Flow-through Instillation of Hypochlorous Acid in the Treatment of Necrotizing Fasciitis

John R. Crew, MD1; Kerry T. Thibodeaux, MD, FACS2; Marcus S. Speyrer, RN, CWS2; Anibal R. Gauto, MD3; Timothy Shiau, PhD4; Liliana Pang4; Keith Bley, PhD5; and Dmitri Debabov, PhD4

Abstract: Introduction. Necrotizing fasciitis (NF) is a rare and rapidly progressing bacterial infection of soft tissues. Bacterial toxins cause local tissue damage and necrosis, as well as blunt immune system responses. A self-propagating cycle of bacterial invasion, toxin release and tissue destruction can continue until substantial amounts of tissue become necrotic. Neutralization of bacterial toxins should improve the results. Materials and Methods. Pure hypochlorous acid (HOCl) (0.01% w/v) with no sodium hypochlorite impurity in saline pH 4-5, which was recently shown to both eradicate bacteria and neutralize bacterial toxins in vitro, was administered via flow-through instillation to 6 patients with NF 4-6 times daily as needed. Utilizing a vacuum-assisted closure, 5-10 mL of pure 0.01% HOCl with no sodium hypochlorite impurity was instilled and removed frequently to irrigate the wounds. Results. Of the 6 patients, no deaths or limb amputations occurred. All infected areas healed completely without major complications. Conclusion. The toxicity and immune dysfunction caused by bacterial toxins and toxins released from damaged cells may be mitigated by flow-through instillation with saline containing pure 0.01% HOCl with no sodium hypochlorite impurity. Randomized controlled clinical trial research of this relatively simple and inexpensive instillation protocol is suggested for identified cases of NF.

Key words: necrotizing fasciitis, negative pressure, tissue repair

Necrotizing fasciitis (NF), commonly referred to in nonmedical discourse as “flesh-eating” inflammation, is a rapidly progressing involvement of the fascia and subcutaneous tissues that can subsequently extend to the muscles and skin. Type I NF is classified as a polymicrobial infection, whereas type II NF is classified as a monomicrobial infection.1 Bacterial toxins released during the course of necrotic inflammations produce direct cytotoxic effects on surrounding tissues, while also causing immune system dysfunction and localized immunosuppression. The authors’ new therapy incorporates the use of an instillation vacuum-assisted closure procedure, also known as negative pressure wound therapy (NPWT), with pure 0.01% hypochlorous acid (HOCl) with no sodium hypochlorite—commonly
known as bleach—impurity. As pure 0.01% HOCl (ie, > 97% relative molar distribution of active chlorine species as HOCl) in a 0.9% saline solution at pH 4-5 has been shown to both rapidly kill bacteria and neutralize bacterial toxins in vitro, clinical administration of pure HOCl with no sodium hypochlorite impurity was recently explored in 1 case of NF of the upper arm. The method of administration used in the treatments presented here evolved to allow treatment of NF in diverse anatomical regions, which included the genitalia (Fournier’s gangrene), lower abdomen and upper thigh, breast, chest, lower leg, and finger. This case series describes using NPWT instillation (I-NPWT) with 0.01% pure HOCl (NeutroPhase, NovaBay Pharmaceuticals, Inc., Emeryville, CA).

**Methods and Materials**

As each necrotizing wound is unique with respect to anatomical location and extent of involvement, elements of the treatment protocol—such as the volume of pure HOCl solution instilled and the degree of negative pressure—were unique for each patient. Generally, before treatment, necrotizing wound areas were cleansed, debrided, and the skin dried. Subsequently, V.A.C. GranuFoam, V.A.C. VeraT.R.A.C, or V.A.C. VeraFlo (all from KCI, an Acelity Company, San Antonio, TX) dressings were sized and placed in the wounds. In-flow tubes constructed using intravenous line extensions with ports were inserted through or under the foam dressings. Areas around the in-flow tubes were sealed with Stomadhesive Paste (CovaTec, Inc, Bridgewater, NJ). Adhesive drapes were attached and placed over the entire area, including the foam dressings. Negative pressure was then turned on and adjusted from 50-125 mm Hg suction. The 0.01% pure HOCl (5-10 mL) was instilled via a syringe through the inlet port into the wound bed with the vacuum off for 5 minutes, and then the vacuum was restored. Larger wounds however, required more than 10 mL. Pure HOCl instillations were performed 4-6 times per day, depending on the overall severity of the wound.

**Results**

Among 6 subjects with NF managed with I-NPWT, all 9 infected areas healed completely without major complications, limb amputation, or patient death. Results are summarized in Table 1.

**Table 1. Summary of results.**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Infection site</th>
<th>Bacteria cultured</th>
<th>Treatment</th>
<th>Healing time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>54</td>
<td>M</td>
<td>Fournier's gangrene</td>
<td>Scrotum and penile base</td>
<td>Serratia, Enterobacter</td>
<td>Debridement, 0.01% HOCl every 4 hours Using NPWT with antibiotics</td>
<td>1 month</td>
</tr>
<tr>
<td>2</td>
<td>41</td>
<td>F</td>
<td>Necrotizing fasciitis</td>
<td>Lower abdomen and right upper thigh</td>
<td>N.D.</td>
<td>Suctioning of necrotic tissue; 0.01% HOCl and NPWT</td>
<td>3 weeks</td>
</tr>
<tr>
<td>3</td>
<td>23</td>
<td>M</td>
<td>Necrotizing fasciitis</td>
<td>Left hand middle finger</td>
<td>Methicillin-resistant Staphylococcus aureus</td>
<td>Antibiotics 0.01% HOCl flow through with NPWT</td>
<td>Closed in 15 days</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td></td>
<td>Necrotizing fasciitis</td>
<td>Lower leg</td>
<td>N.D.</td>
<td>0.01% HOCl flow through with NPWT skin graft</td>
<td>10 weeks with split-thickness skin graft</td>
</tr>
<tr>
<td>5</td>
<td>52</td>
<td>F</td>
<td>Necrotizing fasciitis</td>
<td>Left breast and chest wall</td>
<td>Pseudomonas aeruginosa</td>
<td>Invanz, vancomycin, debridement, 50 mL of 0.01% HOCl every 5 hours</td>
<td>2 months</td>
</tr>
<tr>
<td>6</td>
<td>50</td>
<td>M</td>
<td>Skin necrosis</td>
<td>Lower legs</td>
<td>Methicillin-resistant Staphylococcus aureus</td>
<td>Vancomycin, debridement, NPWT 10 mL of 0.01% HOCl every 4 hours for 6 days; split-thickness skin graft</td>
<td>2 months</td>
</tr>
</tbody>
</table>

N.D.: no data; NPWT: negative pressure wound therapy; HOCl: hypochlorous acid
Patient 1 was a 54-year-old male with abrupt onset of pelvic Fournier’s gangrene (Figure 1). Immediate debridement was performed by removing the necrotic soft tissue of the scrotum and penile base. Testicles and cords were surgically stored immediately in bilateral thigh muscle pockets created to protect them, as their blood supply comes from the abdominal source down the cord. A bacterial culture revealed *Serratia* and *Enterobacter*. Immediately thereafter, the instillation of pure 0.01% HOCl with no sodium hypochlorite impurity every 4 hours was initiated. In contrast to the potential course of Fournier’s gangrene, necrosis did not progress up into the abdomen. Within 2 weeks, the inflammation resolved and healing began, allowing the thigh-stored testicles and cord to be surgically freed and replaced when the split-thickness skin graft (STSG) was used to replace the scrotum 14 days postoperatively. Within 1 month, the area was healed via the use of the STSG for a scrotum and penile base covering.

Patient 2 was a 41-year-old female with NF of the lower abdomen and right upper thigh (Figure 2). The authors began by using multiple small incisions without removing infected fascia, just surgically suctioning out necrotic cellular debris from the subcutaneous tissue, and then using the pure 0.01% HOCl with no sodium hypochlorite impurity instillation/NPWT technique with in-flow through multiple ports. This resulted in far less scarring with less pain and more rapid healing than typical cases.

Patient 3 was a 23-year-old male with a history of IV amphetamine abuse who was diagnosed with NF of the middle finger. The patient cultured methicillin-resistant *Staphylococcus aureus* and, after successful treatments with the flow-through HOCl paradigm, he was discharged in 15 days with primary surgical closure.

Patient 4 was a female with NF of the lower leg. She was intubated for 16 days in a coma that was reversed 2 days after removal of the necrotic tissue and neutralization of the toxic shock syndrome toxin (TSST) with the flow-through pure HOCl paradigm. A skin graft was then applied. She showed complete neurological recovery within 2 days (Figures 3A-3C).

Patient 5 was a 52-year-old female with a *Pseudomonas aeruginosa* infection causing NF of her left breast and chest wall. The patient’s infection was treated with Invanz (Merck & Co, Inc, Whitehouse Station, NJ) and vancomycin intravenously. Following debridement, 50 mL of pure HOCl with no sodium hypochlorite impurity was instilled for 5 minutes every 5 hours using the
previously mentioned V.A.C. Ulta NPWT system. The patient also received hyperbaric oxygen therapy at twice the present normal atmosphere outside the chamber for 90 minutes daily for 4 weeks. After 1 month, her wounds to the abdomen and chest were free of necrotic tissue and NPWT alone was used for these remaining wounds, which healed completely after another month (Figures 4A-4D).

Patient 6 was a 50-year-old male who previously developed painful skin necrosis on both lower legs. He underwent surgical debridement of his lesions and was discharged under the care of visiting nurses. After 3 weeks, he returned with severe necrotizing inflammation involving fascia, muscle, tendon, and skin on both lower legs again (Figures 5A-5C). Cultures were positive for methicillin-resistant *S. aureus*, and he was started on vancomycin intravenously. He underwent multiple surgeries for debridement of all necrotic tissues and was started on wound instillation with pure HOCl with no sodium hypochlorite impurity at 10 mL every 4 hours with NPWT and with in-flow through multiple ports for 6 days. His wounds were skin grafted successfully and have all healed.

**Discussion**

Necrotizing fasciitis is a rapidly progressing, life-
threatening inflammation of the deeper fascia and subcutaneous tissues and derives its name from the frequent spread of necrosis via fascial planes. Many types of bacteria can cause NF, including Group A Streptococcus (*Streptococcus pyogenes*), Group B Streptococcus (*Streptococcus agalactiae*), *S. aureus*, *Vibrio vulnificus*, *Clostridium perfringens*, and *Bacteroides fragilis*. Group A *Streptococcus* is considered the most common cause of NF. Although NF is usually started and driven by bacteria and rarely started or complicated by fungi, instances of fungal-driven NF have been reported in patients with uncontrolled diabetes.

The highly invasive nature of bacterial infections that give rise to NF can be explained by their ability to secrete toxins that cause local tissue destruction and unproductive activation of the immune system. For instance, streptococci can release “superantigens,” exotoxins that produce nonspecific T-cell activation and massive proinflammatory cytokine and chemokine release throughout the body. This highly exaggerated, nonlocalized immune system activation attenuates the ability to target invasive bacteria. So many novel streptococcal superantigens have been described that a comprehensive classification has recently been proposed. *Streptococcus pyogenes* expresses several superantigens that are strong immunostimulants, such as streptococcal pyrogenic exotoxin (Spe) A and SpeC. Similarly, *S. aureus* expresses several types of superantigens that can corrupt the normal immune response. Examples of staphylococcal superantigens include TSST-1 and enterotoxins, of which there are 6 antigenic types. Toxic shock syndrome toxin causes massive proliferation of T-cells and a massive release of proinflammatory cytokines.

Bacteria that cause NF also generate enzymes like hyaluronidase and collagenase, enabling horizontal extension through deep fascial planes. *Streptococcus* and *Staphylococcus* pathogens use hyaluronidase as a virulence factor to destroy the polysaccharide that holds animal or human cells together, making it easier for the pathogen to spread through the tissues of the host organism. As this process progresses, thromboses in blood vessels causes progressive dermis and skin ischemia, leading to bullae formation, ulceration, and skin necrosis. Accordingly, NF-associated bacteria produce direct cytotoxic effects on surrounding tissues as they simultaneously cause immune system dysfunction.

Once a high probability diagnosis of NF is achieved, current therapy is surgical treatment of the necrotic tissue,
which usually entails debridement fasciotomy. Boundaries of the incision should comprise healthy, bleeding tissue. Intensive care, including fluid resuscitation, pressor support, cardiac monitoring, and ventilator support are usually necessary. It is widely agreed that broad-spectrum IV antibiotic therapy should be maintained until the causative organism(s) have been identified. When the causative pathogens are identified, antibiotics should be tailored to the specific infection. However, the importance of early surgery cannot be overestimated, as antibiotics alone cannot cure NF. Other additional therapies such as IV immunoglobulin and postsurgery hyperbaric oxygen can also be useful.

Given the importance of the localized etiology of NF, the removal of tissue debris and destructive toxins is predicted to improve outcomes. Indeed, NPWT has been used for more than a decade for some patients with NF. Generally, NPWT seems to provide benefits to NF patients.

The authors' new paradigm includes the addition of pure HOCl with no sodium hypochlorite impurity to NPWT to create a flow-through instillation procedure, and it is based on the observation that this oxidizing compound can not only kill bacteria at concentrations well tolerated by mammalian cells, but also inactivate bacterial toxins and superantigens in vitro. The authors' discovery case was a 51-year-old female who presented with swelling and tenderness to her left arm and a fever after she had a fall. Culturing Group B Streptococcus, she was diagnosed with cellulitis. Her condition worsened, and she developed leukocytosis with a white blood cell count as high as 16,000. She required an emergency incision and drainage of the upper arm. An instill-type NPWT was placed to instill 10 mL of pure HOCl every 4 hours. Unfortunately, another area of the forearm became symptomatic and required an incision and drainage. Dual instillation NPWT ports were placed. Any surrounding subcutaneous areas were also irrigated with pure HOCl every 4 hours. Simultaneously, she was treated with IV vancomycin, clindamycin, and cefazidime. Her condition improved, and she was discharged with a home NPWT device to instill pure HOCl 3 times every 24 hours. In this case series report, the authors expand their clinical experience from the first case to include 6 additional cases with much more challenging localizations. Note that no diagnostic tests for bacteria or bacterial toxins were required before initiating the flow-through instillation procedure, and no special equipment or supplies were required that are not commonly available in any hospital. No loss of life or limb amputations occurred in the 6 cases. Historically, the mortality rate for NF is about 20%, with amputations occurring in 26%-28% of patients with an extremity involved.

According to the US Centers for Disease Control and Prevention, "Each year in the US, there are about 650-800 cases of necrotizing fasciitis caused by [Group
A Streptococcus]; this is likely an underestimation as some cases are probably not reported or caused by other pathogens. According to [Active Bacterial Core] surveillance data, the number of annual infections does not appear to be rising. Other sources report the incidence of NF to be 0.4 cases per 100,000 inhabitants in the United States, while in Western Europe it is about 1 case per 100,000 inhabitants.13,20,21 Necrotizing fasciitis is seen predominantly in adult patients, with incidence increasing progressively with age, reaching 12 cases per 100,000 in subjects older than 80 years.22 In children, the reported rate is 0.08 cases per 100,000.23 More than half of patients with NF have preexisting conditions that render them susceptible to infections, such as obesity, diabetes mellitus, chronic renal failure, peripheral vascular disease, drug misuse, alcohol abuse, liver disease, malignancy, and chemotherapy.10

In almost all NF cases, there is a precipitating event such as surgery or an injury that penetrates the skin. Establishing the diagnosis of NF is challenging but critical, as rapid diagnosis results in early therapy and decreased mortality and morbidity. Sadly, early diagnosis is missed in as many as 85%-100% of cases.13 While existing treatment practice places substantial emphasis on rapid eradication of the bacterial infection that has initiated the NF, there are few or no attempts to either neutralize bacterial toxins or to mitigate the prolonged and potentially destructive immune system response to bacteria and their toxins. Pure 0.01% HOCl is well-tolerated by human tissues and has both broad-spectrum antimicrobial activity and can rapidly neutralize bacterial toxins.2,18,24 Pure HOCl with no sodium hypochlorite impurity has a substantially higher therapeutic index than sodium hypochlorite (ie, Dakin’s solution, commonly known as diluted bleach).18 A randomized controlled clinical trial is needed to evaluate potential advantages of the regimen augmented with instillation of pure 0.01% HOCl compared to standard care.

Conclusion

In summary, NF is a life-threatening necrosis-inducing inflammation that is present worldwide and will continue to grow in prevalence despite extremely high doses of antibiotics. It appears the toxicity and immune dysfunction caused by bacterial toxins and superantigens, in combination with the cellular toxins released from damaged cells, may be mitigated by flow-through instillation with saline containing pure 0.01% HOCl with no sodium hypochlorite impurity. The authors encourage expanded training and vigilance regarding the diagnosis of NF and they urge randomized controlled clinical research of this relatively simple and inexpensive instillation protocol for identified cases.

References


WOUNDS® www.woundsresearch.com


