



Letters to the Editor

Acute Fulminant Clostridium-Perfringens Sepsis with Massive Intravascular Hemolysis in a Young Woman with Sick Cell Disease

Keywords: Sick cell disease, Asplenia, Infection, Sepsis, Hemolysis, Clostridium Perfringens.

Published: November 01, 2026

Received: August 17, 2026

Accepted: October 11, 2026

Citation: Torti L., Polzoni M., Ardu N., Maffei L., Basso B., Del Principe M.I. Acute fulminant Clostridium-Perfringens sepsis with massive intravascular hemolysis in a young woman with sickle cell disease. *Mediterr J Hematol Infect Dis* 2026, 18(1): e2026080, DOI: <http://dx.doi.org/10.4084/MJHID.2026.080>

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To the editor.

Sickle cell disease (SCD) is an inherited hemoglobinopathy caused by a single amino acid substitution of the beta (β)-globin subunit (p.Glu6Val).

SCD is the most important hemoglobinopathy worldwide in terms of frequency and social impact, recognized as a global public health problem.¹⁻²

According to the Italian National Survey, the estimated total number of SCD patients in Italy in 2025 ranged from 2,348 to 2,675.³

Vaso-occlusion, hemolytic anemia, and vasculopathy are its hallmarks, leading to high morbidity and mortality.

Hyposplenism increases susceptibility to severe infections, connected to acute complications, including chest syndrome, vaso-occlusive crises, osteomyelitis, meningitis, urinary tract infections, and sepsis.⁴⁻⁷

Herein, we report a case of a 45-year-old SCD woman who developed fulminant and massive intravascular hemolysis (MIH) following Clostridium perfringens (CP) bacteremia and a review of the literature regarding this topic.

Intravascular hemolysis is one of the major complications of CP infection, mediated by the organism's α -toxin and associated with a mortality rate near 80%.

To the best of our knowledge, no cases of CP-associated massive intravascular hemolysis have previously been reported in patients with hemoglobinopathies.

We selected publications based on their relevance to the clinical presentation, pathophysiology, and outcomes of CP infection and toxin-mediated hemolysis.

The literature search was performed using PubMed/MEDLINE. The following search strategy was used: ("sickle cell disease" or "sickle cell anemia" or SCD) and ("Clostridium perfringens" and sepsis or

hemolysis).

Case Report. Our patient's history began in Brazil, where at 7 years of age, she was referred to hematology clinic for anemia and diffuse musculoskeletal pain, with a subsequent SCD diagnosis. She received periodic transfusion support during vaso-occlusive crises (an average of 2 crises per year). Over time, she consistently presented with a vaso-occlusive phenotype rather than hemolytic, with hemolysis indices only slightly increased.

At age 23, she started hydroxycarbamide therapy at a dose of 20 mg/kg/day, with good tolerance and clinical benefit.

She moved to Italy in 2021 and, after evaluation at our center, continued to receive periodic transfusion support. Genotype determination showed an S/S HBB result.

General clinical and laboratory features of our patient are shown in **Table 1A**.

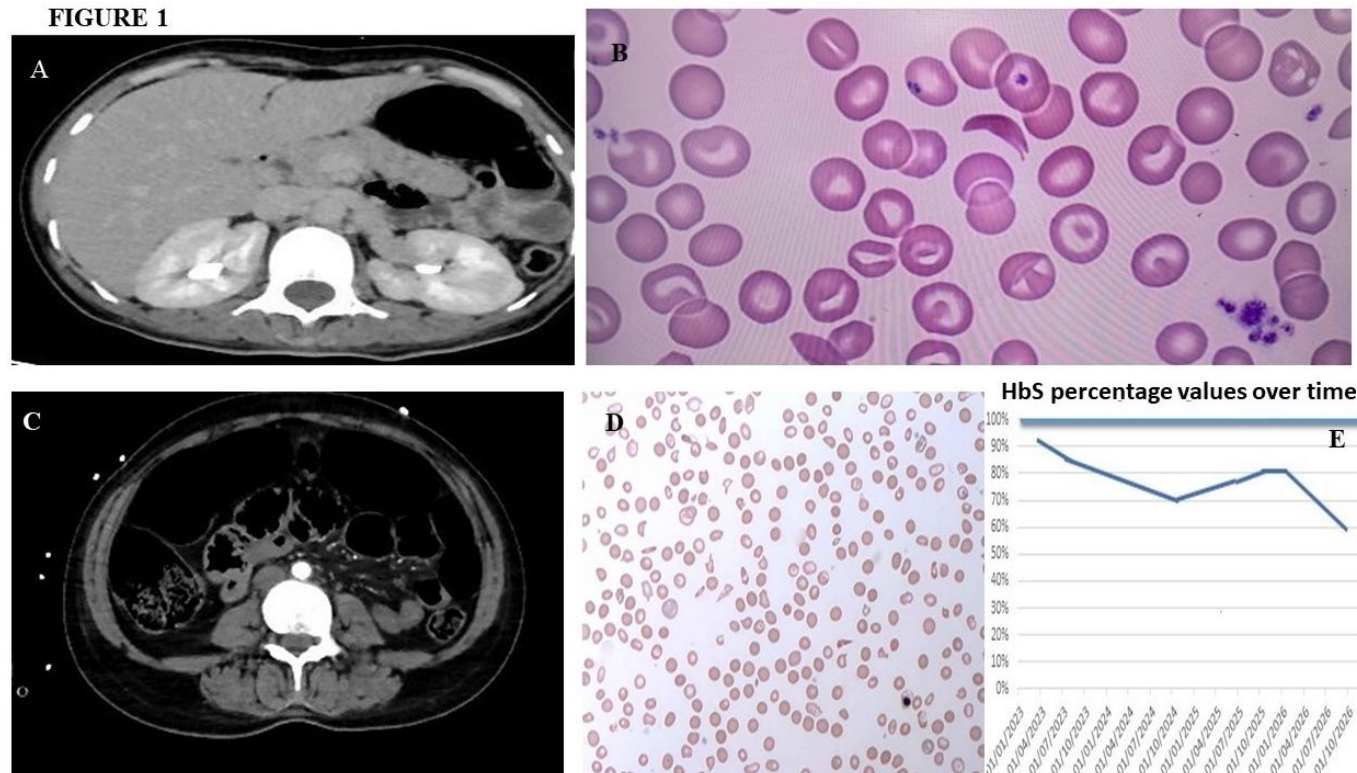
The spleen progressively shrank over time due to vascular and fibrotic changes. The last ultrasound scan showed a longitudinal spleen diameter of 4 cm (normally it was 13 cm). The computed tomography (CT) scan in January of this year described an absent spleen, not viewable, consistent with an autosplenectomy with progressive, irreversible loss of splenic function and tissue volume caused by repeated vaso-occlusive episodes. (**Figure 1 A**). She also had nuclear inclusions in her erythrocytes on previous peripheral blood smears, compatible with Howell-Jolly bodies (**Figure 1B**).

Comorbidities are shown in **Table 1A**. Given the patient's hyposplenism, all appropriate and proper vaccinations had been administered.

We periodically performed manual erythroexchange in order to quickly reduce the percentage of hemoglobin S (HbS%).

Therefore, the mean HbS percentage over the last

FIGURE 1



year was 46% (**Figure 1E**).

In July 2026, she was hospitalized for severe pain in the upper and lower limbs and anemia and was treated with prophylactic antibiotics and transfusional therapy.

During hospitalization, diffuse kidney pain and a positive Giordano's sign led to suspicion of pyelonephritis, which was confirmed by abdominal and pelvic CT scan; no pathogens were isolated. Empirical broad-spectrum intravenous (IV) antibiotic therapy with tazobactam/piperacillin, with clinical benefit, was administered, along with hydration and analgesic therapy. After some days, she was discharged with improvement in pain and resolution of the renal condition, with prescription of oral trimetoprim/sulfamethoxazole therapy at home. The total length of this first hospitalization was 72 hours and concluded with her discharge home.

However, only 24 hours later, she returned to our Emergency Department in distress, with generalized body pain, tachypnea, and tachycardia. Only mild fever was present (TC 38C) (**Table 1 B**).

Blood and urine cultures were collected, and inflammation markers, specifically C-reactive protein, were slightly elevated. Blood results are shown in Table 1B. The patient underwent peripheral venous blood cultures consecutively at three different venous sites, half an hour apart, during a fever peak.

Antibiotic treatment with tazobactam /piperacillin was promptly started to ensure broad-spectrum coverage.

Physical examination revealed conjunctival icterus, along with diffuse crackles on chest auscultation, and High-resolution chest CT showed a pattern of severe

bilateral pneumonia.

Therefore, IV antibiotic therapy was modified by empirically adding ceftriaxone and fosfomycin, selected for their favorable pulmonary alveolar penetration, after lung involvement was identified.

However, during the night, the patient developed cardiac arrest with asystole. Emergency resuscitation was performed; she was sedated, intubated, and started on intravenous adrenaline at 0.02 mcg/kg/min. Laboratory values reported at the time of this severe clinical deterioration are shown in **Table 1C**. The patient presented with severe anemia, markedly elevated hemolysis indices, and hyperkalemia, with no evidence of bleeding.

Over the next few hours, her Hb fell quickly to 5 g/dl, and a peripheral blood smear showed anisopoikilocytosis and spherocytes without schistocytes (**Figure 1D**). An emergency second whole-body CT scan revealed multiple pulmonary opacities, gallstones, multiple clustered intestinal loops showing no enhancement after contrast administration, indicating probable intestinal ischemia, with free air present (**Figure 1C**).

Multi-organ failure and severe sepsis rapidly ensued with quick deterioration of vital signs.

Despite mechanical ventilation, cardio-circulatory support, transfusion treatment, and corticosteroid therapy started for sepsis, the patient passed away within the next few hours, to our great sorrow.

In **Table 1D**, you can find the laboratory exams before the death of our patient.

The first peripheral blood culture result positive for CP came through after 16 hours and 39 minutes,

Table 1 A. General clinical and laboratory features of our patient.

Age	45 years old
Sex	Female
Ethnicity	Caucasian
Start of blood transfusion	At the age of 17
Asplenia	Yes
Splenectomy	No
Comorbidity	Gallstones, Hip aseptic osteonecrosis, hypothyroidism dolichocolon and coprostasis
Mean Hemoglobin pre value (in the last year)	9,1 mg/dl
Mean total bilirubin value (in the last year)	2,1 mg/dl
Mean LDH value (in the last year)	300 U/l
Transfusional interval	25 days
Mean value White blood cells (last year)	11.900/mm ³ (11.100-13.300)
Platelet/Neutrophil ratio PNR (at hospital admission)	91
Neutrophil/Lymphocyte ratio	4,3
HbS percentage post (mean value in the last year)	46%
Kind of iron chelation	Deferasirox 15 mg/proKg
Hydroxycarbamide therapy	Yes (20 mg/prokg)

Table 1 B. Laboratory features on admision of our patient

Hemoglobin value	9,4 g/dl
Platelet count	190.000/mm ³
Lactate dehydrogenase value	310 U/l
Lactate value	2,2 mmol/L
Potassium value	3,6 mEq/l
Total bilirubin value	2,1 mg/dl
Reticulocyte percentage	3%
Urine exam	Normal
Creatinine value	1 mg/dl
Fibrinogen value	520 mg/dl
PTT value	28 sec
INR	0,9
Antitrombin III	96%
Ddimer	453 ng/ml

Table 1 C. Laboratory features at the time of the transfer to the intensive care.

Hemoglobin value	5,2 g/dl
Platelet count	70.000/mm ³
Lactate dehydrogenase value	710 U/l
Lactate value	4 mmol/L
Potassium value	7,7 mEq/l
Total bilirubin value	5,1 mg/dl
Reticulocyte percentage	21%
Urine exam	Hemoglobinuria
Creatinine value	2,5 mg/dl
Fibrinogen value	100 mg/dl
PTT value	38 sec
INR	2,3
Antitrombin III	40%
Ddimer	6432 ng/ml

Table 1 D. Laboratory features before death.	
Hemoglobin value	5 g/dl
Platelet count	50.000/mm ³
Lactate dehydrogenase value	730 UI/l
Lactate value	8 mmol/L
Potassium value	5,3 mEq/l
Total bilirubin value	5,3 mg/dl
Reticulocyte percentage	22%
Urine exam	Hemoglobinuria
Creatinine value	3,9 mg/dl
Fibrinogen value	80 mg/dl
PTT value	39 sec
INR	3,1
Antitrombin III	20%
Ddimer	12430 ng/ml

showing CP germ.

We took her peripheral blood and cultured it at 37 C under an extractor hood, deprived of oxygen. The bacterium CP was identified by biochemical and mass spectrometric analysis. The first was based on its characteristics as a Gram-positive, non-motile, obligate anaerobe capable of fermenting various sugars with sulfite reduction, and the second was by mass spectrometry using matrix-assisted laser ionization time-of-flight technology, identifying the species within minutes directly from an isolated colony by protein profiles. Unfortunately, the results were positive for multidrug-resistant CP, resistant to amoxicillin/clavulanic acid, metronidazole, and clindamycin, which are often used against this infection, and sensitive to tazobactam/Piperacillin (European Committee on Antimicrobial Susceptibility Testing). This result was obtained based on the Kirby-Bauer disk diffusion test, using anaerobic agar supplemented with 5% defibrinated horse blood.⁸

The second hospital admission lasted 48 hours. It followed a presentation at our hospital's emergency department just 24 hours after initial discharge from another hospital and ended with the patient's death.

Discussion and Conclusions. People with SCD have increased susceptibility to infection through functional asplenia, immune dysregulation, chronic inflammation, repeated hospital admissions. In an interesting African study, the most common causes of death included infections in 78% of cases (data based on autopsy examinations).⁹

CP are Gram-positive, spore-forming anaerobic organisms normally found in soil and in the gastrointestinal tracts of humans and animals; they are rare but extremely lethal pathogens responsible for fulminant sepsis in immunocompromised patients.

Probably, the sickle cell vasculopathy and the

subsequent hypoperfusion related to the vaso-occlusive process led to a broad small intestinal ischemia, ending with an intestinal perforation, explaining the presence of free intraperitoneal air reported and contributing to the dissemination of the bacterium into the bloodstream.

The absence of the spleen is certainly the major contributor to the immune deficiency in this patient, with consequent failure of opsonization, leading to an increased risk of severe sepsis.

Intestinal ischemia and probable perforation represented a plausible gastrointestinal portal of entry, although whether the intestinal injury preceded or resulted from the fulminant septic process cannot be established.

At least 12 different toxins are produced by CP, of which alpha-toxin is a phospholipase C (lecithinase) that degrades phospholipids in erythrocyte membranes, leading to accelerated hemolysis. It also inhibits myocardial contractility and causes disseminated intravascular coagulation, peripheral vasodilatation, and septic shock.¹⁰⁻¹¹

The main challenge in this field is stopping accelerated hemolysis early.

The crucial question is "Did the pre-existing membrane abnormalities of HbS red cells (HRC) contribute to the exceptional severity and rapidity of CP-induced MIH?"

The answer is marginally yes, but we can't demonstrate this without clear evidence; it remains only a hypothesis.

Undoubtedly, hemolysis is a fundamental feature of SCD that contributes to its pathophysiology. In SCD, the percentage and concentration of HbS directly drive sickling and hemolysis-driven destruction of RBCs. Higher HbS proportions (such as major (> 90%) in HbSS homozygosis) cause severe, chronic hemolytic anemia, whereas lower HbS fractions greatly reduce this

Table 2. Overview of the literature regarding *Clostridium Perfringens* infection.

Main diagnosis	Age (years old)	Number of patients	Sepsis	Sex	Treatment	Exitus	MIH
Acute myeloid leukemia ¹⁹	42, 58 and 21	3	Yes	Female (1) Male (2)	Fluid resuscitation, antibiotic treatment	Yes (1)	Yes
Acute myeloid leukemia ²⁰	74	1	Yes	Male	Wide spectrum antibiotics	Yes	Yes
Acute myeloid leukemia ²¹	1	1	Yes	Male	Wide spectrum antibiotics	Yes	Yes
Multiple myeloma IgGLambda ²²	68	1	Yes	Female	Wide spectrum antibiotics	Yes	Yes
Multiple myeloma and agnogenic myeloid metaplasia ²³	65, 70	2	Yes	Female and male	Wide spectrum antibiotics	Yes	Yes
Acute myeloid leukemia ²⁴	74	1	Yes	Male	Wide spectrum antibiotics	Yes	Yes
Cholangiocarcinoma, Diabetes ²⁵	77	1	Yes	Female	Wide spectrum antibiotics	Yes	Yes
Malignancies, colorectal, pancreatic and gastric cancer ²⁶	67,5 (44-87)	24	Yes	Male (21)	Wide spectrum antibiotics	Yes (17)	Yes
Rectum adenocarcinoma, prostatic hypertrophy ²⁷	81	1	Yes	Male	Wide spectrum antibiotics	Yes	Yes
Malignancies, Liver cirrhosis, Biliary tract disease, Trauma ²⁸	Medium age 74 (32-99)	60	Yes	Male (38) Female (22)	Antimicrobial treatment	All with MIH	Yes (6)

risk.

The patient had a reduced circulating HbS fraction as a consequence of chronic transfusion/erythroexchange; whether this modified susceptibility to toxin-mediated hemolysis cannot be determined.

CP alpha-toxin was presumably, in our view, the major pathogenic factor in this context, acting not only on erythrocytes but also on human thrombocytes, but not on leukocytes.¹²

Pre-existing membrane abnormalities may have amplified hemolysis severity.

Phosphatidylserine (PS) exposure was well documented and increased in HRC.¹³

Externalized PS is prothrombotic and attracts phagocytes, and activated endothelial cells may facilitate CP enzymes, especially when erythroid bone marrow reserve is impaired. Moreover, severe bacterial infections generally cause low oxygen and inflammation, which can trigger or worsen HbS polymerization.

Recently, a multifactorial action of CP toxins on red cell metabolism, as well as impaired erythropoiesis by inhibiting erythroid differentiation, was described, with increased neutrophil adhesion to fibrinogen and fibronectin.¹⁴⁻¹⁶

Finally, we think that the pathogenesis of MIH is certainly complex and multifactorial, probably quickly fulminant in relation to multiple combined and additive mechanisms.

CP alpha toxin was almost certainly the dominant mechanism of the catastrophic intravascular hemolysis; pre-existing SCD-associated red-cell membrane abnormalities and reduced hematological reserve may conceivably have amplified its clinical consequences, but this remains unproven.

Because these cases are rare, appropriate treatment strategies have not yet been firmly established.

Clindamycin is particularly favored in sensitive cases

because it inhibits bacterial toxin production.

In this case, the antibiogram showed CP was sensitive to tazobactam/piperacillin, which was started empirically before the blood culture results. However, in our opinion, the antibiotic's permeability within hypoperfused, ischemic tissues likely failed to effectively counteract the widespread infection driving multiorgan failure.

Emergency surgical intervention to obtain release of the convoluted intestinal loops was indicated but not performed due to hemodynamic instability. We planned to perform a biological second -level DNA characterization by PCR DNA study of CP-toxin, but the sample was not dispatched because the patient prematurely died.

Prompt intervention in an intensive care unit (ICU), including fluid resuscitation, vasopressors for shock, and ventilatory support, as in our case, is strongly suggested.

Plasma exchange, renal replacement therapy, hemopurification strategies to remove circulating enzymes, and monoclonal antibodies against CP toxins are nowadays still considered only experimental procedures.¹⁷⁻¹⁸

CP sepsis can complicate malignant disease, in particular gastrointestinal carcinomas or genitourinary tract and hematologic neoplasms. This fatal complication has been described until now in patients with Hodgkin's disease, multiple myeloma, chronic myeloid leukemia, and acute leukemias. To the best of our knowledge, this complication in thalassemia or SCD-positive patients has never been reported.

Over the past 60 years, approximately 130 case reports of CP with MIH have been published, and this number is increasing.¹⁹⁻²⁸

In **Table 2**, we highlight some of the leading reported papers.

No nationwide registry exists for CP sepsis; therefore, the exact number of affected patients is

unknown. Creating a national multicenter registry for CP sepsis is a first step toward improving treatment strategies, and urgent collaboration among ICUs will be needed.

Physicians must keep this clinical picture in mind in immunocompromised patients with neutropenia due to bone marrow infiltration, steroid therapy, asplenia (as in our patient), or other predisposing factors.

Finally, the hematology scientific community treating patients with immune impairment needs to discuss this acute complication, compare clinical course

and outcomes, and optimize effective treatment. We are moving forward.

Author's contributions. Lorenza Torti designed the study, collected clinical data and wrote the manuscript. Maria Ilaria Del Principe reviewed the manuscript and supervised the study. Mauro Polzoni, Nicolina Ardu, Laura Maffei and Beatrice Basso followed the patient from a clinical point of view and collected clinical data. All the authors read and approved the manuscript.

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Competing interests: The authors declare no competing interest.

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