution of the lung abscesses, but the scan was notable for non-enhancing liver lesions consistent with residual scarring versus abscess. Because erythrocyte sedimentation rate was still mildly elevated at that time, antibiotic therapy was continued with PO

ciprofloxacin and TMP-SMX. After six months of therapy, all antibiotics were discontinued for his *C. violaceum* infection because of clinical return near baseline and normalized inflammatory markers. He ultimately developed auto-amputation of the distal end of his right thumb and several toes, and required skin grafting of the dorsum of his right foot but returned to school four months after initial illness and he has no other permanent sequelae of his life-threatening infection.

Since there is a reported increased susceptibility to *C. violaceum*-induced disease in patients with CGD [5,9,10], testing was performed, and our patient was found to have the c.75-76delGT mutation in a homozygous state, confirming the diagnosis of CGD. Additionally, on further review of his medical records, the abscess that was drained when he was two years old grew *Nocardia*, an organism found more commonly in patients with immune dysfunction. Currently, the patient is being maintained on prophylactic TMP-SMX and itraconazole, in addition to interferon-gamma therapy.

Discussion

This case report highlights the importance for *C. violaceum* infection to be considered in the patient with abscesses who presents with sepsis and multi-system organ failure, when receiving adequate gram-positive coverage for more common pathogenic sources or if cultures reveal the presence of gram-negative rods.

As an uncommon, but highly virulent pathogen, infection with *C. violaceum* is associated with very high morbidity and mortality [4]. A constellation of findings commonly attributed to *C. violaceum* infection includes fever, presences of abscesses and skin lesions. In fact, rapid progression of sepsis, and the presence of multi-organ abscesses is a notable feature of *C. violaceum* infection [4,11–12]. Predisposing risk factors for acquiring this infection includes wading in water, play or fall in muddy water, with the highest risk for mortality associated with young age, presence of abscesses, shorter duration of clinical course and inappropriate antimicrobial therapy [13]. Unfortunately, due to its uncommon occurrence, despite the high mortality, there are currently no controlled trials comparing appropriate antibiotic therapy for this infection.

Generally *C. violaceum* displays sensitivities similar to what was reported with our patient, with some variation in susceptibility to third-generation cephalosporins, aminoglycosides, penicillins and TMP-SMX [6,7,14,15]. Bosch et al. reported a septic patient who displayed sensitivities to cefepime, piperacillin/tazobactam, and gentamicin similar to our patient, however, it was resistant to TMP-SMX; they successfully treated with amikacin and cefepime [16]. Conversely, Campbell et al.

reported a four-year-old patient with bacteremia whose isolate had no documented resistance [2]. In our patient, due to reported variability in resistance patterns, once the organism was identified as *C. violaceum*, he was placed on ciprofloxacin and TMP-SMX therapy. This was tailored to meropenem and ciprofloxacin once the susceptibility profiles for the organism were determined. Many reports have successfully used ciprofloxacin, either alone [15] or in combination with piperacillin [7] or TMP-SMX [17]. Ciprofloxacin has been stated to be the most effective antibiotic for *C. violaceum* [18], including a comparative study by Aldridge et al. that demonstrated the superiority of its *in vitro* activity against clinical strains of *C. violaceum* [19]. However, others have reported resistance to ciprofloxacin [15,20], with the mechanism of resistance thought to include efflux pumps and the presence of penicillin-binding proteins [20]. A review by Sirinavin et al., further suggests that effective antimicrobials for severe *C. violaceum* infection include ciprofloxacin, TMP-SMX, chloramphenicol and imipenem [4]. Together with these previously published studies, our case report would suggest treatment of invasive infection with ciprofloxacin in conjunction with a *second* antimicrobial agent due to the potential ciprofloxacin resistance.

Patients with CGD are particularly vulnerable to *C. violaceum* infection due to the fact that this is a catalase positive bacterium [5,9,10,21]. However, fulminant disease has been reported in non-CGD patients, and the most important predictors for mortality are presence of bacteremia, disseminated infection and use of ineffective antibiotics [4,11,13]. Nonetheless, as the literature demonstrates, in patients with *C. violaceum* infection, it is important to determine if the patient has an underlying immune disorder such as CGD or G6PD deficiency [22], as it necessitates maintenance antibiotic therapy. Workup for CGD should particularly be considered in patients who have a previous history of unusual infection of the skin or lymph node with other catalase positive organism such as *staphylococcus aureus*, *Nocardia* or *Aspergillus*. Seigel et al. reported a 14-year old teenager who developed necrotizing fasciitis secondary to *C. violaceum*, who was subsequently found to have CGD [23]. In many cases, as in our patient, *C. violaceum* can be the first infectious disease that leads to the diagnosis of CGD [23,24].

Relapse can occur with *C. violaceum* infection in humans, especially if the antibiotics were discontinued prematurely, or if the patients received inappropriate antibiotics for the initial infection, and in the presence of abscess, presumably because

of viable organisms remaining in abscess cavities [13,25,26]. In a case report by Ponte et al., a nine-year old patient died from *C. violaceum* bacteremia that relapsed within 48 hours of completing a 21-day course of appropriate antibiotics [27]. Sirinavin et al. reported a case of a three-year old child who had multiple relapses despite completing a 21-day course of treatment [4]. Current reports suggest treatment duration of up to three months [4,6,13]. In our patient's case, imaging of the liver obtained at four months into therapy demonstrated liver lesions with persistently elevated inflammatory markers, thus in the face of these findings and his known immunodeficiency, treatment was continued. After six months of therapy, the patient's inflammatory markers returned to normal, therefore antibiotic treatment was stopped and he was changed to prophylactic therapy for his CGD. The outcome of our patient, though significant for multiple auto-amputation of digits, is remarkable for no residual end-organ damage and, now, greater than one year later, the patient has essentially achieved full recovery.

Conclusions

This case highlights the need for consideration of *C. violaceum* infection in patients who develop refractory shock despite adequate antibiotic coverage for presumptive gram-positive sepsis secondary to abscesses, especially in those with a history of exposure to stagnant water. Secondary to variable resistance patterns of *C. violaceum*, it highlights the need to consider combination therapy of effective antimicrobial agents. A minimum duration of 3 months should be considered in those with invasive *C. violaceum* infection, with a longer duration of up to 6 months (as in our patient) that should be guided by the individual patient's clinical course.

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Conflict of interest

The other authors have no conflicts of interest to disclose.

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