

Received: 2021.01.04
Accepted: 2021.03.10
Available online: 2021.03.19
Published: 2021.04.21

e-ISSN 1941-5923
© Am J Case Rep, 2021; 22: e930889
DOI: 10.12659/AJCR.930889

Epinephrine Auto-Injection After Allergic Reaction Leading to Gas Gangrene of the Leg

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1 **Vincent Peyko**
DE 2 **Darius Shams**
CDE 3 **Allison R. Lauver**

1 Department of Pharmacy, Mercy Health – St. Elizabeth Boardman Hospital, Boardman, OH, U.S.A.
2 Department of Emergency Medicine, Mercy Health – St. Elizabeth Boardman Hospital, Boardman, OH, U.S.A.
3 Department of Pharmacy, Mercy Health – St. Elizabeth Youngstown Hospital, Youngstown, OH, U.S.A.

Corresponding Author: Vincent Peyko, e-mail: vpeyko2@gmail.com
Conflict of interest: None declared

Patient: Male, 60-year-old
Final Diagnosis: Gas gangrene
Symptoms: Pain
Medication: —
Clinical Procedure: Fasciotomy • surgical debridement
Specialty: Critical Care Medicine • Infectious Diseases

Objective: Rare disease

Background: Clostridial myonecrosis, also known as gas gangrene, is a highly lethal necrotizing soft tissue infection. While commonly associated with trauma, clostridial myonecrosis may be the result of parenteral injection of medications. Epinephrine is the most commonly reported medication leading to gas gangrene.

Case Report: A 60-year-old man presented to the Emergency Department (ED) with “the worst pain in his life” to the right thigh near the site at which he auto-injected epinephrine after multiple bee stings 10-11 h prior to arrival. Initial heart rate was 112 beats/min but all other vital signs were unremarkable at presentation. Due to extreme pain, a computed tomography (CT) scan was ordered, revealing prominent gas within the anterior compartment of the right thigh, mostly involving the vastus lateralis and rectus femoris, suggesting necrotizing fasciitis. Antimicrobials were initiated immediately and the patient was taken for surgical debridement within 70 min after obtaining the CT results. *Clostridium perfringens* was cultured from the patient's tissue. After several surgical debridement's, appropriate antimicrobial therapy, supportive care, and wound care, the patient's limb remained intact and he was discharged after 11 days.

Conclusions: With millions of epinephrine auto-injectors prescribed yearly in the United States, awareness of clostridial gas gangrene following epinephrine auto-injection for the provider may help guide decision-making in patients presenting with extreme pain, redness, or swelling near the injection site after epinephrine injection.

Keywords: *Clostridium perfringens* • Epinephrine • Gas Gangrene

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/930889>

 2022  —  1  13



Background

Clostridial myonecrosis, also known as gas gangrene, is an infection primarily of muscle tissue, of which more than 90% of cases are caused by *Clostridium perfringens* [1]. This is a highly lethal necrotizing soft tissue infection of skeletal muscle caused by toxin and/or gas-producing clostridial species [1]. The term necrotizing fasciitis lies within the general category of necrotizing soft tissue infections, which consists of 3 variants: necrotizing fasciitis, necrotizing cellulitis, and myonecrosis [1]. In the clinical setting, the term necrotizing fasciitis is often used for these overlapping variants [1].

Clostridium perfringens, formerly *Clostridium welchii*, is a gram-positive, spore-forming, anaerobic, rod-shaped bacteria [2]. This bacterium was first isolated by William H. Welch in 1891 and linked to gas gangrene symptoms seen in British and French soldiers during World War I [2]. Much of the literature on this topic is more than 50 years old, particularly prior to 1968, old enough that it refers to *Clostridium welchii*, prior to being renamed to *Clostridium perfringens* [3,4].

Contaminated wounds of the battlefield or traumatic accidents with extensive contamination are the most common etiology of clostridial gas gangrene [3-5]. Parenteral administration of medications is under-recognized as a potential source of gas gangrene, but there are many case reports in the literature describing gas gangrene as a result of parenteral administration of medications, particularly epinephrine [4,5].

We present the case of a patient who appropriately auto-injected himself in the anterolateral thigh with epinephrine, which led to clostridial myonecrosis in less than 24 h.

Case Report

A 60-year-old man presented to the Emergency Department (ED) with right-sided leg pain. The patient was allergic to bee venom and on the previous day was working in his garden and was stung on the face and neck by several bees. He injected himself with his prescribed epinephrine auto-injector through his jeans into his right anterolateral thigh. The patient had no problems for the rest of the day, but the following morning, 10-11 h after auto-injection, he presented to the ED reporting "the worst pain in my life," down his right thigh, where he had injected himself.

His past medical history included prostate cancer, hypertension, and hypothyroidism. Past surgical history included eye and ankle surgery. On physical examination, he generally appeared in acute distress, was morbidly obese, and diaphoretic. The right anterolateral thigh had extreme tenderness,



Figure 1. Anterolateral right thigh after initial debridement.

enough so that firm palpation for crepitus was not possible. Distal pulses were intact and the skin was warm. All other aspects of physical examination were normal.

On arrival to the ED, his blood pressure was 155/83 mmHg, heart rate was 112 beats/min, respiratory rate was 16 breaths/min, and oxygen saturation was 97% on room air. His initial temperature was 36.6°C, but increased to 38.5°C 1 h later. The patient weighed 142.9 kg.

Pertinent initial laboratory findings included: ALT 60 U/L, AST 42 U/L, bilirubin 1.5 mg/dL, WBC 9.8 E9/L, neutrophils 93.4%, and platelets 120 E9/L.

The thigh did not appear extremely erythematous or warm, with only a small induration where the patient had auto-injected. The lack of findings on physical exam with stable vital signs and laboratory values did not initially suggest an infectious etiology of the pain. However, due to the extreme pain, a computed tomography (CT) scan was ordered, which revealed prominent gas within the anterior compartment of the right thigh, mostly involving the vastus lateralis and rectus femoris, suggesting necrotizing fasciitis. Clindamycin 900 mg IV, piperacillin-tazobactam (PTZ) 4.5 g IV, and vancomycin 2.5 g IV were all immediately ordered, with clindamycin and PTZ initiated pre-operatively and vancomycin initiated intra-operatively.

Within 70 min of CT imaging results, the patient was in surgery for right leg debridement. A 10-cm incision was made in the anterolateral thigh with a Bovie-cut that was continued through the fascia. Immediately, the muscle bulged out, had palpable and visible crepitus, and dark malodorous liquefied muscle. The incision was extended toward the greater trochanter and the knee for a total incision of 30 cm in length, 10-cm width, and 5-cm depth (Figure 1). Anterior compartment fasciotomy was performed through an anterolateral incision with cautery, where muscle immediately bulged out, confirming compartment syndrome. The majority of the vastus lateralis, the

lateral aspect of the rectus femoris, and some of the Iliotibial band tendon were debrided.

On the following day, laboratory values were blood urea nitrogen (BUN) 39 mg/dL, serum creatinine 2.4 mg/dL, anion gap 17 mmol/L, lactic acid 3.1 mmol/L, C-reactive protein 16.3 mg/dL, total CK 11 603 U/L, ALT 61 U/L, AST 180 U/L, bilirubin 5.1 mg/dL, WBC 23.6 E9/L, neutrophils 88.7%, and platelets 200 E9/L.

Nephrology was consulted due to acute kidney injury (AKI). The patient had a metabolic acidosis secondary to AKI. Bicarbonate infusion 150 mEq in 1000 mL dextrose 5% water (D5W) was initiated at a rate of 200 mL/hr.

The wound was debrided again, clindamycin was discontinued, with PTZ 3.375 g IV over 4 h every 8 h, and vancomycin by level were the antibiotics that were continued.

By post-op day 2, the patient required intermittent hemodialysis, as his renal function continued to deteriorate, with only 20 mL urine output. Intermittent hemodialysis was planned to be continued beyond hospital discharge. The patient was subjectively feeling better. He was afebrile and hemodynamically stable, with no uncontrolled pain. The WBC was 13.0 E9/L with liver function tests (LFTs) down-trending, and bilirubin normalized to 1.0 mg/dL. Total CK was 12 765 U/L. Dressings were changed wet to dry twice daily and the wound appeared to be in good condition. Hyperbaric oxygen therapy was initiated with a plan of 10 total treatments.

By post-op day 4, *Clostridium perfringens* was identified from wound cultures. Vancomycin was discontinued. Total CK continued to downtrend at 2278 U/L and the WBC was 10.4 E9/L. The patient was regaining strength in right leg and moved from the ICU to the medical floor.

On post-op day 5, antibiotics were changed to ertapenem 500 mg IV once daily. Excisional debridement of fascia and muscle was performed with placement of a vacuum-assisted wound closure device (wound vac) for topical negative-pressure therapy, and he was tolerating an oral diet.

By post-op day 8, the patient continued to improve and was taken back to the OR for debridement, wound vac change, and placement of a tunneled dialysis catheter.

By post-op day 11, the patient was discharged in stable condition and placed in a long-term acute care facility. He was feeling much better but would need long-term, 3 times per week, intermittent hemodialysis and 3 more days of IV antibiotics to complete a 14-day course.

Seven days after discharge, it was decided to continue hyperbaric oxygen therapy beyond the initial plan of 10 sessions, as he was still continuing intermittent hemodialysis.

Thirty days after initial presentation, the patient had his dialysis catheter removed, as the acute kidney injury had resolved.

By 36 days after discharge, the patient had completed HBO therapy, the wound was healing very well and closing up, he was able to walk “fairly decently,” and did not have any significant pain.

Discussion

Clostridial myonecrosis occurs through 1 of 3 mechanisms: (1) Areas of major trauma, surgery, or thermal burn complications; (2) Minor trauma from skin punctures like parenteral injections of medications or insect bites; and (3) Non-traumatic or spontaneous infections through activation of dormant clostridial spores or bacteremic spread from a primary site [1].

Clostridial spores originate from decaying vegetation and are often found on normal skin [6]. Clostridial infections from injection occur as spores are transmitted from the skin surface to deep tissue [6]. Our patient was working in his garden and he injected himself into his thigh through the jeans. The rate of infection increases by 100 000-fold in guinea pig thigh models injected with 2 mcg of epinephrine [7]. Rapid reproduction is possible due to suitable, nutrient-rich conditions of the muscle, which enable spores to germinate. Local conditions conducive to germination may be enhanced by tissue necrosis and local ischemia induced through vasoconstriction produced by epinephrine, which can lower local oxygen tension, enabling anaerobic organisms to flourish [3,6]. The incubation time of clostridial myonecrosis is typically less than 24 h, with many patients presenting to the hospital with signs and symptoms of septic shock [8]. Our patient did present within 24 h of symptom onset, but did not have signs or symptoms of septic shock. Renal failure is a common complication of clostridial myonecrosis due to the effects of hypotension and the direct nephrotoxicity of clostridial toxins, which progressed in our patient within 24 h of presentation [8].

Treatment involves the combination of surgical debridement, antibiotics, intensive care support, wound care, and rehabilitation [8].

Early, aggressive surgical intervention is imperative, with delays in surgery of more than 12 h associated with higher morbidity [8]. Amputation is usually necessary to control infection and save life, with limb preservation being rare; however, there is no evidence amputation controls infection better than adequate

surgical debridement [8]. Wide resection of all necrotic tissue is essential, with only muscle that bleeds when cut and contracts upon stimulation being left. Fasciotomies are vital to prevent compartment syndrome. Our patient had all devitalized tissue surgically removed with fasciotomy to treat compartment syndrome while salvaging the limb [8].

Prompt initiation of antimicrobials covering aerobic and anaerobic spectrums is necessary [8]. Clinical trials have not identified optimal regimens; however, combinations with PTZ and clindamycin are suggested for *Clostridium perfringens* [8]. Because clostridial septicum may be resistant to penicillin or clindamycin, empiric vancomycin would also be reasonable to add [8]. We initiated clindamycin, PTZ, and vancomycin in the ED to appropriately cover potential clostridial gas gangrene.

Our patient had 22 ninety-minute hyperbaric oxygen (HBO) therapy sessions. Despite a lack of randomized controlled studies, HBO therapy has demonstrated a statistically significant reduction in mortality for patients with necrotizing soft tissue infections [9]. A retrospective study evaluating over 20 years of data identified 405 patients that received HBO therapy, with a mortality rate of 4.5% vs 9.4% mortality in patients not receiving HBO therapy ($P=0.001$) [9].

HBO therapy increases tissue oxygen tension, which can illicit bacteriostatic effects on clostridial species and halt toxin production [10]. Raising oxygen tension can improve neutrophil function and improve the action of antibiotics, while HBO can also stimulate fibroblasts and assist with wound healing and closure [10].

Likewise, topical negative-pressure therapy (TNP) lacks significant evidence to demonstrate definitive conclusions to aid wound healing. Our patient had a wound vac placed 5 days after initial presentation, which was maintained through day 36. Studies do support the mechanisms central to TNP, which include increased dermal perfusion, stimulation of granulation tissue formation, reduced edema and interstitial fluid, reverse tissue expansion, and reduced bacterial colonization [11].

Despite robust evidence, TNP is recommended for acute wounds associated with necrotizing fasciitis [11].

Infection after parenteral injection is rare, with less than 40 cases of gas gangrene associated with injections reported since 1960 [6]. Intramuscular and subcutaneous injections were implicated with a variety of drugs leading to infection [6]. However, the most commonly reported medication leading to gas gangrene is epinephrine [6]. While under-recognized, with few published reports in the recent past, epinephrine auto-injector package inserts do carry the warning of gas gangrene risk [12].

Mitigation of this risk is difficult. Skin preparation with alcohol swabs will not kill clostridial spores. However, it would be prudent to avoid injection through soiled skin or clothing, if possible.

Although parenteral administration of epinephrine is a rare etiology for gas gangrene, gas gangrene is rare in general. However, the extreme urgency to save life and limb mandates prompt recognition. The aggressive combination of multiple surgical debridements, fasciotomy, antimicrobial therapy, renal replacement therapy, and wound care led to total limb salvage and recovery for our patient [8].

Conclusions

In recent years, there has been a 67% increase with 3.6 million Americans using epinephrine auto-injectors [13]. Given the risk to loss of life or limb, any delay of recognition of clostridial gas gangrene can be devastating to the patient. Awareness of clostridial gas gangrene following epinephrine auto-injection for the provider may help guide decision-making in patients presenting with extreme pain, redness, or swelling near the injection site after epinephrine auto-injection.

Conflicts of Interest

None.

References:

1. Larson K, Grone G, Austin, et al. Epinephrine auto-injection radically increases risk for clostridial infection and necrotizing fasciitis. *Emerg Care J.* 2017;13:6256
2. Kiu R, Hall LJ. An update on the human and animal enteric pathogen *Clostridium perfringens*. *Emerg Microbes Infect.* 2018;7(1):141
3. Gas gangrene from adrenaline. *Br Med J.* 1968;1(5594):721
4. Hallagan LF, Scott JL, Horowitz BC, Feied CF. *Clostridial myonecrosis* resulting from subcutaneous epinephrine suspension injection. *Ann Emerg Med.* 1992;21(4):434-36
5. Koons T, Boyden G. Gas gangrene from parenteral injection. *JAMA.* 1961;175:46-47
6. Stuart Hannah RC, Heddle R, Smith W. Fatal gas gangrene related to self-injection treatment of anaphylaxis. *Ann Allergy Asthma Immunol.* 2011;106(6):538
7. Chin RL, Martinez R, Garmel G. Gas gangrene from subcutaneous insulin administration. *Am J Emerg Med.* 1993;11(6):622-25
8. Aggelidakis J, Lasithiotakis K, Topalidou A, et al. Limb salvage after gas gangrene: A case report and review of the literature. *World J Emerg Surg.* 2011;6:28
9. Soh CR, Pietrobon R, Freiburger J, et al. Hyperbaric oxygen therapy in necrotising soft tissue infections: A study of patients in the United States Nationwide Inpatient Sample. *Intensive Care Med.* 2012;38(7):1143-51
10. Wilkinson D, Doolette D. Hyperbaric oxygen treatment and survival from necrotizing soft tissue infection. *Arch Surg.* 2004;139(12):1339-45
11. Bovill E, Banwell P, Teot L, et al. International Advisory Panel on Topical Negative Pressure. Topical negative pressure wound therapy: A review of its role and guidelines for its use in the management of acute wounds. *Int Wound J.* 2008;5:511-29
12. Epinephrine. [package insert] EPIPEN®; EPIPEN, Jr®. Meridian Medical Technologies, Columbia, MD ©2017. April 2017
13. Tunney K. Millions of Americans use EpiPens. *Bustle.* Aug 2016. [Accessed September 2020] <https://www.bustle.com/articles/180800-how-many-people-use-epipens-in-america-my-lans-price-increase-is-taking-advantage-of-its-users>