

Acute Infectious Purpura Fulminans Caused by Escherichia Coli Infection: Pathogenesis and Clinical Diagnosis and Treatment Review

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Abstract: Acute infectious purpura fulminans (AIPF) is a rare yet highly lethal complication of sepsis characterized by systemic coagulation dysfunction, hemorrhagic skin necrosis and progressive acral ischemia, which is mostly triggered by encapsulated pathogens such as *Neisseria meningitidis* and *Streptococcus pneumoniae*. Increasing clinical evidence suggests that *Escherichia coli* may act as a rare causative pathogen of AIPF. In contrast to classic encapsulated bacteria-induced AIPF, *E. coli*-associated AIPF frequently presents with insidious infectious foci, and the interplay between endotoxin-mediated inflammation and coagulation accelerates disease progression. Clinicians often exhibit insufficient awareness of this entity, leading to frequent misdiagnosis of its early cutaneous manifestations as either disseminated intravascular coagulation or vasopressor-related ischemic injury. The available evidence primarily stems from isolated case reports, indicating a lack of systematic clinical research. This review aims to summarize the epidemiology, clinicopathological features, diagnosis, and management of *E. coli*-related AIPF to enhance clinicians' capacity for early recognition and treatment of this disorder.

1. Introduction

Acute infectious purpura fulminans (AIPF) is a life-threatening complication associated with severe sepsis, exhibiting an overall mortality rate as high as 60% [1]. This condition is predominantly observed in pediatric patients infected with *Neisseria meningitidis* and *Streptococcus pneumoniae*. However, recent clinical case reports have highlighted occurrences in adults infected with gram-negative bacilli, particularly *Escherichia coli*. The epidemiology of *Escherichia coli*-associated AIPF reveals significant differences compared to classic pathogens. Notably, while classic pathogens tend to infect children, *Escherichia coli*-associated AIPF primarily affects three high-risk populations: postoperative patients, individuals with hematologic malignancies, and neonates. A retrospective study conducted from 2017 to 2022 identified Gram-negative bacteria as the leading cause of

infection in postoperative AIPF cases, with *Escherichia coli* and *Klebsiella pneumoniae* accounting for more than half of the combined cases [2]. Zieneldien[3] et al. reported a severe case involving a patient with relapsed myeloid leukemia who, during chemotherapy, experienced impaired intestinal mucosal barrier integrity. This impairment led to *Escherichia coli* sepsis and AIPF, which rapidly progressed to compartment syndrome and acral gangrene, ultimately necessitating amputation. In contrast to *Neisseria meningitidis* and *Streptococcus pneumoniae*, which are primarily transmitted via the respiratory tract, the infection sources in patients with *Escherichia coli*-associated AIPF are predominantly found in the urinary tract and abdominal cavity [4,5].

2. Etiology and Pathogenesis

2.1 Vascular Injury and Abnormal Activation of the Coagulation System

Lipopolysaccharide (LPS) released by *Escherichia coli* can induce programmed cell death, such as apoptosis, in vascular endothelial cells. This process results in the disruption of intercellular junctions, increased vascular permeability, and subsequently, extravasation plasma extravasation and edema [6]. Simultaneously, it exposes procoagulant subcutaneous collagen and matrix, prompting a transition in endothelial cells from an anticoagulant to a procoagulant phenotype. Additionally, LPS activates NF- κ B and AP-1 (c-Fos/c-Jun) through the LPS-LBP-CD14-TLR4/MD-2 pathway, thereby inducing transcription of the tissue factor (TF) gene [7]. Importantly, *E. coli* can directly deliver LPS to monocytes and macrophages via outer membrane vesicles (OMVs), activating Caspase-11. Through the Caspase-11/GSDMD non-canonical inflammasome pathway, this activation induces TF expression on the cell membrane, initiating the extrinsic coagulation pathway [8]. Furthermore, the lipid A moiety of circulating LPS can directly induce conformational changes in factor XII (FXII) [9]. Upon activation, FXII not only initiates the intrinsic coagulation pathway but also releases bradykinin, which increases vascular permeability through the kallikrein system and is closely linked to inflammatory responses [10]. The aforementioned pathway rapidly damages blood vessels and triggers the coagulation cascade through a dual mechanism involving both direct activation and inflammatory amplification.

2.2 Deficiency of Anticoagulant and Fibrinolytic System

Under physiological conditions, protein C is activated to form activated protein C (APC) after binding to the thrombomodulin (TM)-thrombin complex, mediated by the endothelial protein C receptor (EPCR). APC inhibits thrombin generation by inactivating FVa and FVIIIa, while also inhibiting PAI-1 to promote fibrinolysis, stabilize the endothelial barrier, and suppress inflammatory responses [11]. During *E. coli* infection, explosive thrombin generation leads to the extensive consumption of protein C [12]. Concurrently, lipopolysaccharide (LPS) released by bacteria significantly diminishes the efficiency of protein C activation by downregulating EPCR and TM expression, as well as inducing their cleavage [13]. Furthermore, the LPS/TLR4 pathway induces the release of inflammatory factors such as TNF- α , which inhibits the hepatic synthesis of protein C, protein S, and antithrombin III [12]. The synergistic effect of these pathways leads to dysfunction of the protein C system, which is central to the entire pathological process [1], ultimately triggering disseminated, uncontrolled intravascular thrombosis and consumptive coagulopathy.

2.3 Ischemic Necrosis of Skin

AIPF is a severe thrombotic subtype of disseminated intravascular coagulation (DIC), primarily affecting the skin due to its unique anatomical and physiological characteristics. The skin has a high

microvascular density and a large surface area, which provide a substantial interface for bacterial toxins and inflammatory mediators. The endothelium of the skin relies heavily on the thrombomodulin (TM)/protein C (PC) system to maintain anticoagulant homeostasis; when this system fails, the skin is the first organ to lose its protective functions. [14]. In this context, *E. coli* releases LPS, which prompts neutrophils to release neutrophil extracellular traps via the Caspase-11/GSDMD pathway as damage-associated molecular patterns (DAMPs). This process activates platelets and damages the endothelium, thereby promoting extensive microthrombus formation [8,15]. Microthrombi exhibit a sequential pattern of arteriovenous obstruction: arteriolar embolism interrupts distal perfusion, leading to full-thickness skin ischemia, blistering, and necrosis. Subsequently, the obstruction of postcapillary venule reflux results in venous stasis and vessel wall destruction, which causes erythrocyte extravasation and the formation of a non-blanching reticular purpuric rash, ultimately culminating in comprehensive pathological picture that ranges from ischemia to hemorrhagic necrosis [1].

3. Clinical Features and Diagnosis

3.1 Clinical Manifestations

AIPF associated with *E. coli* presents with a sudden onset and is characterized by systemic infection signs, including high fever, chills, tachycardia, and tachypnea. These symptoms develop rapidly and can lead to multiple organ failure, particularly affecting the respiratory and circulatory systems [2]. The characteristic purpuric rash and its dynamic evolution are crucial for diagnosis. In the early stage, painful reticular red-blue ecchymoses are observed on the distal extremities and prominent areas of the body, such as the tip of the nose, auricles, knees, and heels [16]. The degree of pain at this stage is markedly inconsistent with the local signs, which aids in differentiating this condition from simple disseminated intravascular coagulation [5]. Subsequently, the rash rapidly transforms into retiform purpura characterized by irregular borders that do not blanch under pressure. This condition can be differentiated from ischemic injury induced by vasopressors, which typically presents with well-demarcated skin lesions. Following this, tense, hemorrhagic bullae or blood blisters may develop in the purpuric areas, resulting in the formation of black eschars upon rupture. In the terminal stage, the condition progresses to full-thickness skin necrosis, hemorrhagic necrosis, and gangrene, with a distinct demarcation between necrotic and viable tissue. This stage is often complicated by necrotizing fasciitis, which frequently necessitates amputation to mitigate the damage [17].

3.2 Laboratory Examinations

Laboratory tests reveal signs of infection characterized by significantly elevated white blood cell counts and procalcitonin (PCT) levels. Concurrently, these tests indicate severe DIC manifestations, such as thrombocytopenia, elevated D-dimer levels, and prolonged coagulation times. Additionally, notably decreased levels of circulating protein C, protein S, and antithrombin are characteristic findings. Furthermore, due to extremely rapid fibrinogen turnover, patients typically present with significantly elevated plasma C-reactive protein levels, alongside an "ESR-CRP dissociation" phenomenon, where the erythrocyte sedimentation rate (ESR) is inappropriately low.

In contrast, thrombotic thrombocytopenic purpura, which must be differentiated from this condition, primarily presents with schistocytes on peripheral blood smears, elevated lactate dehydrogenase (LDH) levels, and decreased haptoglobin. Furthermore, etiological examinations, such as blood cultures or cultures from sterile sites of infection yielding *E. coli*, provide the most direct evidence of infection. Unlike thrombotic thrombocytopenic purpura, which features platelet-

rich microvascular thrombi, and immune thrombocytopenic purpura, characterized by perivascular hemorrhage, skin biopsies from lesions in patients with acute infectious purpura fulminans reveal fibrin-rich acellular thrombi in dermal small vessels and microvessels, accompanied by endothelial necrosis, perivascular neutrophil infiltration, and erythrocyte extravasation[1,16].

4. Therapeutic Strategies

The primary treatment strategy involves the prompt and appropriate correction of coagulation function, alongside active infection control and careful management of wounds and organ function support. The core mechanism underlying this disease is the dysfunction of the protein C system, making the early infusion of protein C concentrate crucial for effective treatment [18]. Previous studies indicate that patients who initiate treatment within 18 hours of symptom onset experience significantly better outcomes compared to those whose treatment is delayed beyond 60 hours, with the latter group facing a markedly increased risk of amputation [1,19]. Research conducted by Bendapudi et al. demonstrates that fresh frozen plasma can serve as an effective emergency bridging measure [20]. Furthermore, sepsis induced by *Escherichia coli* necessitates early and aggressive anti-infective therapy, employing broad-spectrum β -lactam agents that target Gram-negative bacteria, such as carbapenems and piperacillin-tazobactam. Additionally, prompt measures to control the source of infection, including abscess drainage, debridement of necrotic tissue, and removal of infected catheters, are essential [5]. It is important to note that during the acute phase, debridement should be approached conservatively; dry necrotic tissue may be preserved as a natural biological dressing, and emergency decompression is warranted only in cases of confirmed wet gangrene or gas gangrene, as the distinction between necrotic and viable tissue often takes weeks to months to become evident. Finally, nearly all patients with this disease present with concomitant septic shock, necessitating early aggressive hemodynamic resuscitation and active organ support therapy for hepatic and renal function [4].

5. Conclusion

Escherichia coli bacteremia-induced purpura fulminans is a rare and rapidly progressive consumptive coagulopathy syndrome associated with sepsis, most commonly observed in patients with urinary tract infections and infections following emergency surgeries. Currently, there is a paucity of high-quality clinical data to inform diagnostic and therapeutic decisions, and many clinicians demonstrate insufficient vigilance regarding this disease. Early intervention informed by pathophysiological mechanisms may improve patient prognosis. The core pathophysiological mechanisms of this condition involve the release of lipopolysaccharides by bacteria, which damages the vascular endothelium and abnormally activates the coagulation system, ultimately resulting in the depletion of the protein C system. Clinicians should establish an early diagnosis based on the dynamic evolution of characteristic purpura and differentiate it from conditions such as thrombotic thrombocytopenic purpura and immune thrombocytopenia. Early protein C replacement therapy, active infection control, and appropriate wound management are essential for enhancing patient prognosis. Furthermore, the potential of monoclonal antibodies that target inflammatory pathways to delay disease progression by interrupting the inflammation-coagulation coupling represents a promising therapeutic avenue that warrants further investigation.

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