

Fournier Gangrene Alarm: More Cases Linked to Diabetes Drugs

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May 06, 2019

Fournier gangrene (FG), a necrotizing infection of the perineum, is a relatively rare but potentially fatal complication of treatment with sodium-glucose cotransporter-2 (SGLT2) inhibitors, new data from the US Food and Drug Administration (FDA) suggest.

The FDA had previously [added a warning](#) about FG to the labels of all SGLT2 inhibitors, used to treat [type 2 diabetes](#), in August 2018, based on 12 cases reported from March 2013 to May 2018.

Now, findings from a review of 55 cases reported to the FDA Adverse Event Reporting System (FAERS) through January 2019 have been [published online](#) May 6 in *Annals of Internal Medicine* by Susan J. Bersoff-Matcha, MD, of the FDA's Center for Drug Evaluation and Research, Silver Spring, Maryland, and colleagues.

All of the patients required hospitalization, some needed multiple surgeries, and there were three fatalities.

"Serious complications and death are likely if FG is not recognized immediately and surgical intervention is not carried out within the first few hours of diagnosis," Bersoff-Matcha and colleagues stress.

Pain Out of Proportion to Physical Exam Findings a Strong Clue

Pain that seems out of proportion to physical exam findings is a strong clue to [necrotizing fasciitis](#) and FG, the authors say, while systemic symptoms of FG such as fatigue, fever, and malaise, may be variable and nonspecific. Local symptoms may include tenderness, erythema, and swelling.

While diabetes itself also increases the risk for FG, the 55 reports associated with SGLT2 inhibitors in the 6 years since [canagliflozin](#) (*Invokana*, *Vokanamet*, Janssen), the first in class, was approved far exceeds the 19 FG cases reported over 35 years among patients receiving other classes of glucose-lowering drugs.

"If FG were associated only with diabetes...and not SGLT2 inhibitors, we would expect far more cases reported with the other antidiabetic agents, considering the 35-year timeframe and the large number of agents," the authors write.

Awareness of the association between FG and SGLT2 inhibitor use should be considered when deciding whether to prescribe the drugs, they advise.

"Although the risk for FG is low, serious infection should be considered and weighed against the benefits of SGLT2 inhibitor therapy."

FG Is Serious, Disfiguring, and Can Be Fatal

In their FAERS search, the authors included all reports of FG submitted between March 1, 2013, the day canagliflozin was approved, through January 31, 2019, in patients treated with FDA-approved SGLT2 inhibitors.

All patients had a necrotizing infection of the perineum (vulva/vagina or scrotum or buttocks), with surgical debridement in response to the infection.

A search of the medical literature yielded four such case reports, all of which had been reported to FAERS.

Cases were reported for all of the FDA-approved SGLT2 inhibitors except [ertugliflozin](#) (*Steglatro*, Merck), which was approved [most recently](#) (December 2017).

Patients were a median age of 56 years, most were men (39/55 cases), and most were reported in the United States (44 cases). The average time from initiation of the SGLT2 inhibitor to FG onset was 9 months, but the range was wide, from 5 days to 49 months.

All patients were severely ill with FG and were hospitalized. Although the number of surgeries was not consistently reported, at least 25 patients needed more than one surgical debridement, including one patient with a reported 17 trips to the operating room.

Eight patients underwent a procedure for fecal diversion and at least four patients had [skin grafting](#). The clinical course for some patients was complicated by [diabetic ketoacidosis](#) (n = 8), [sepsis](#) or [septic shock](#) (n = 9), or [acute kidney injury](#) (n = 4).

Some patients may have had more than one complication.

Necrotizing fasciitis of a lower extremity developed in two patients during hospitalization and required amputation. Another patient required a lower-extremity bypass procedure for gangrenous toes.

Three patients died.

Duration of acute hospitalization for the surviving patients ranged from 5 to 51 days. The SGLT2 inhibitor was discontinued in at least 22 of the 52 survivors.

Six patients had more than one visit with a provider before being diagnosed with FG, "indicating that the provider may not have recognized the diagnosis because of its nonspecific symptoms," Bersoff-Matcha and colleagues emphasize.

The authors are all FDA employees and have reported no further disclosures.

Ann Intern Med. Published online May 6, 2019. [Abstract](#)

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Cite this: Fournier Gangrene Alarm: More Cases Linked to Diabetes Drugs - *Medscape* - May 06, 2019.