CASE REPORT

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# Fournier's Gangrene and Sodium-Glucose Co-Transporter-2 Inhibitors: A Critical Combination in the Critical Care Unit

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**Abstract**

This paper describes the holistic management and contribution of critical care to the successful treatment of the life-threatening condition, Fournier's gangrene, in patients prescribed sodium-glucose co-transporter-2 (SGLT2) inhibitors, using a case report for illustration. A gentleman in his 70s, prescribed empagliflozin, an SGLT2 inhibitor for managing his diabetes and heart failure, presented in a moribund state to the Emergency Department. The interplay of his co-morbidities and medication regimen created a scenario that heightened his risk of developing the life threatening condition of Fournier's gangrene, which was successfully managed. We highlight several critical considerations for a favorable outcome in the setting of critical care. A comprehensive system approach with awareness of the risks associated with SGLT2 inhibitor therapy is crucial to effectively managing Fournier's gangrene in critical care.

**Keywords:** Acute medicine; Critical care; Emergency medicine; Intensive care.

## Introduction

Fournier's gangrene is a rare and life-threatening form of necrotizing fasciitis that primarily affects the genital, perineal, and perianal regions.[1] It is marked by rapid bacterial proliferation, extensive tissue damage, and high mortality rates if not promptly diagnosed and treated. This condition typically necessitates aggressive surgical debridement and broad-spectrum antibiotic therapy. There is an acknowledged higher incidence of Fournier's gangrene among patients with diabetes mellitus.[2] Moreover, an additional risk is now recognized in patients prescribed a novel class of drugs for managing both type 2 diabetes mellitus and heart failure.

Recent advancements in the treatment of both type 2 diabetes mellitus and heart failure have led to the widespread use of sodium-glucose co-transporter-2 (SGLT2) inhibitors.[3] Although these medications are generally considered safe, emerging reports suggest a potential association with the development of Fournier's gangrene.[4]

Despite multiple case reports of Fournier's gangrene,[1-6] there is a scarcity of literature focusing on the critical care management of patients who develop this condition in conjunction with SGLT2 inhibitor therapy.

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This review aims to thoroughly analyze the link between SGLT2 inhibitors and Fournier's gangrene, highlighting the challenges these anti-diabetic agents pose in the critical care setting of this necrotizing fasciitis. We explore the current understanding of the risks associated with SGLT2 inhibitors and emphasize the comprehensive care needed for patients suffering from Fournier's gangrene, illustrated through a case study.

## Case Report

Signed informed consent was obtained from the patient for this report.

A 75-year-old gentleman presented to the Emergency Department with a six-day history of gluteal pain accompanied by rapidly progressive redness and blistering of the adjacent skin. His medical history included type 2 diabetes mellitus diagnosed in 2016, significant left ventricular systolic dysfunction (ejection fraction of 30%) since 2022, iron deficiency anemia, and hypertension. His regular medications included sacubitril 97 mg/valsartan 103 mg, ivabradine 2.5 mg, bisoprolol 1.25 mg, spironolactone 12.5 mg, bumetanide 1 mg, empagliflozin 10 mg, and gliclazide 160 mg. His HbA1C level was 57 mmol/mol.

Upon arrival, he was profoundly hypotensive with a blood pressure of 72/42 mmHg and a heart rate of 101 beats per minute. His temperature was 36.4 °C. Examination revealed erythematous and blackened skin in the perineal area. He was diagnosed with septic shock, presumed to originate from the perineal infection. Immediate resuscitative measures included administering a total of 3 liters of intravenous crystalloid fluid boluses.

An urgent computed tomography (CT) scan of the abdomen and pelvis revealed extensive scrotal and subcutaneous emphysema, supporting a diagnosis of Fournier's gangrene.

Based on advice from a microbiologist, empirical antibiotic treatment was initiated with intravenous meropenem 1 g three times daily and clindamycin 1.2 g four times daily. A comprehensive sepsis screening was also performed.

The Fournier Gangrene Severity Index (FGSI) was calculated,[7] assessing nine parameters: temperature, heart rate, hematocrit, leukocyte count, and serum levels of sodium, potassium, creatinine, and bicarbonate. The degree of deviation from normal ranges is graded from 0 to 4. The scores were as follows:

- Temperature (°C): 36.4 °C = score 0
- Heart rate (beats per minute): 101/min = score 0
- Respiration rate (breaths per minute): 21/min = score 0
- Serum sodium (mmol/L): 135 mmol/L = score 0
- Serum potassium (mmol/L): 4.0 mmol/L= score 0
- Serum creatinine (mg/100 mL): 145 mmol/L = score + 1
- Hematocrit (%): 40 = score 0
- White blood cell count (total/$mm^3$ ×1000): 14.2 × $10^9$/L = score 0
- Serum bicarbonate (venous, mmol/L): 18.9 mmol/L = score + 3

An emergency surgical consultation resulted in a decision to proceed with debridement. Radical debridement of the perineal area was performed, involving extensive necrotic tissue in the skin, fatty tissue and superficial muscles. This required dissection extending to the left scrotum (sparing the testes and urethra), the left side of the ano-rectal sphincter complex, and to the left gluteus muscle. Cavitation extending laterally to the rectum and anal canal, approximately 6 cm in length, was noted and subsequently packed. He was transferred to critical care with his trachea intubated and supported by mechanical ventilation. A plan was made for a repeat examination under anesthesia 48 hours postoperatively to assess the need for further debridement.

The patient initially required a noradrenaline infusion of 0.35 mcg/kg/min[8] alongside 0.4 units/mL vasopressin to maintain a mean arterial blood pressure of 65 mmHg. Significant systemic hypoperfusion was evidenced by metabolic acidosis with a pH of 7.2 and a base excess of -12.6 mmol/L. Following further discussions with microbiologists, intravenous immunoglobulin (2 g/kg)[9] was initiated in addition to the previously started antibiotics. Over the next 48 hours, the requirement for inotropes decreased to 0.09 mcg/kg/min of noradrenaline, with the metabolic acidosis resolving. Inflammatory markers also improved (Figures 1 and 2). Clindamycin was discontinued after 48 hours, while meropenem was continued. Blood cultures taken at admission grew Bacteroides fragilis, which was sensitive to the empirical antibiotic therapy started upon admission.

A repeat examination at 48 hours revealed a healthy wound and testicles, requiring only minor debridement to the left groin, left-sided periurethral area, and left but-

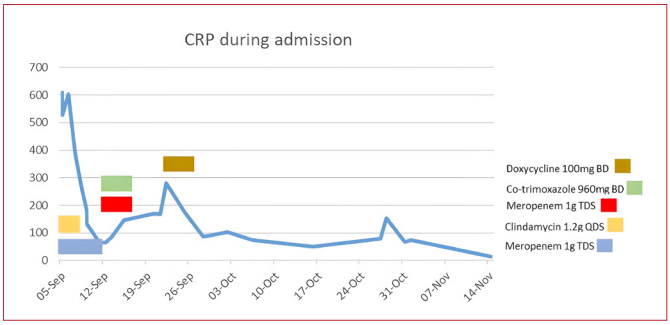


**Figure 1.** C-reactive protein (CRP) levels during admission with an overlay of antibiotic therapy.

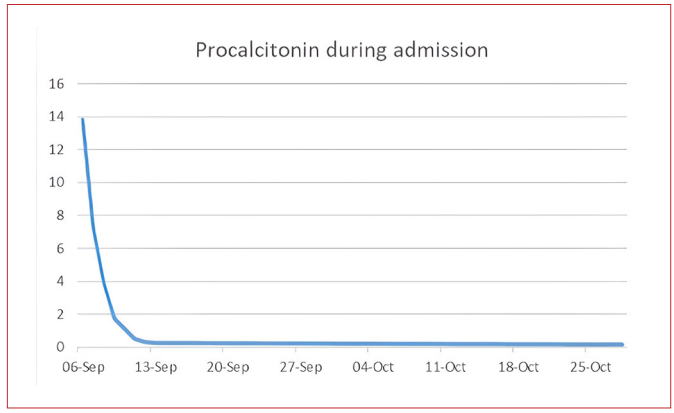


**Figure 2.** Procalcitonin levels during admission.

tock. A fecal management system[10] was placed, and a referral was made to plastic surgeons for potential reconstruction of the perineum.

Vasopressor support was no longer needed 48 hours after the re-look operation. A low thoracic epidural was then inserted for analgesia. His trachea was extubated six days after admission. Antibiotic therapy was stepped down to intravenous metronidazole and oral co-trimoxazole.

Subsequently, his main symptom was ongoing intensive care acquired hyperactive delirium,[11] which was managed with standard protocols,[12] including the administration of intravenous haloperidol. He was discharged to the ward for ongoing management eleven days after his initial presentation.

He subsequently underwent a diversion colostomy six weeks after initial presentation. After a further six weeks of rehabilitation, our patient was discharged home.

## Discussion

Fournier's gangrene has a very high mortality rate; therefore, early recognition of the onset of the disease is critical for ensuring a favorable outcome. The higher incidence of this condition is well-known in diabetic patients, particularly those prescribed SGLT2 inhibitors. However, this association is not widely recognized among patients taking these drugs or among clinicians who are not diabetologists. This lack of awareness was demonstrated by the poor recognition of the prodromal signs and symptoms by our patient and his family. Even after the diagnosis was made, the association with the use of empagliflozin as SGLT2 inhibitor therapy was not immediately recognized, and the medication was discontinued only after admission to the critical care unit. In addition to empagliflozin therapy, our patient had other risk factors for the development of Fournier's gangrene, such as hypertension and being over 50 years of age. We used the Fournier Gangrene Severity Index[7] in our patent to provide an indication of survival. Although this score has received variable reviews in the literature, with one recent review suggesting that a score of over 9 may predict higher mortality, we used it only as an adjunct to evidence-based management. Our patient scored 4 on the FGSI.

### Pharmacology of SGLT2 Inhibitors

Empagliflozin is a member of the SGLT2 inhibitors class, which functions by inhibiting glucose reabsorption in the renal tubules, thus increasing urinary glucose excretion.[13] This mechanism helps lower blood glucose levels in patients with type 2 diabetes. While generally well-tolerated, adverse effects associated with empagliflozin include urinary tract infections and genital mycotic infections. However, these side effects are common across all SGLT2 inhibitors and are unlikely to be the cause in our male patient.[14]

### The Empagliflozin-Fournier's Gangrene Link

Recent case reports and studies have suggested a potential association between the use of SGLT2 inhibitors, including empagliflozin, and an increased risk of Fournier's gangrene (FG).[15] The exact mechanism by which these drugs may contribute to the development of this condition is not fully understood. Some hypotheses include the promotion of genital mycotic infections due to increased glucose in the genitourinary tract and the potential inhibition of immune responses.

Among all SGLT2 inhibitor therapies, empagliflozin is associated with the highest number of reports, totaling 232, while an empagliflozin and metformin combination therapy has shown the strongest association with the oc-

currence of FG. Canagliflozin was the second most prominent SGLT2 inhibitor associated with this issue. According to one study, 391 patients required initial or prolonged hospitalization (72.14%), and 26 patients died (4.81%). Interestingly, this paper reported no cases of FG associated with dapagliflozin/saxagliptin, ertugliflozin/metformin, ertugliflozin/sitagliptin, ipragliflozin, luseogliflozin, or tofogliflozin.[16]

## Regulatory Actions and Recommendations

Health regulatory agencies, including the U.S. Food and Drug Administration (FDA) and the UK Medicines and Healthcare Products Regulatory Agency,[4] have acknowledged the potential risk of Fournier's gangrene associated with SGLT2 inhibitors. Healthcare professionals are advised to monitor patients for signs and symptoms of Fournier's gangrene, which include pain, tenderness, redness, or swelling in the genital or perineal area, and to discontinue SGLT2 inhibitors if the condition is suspected or diagnosed.

## The Critical Care Management of Fournier's Gangrene

### *Prognostication*

The Fournier's Gangrene Severity Index (FGSI)[7] utilizes a number of physiological measures and variables to calculate a score. This score[17] combines physiological parameters such as body temperature, heart rate, respiratory rate, hematocrit, white blood count, and serum levels of sodium, potassium, creatinine, and bicarbonate, with weighting according to the degree of abnormality. In one validation study, the median FGSI score at admission was 2 (range 0–9) for survivors and 6 ( range 2–14) for non-survivors (p=0.004).[18] The FGSI provides a valuable guide for clinicians to discuss outcomes early in the care process with the multidisciplinary team and the next of kin.

### *Surgical Debridement*

Urgent and extensive surgical debridement is the cornerstone of treatment for Fournier's gangrene. This involves the removal of necrotic tissue to halt the spread of infection. Repeat debridement may be necessary, with early involvement of plastic surgeons recommended. Early consideration should also be given to fecal diversion techniques, which range from using devices such as the Flexi-Seal® Faecal Management System[19] (used in our patient), to intestinal diversion procedures with an external stoma. The latter ensures that fecal contamination of the debrided area is avoided. In our patient, this could have been considered earlier.

### *Early Appropriate Antibiotic Therapy*

In our case, early consultation with microbiologists ensured that appropriate empiric broad-spectrum antibiotic therapy was initiated promptly. This therapy covers a wide range of bacteria, including both aerobic and anaerobic organisms. Common choices include combinations of beta-lactam/beta-lactamase inhibitors, carbapenems, or piperacillin-tazobactam.

### *Fluid Resuscitation and Hemodynamic Support*

Fluid resuscitation and hemodynamic monitoring should adhere to the current guidelines on the management of sepsis.[20]

### *Nutritional Support and Diabetes Management*

Evaluating the nutritional status of the patient is important, as they are likely to stay in the critical care unit for an extended period and remain in a catabolic state for some time. Malnutrition, common in critically ill patients, may impair wound healing due to the variable metabolic needs associated with the condition. Research indicates[21] that patients with necrotizing fasciitis have increased energy requirements, potentially needing up to 124% of their basal caloric needs. Our patient's nutritional requirements were regularly assessed and managed by the critical care dietician through a combination of parenteral and enteral feeding regimens.

There is no consensus on whether SGLT2 inhibitors may be recommenced once patients stabilize in the context of Fournier's gangrene.[22] We chose not to restart empagliflozin for our patient.

### *Wound Care*

Close collaboration with the tissue viability team and their appropriate interventions were critical to our success with our patient. The use of specialist-guided, appropriate wound dressings to promote healing and prevent infection is important. Additionally, there are encouraging reports of negative pressure wound therapy providing improved infection control and analgesia.[23]

## Conclusion

While empagliflozin has shown efficacy in managing type 2 diabetes and heart failure, healthcare providers should be aware of the potential risk of Fournier's gangrene associated with its use. Patients taking empagliflozin should be educated about the signs and symptoms of Fournier's gangrene, and prompt medical attention should be sought if such symptoms arise. The decision to use empagliflozin should be made on an individual basis, weighing the benefits of glycemic control against the potential risks associated with this medication. Ongoing research is needed to further clarify the relationship between SGLT2 inhibitors and Fournier's gangrene, providing greater clarity for both clinicians and patients.

The management of established Fournier's gangrene is complex and necessitates a coordinated effort among healthcare professionals. Timely intervention and comprehensive care are essential to improving outcomes for these critically ill patients.

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