

# Necrotizing clostridial soft tissue infection: does IVIG have a role?

## Abstract

Necrotizing soft tissue infections are fulminant infections associated with a severe systemic inflammatory response. The Center for Disease Control and Prevention reports an annual incidence of 500 to 1000 cases. They are characterized by rapid progression along tissue planes, necrosis, and a fatal course. Early diagnosis, treatment with antimicrobials, and surgical management are the cornerstones of treatment. We report a case of clostridial soft tissue infection of the abdominal wall and thigh that was rapidly spreading despite treatment with antimicrobials and multiple surgical debridements. The patient had chronic medical conditions and severe sepsis requiring vasopressors for hemodynamic support. He showed dramatic improvement after receiving high dose intravenous immunoglobulin (IVIG) for one day. No further spread of gas gangrene was noted, and pressors were weaned off over the next three days. Traditionally, IVIG is reserved for necrotizing soft tissue infections (NSTIs) caused by a group A *Streptococcus*. However, large batches of pooled IVIG contain antibodies to clostridial exotoxins. Our report highlights the importance of IVIG as an adjunct to conventional treatment under certain circumstances.

**Keywords:** Clostridium, Erythema, Perfringens, Immunoglobulin, Myonecrosis

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**Abbreviations:** IVIG, Intravenous Immunoglobulin; NSTIs, Necrotizing Soft Tissue Infections; COPD, Chronic Obstructive Pulmonary Disease; CVP, Central Venous Pressure

## Background

Clostridial soft tissue infections are rare. They amount to 5% of all infections but can be rapidly fatal. Clostridial infections are notable for their rapid progression. Gas gangrene, myonecrosis, and fasciitis are most commonly caused by *Clostridium perfringens*, a Gram positive, anaerobic, spore forming bacillus. They are ubiquitous and are found in soil. Clostridial myonecrosis is usually caused by deep penetrating wounds but spontaneous infections have been reported in immune-compromised hosts.

## Case report

A 61 year old man had a long history of large ventral hernia. He presented to the emergency department of a community hospital with a one day history of severe abdominal pain, nausea, and vomiting. Of note, his medical history was significant for hypertension, COPD, diabetes, and alcoholic cirrhosis. On arrival in the emergency department, he had a heart rate of 93, systolic blood pressure of 85mm of Hg, and diastolic blood pressure of 62 mm of Hg, and  $spO_2$  of 97%. CT scan of the abdomen showed 19 x 16 cm ventral hernia with loops of large bowel. There were no ischemic changes in the wall of the bowel but significant mesenteric stranding. All positive findings in the lab work are listed in Table 1.

The patient was transferred to our institution after three days, due to worsening physical examination, rising creatinine, and a persistently high lactate level of 25 mg/dl. An emergent exploratory laparotomy was undertaken and he was started on IV cefoxitin and flagyl. On entry into the abdominal cavity, 25 cm of necrotic bowel with two areas of frank gangrene was found. Bowel was excised and sent for pathology along with omental tissue and part of the abdominal wall showing sub epidermal blistering. Patient was resuscitated intra-operatively with three units of fresh frozen plasma, one liter of albumin and 1500ml of

normal saline. Blood loss was estimated to be 800ml. Central Venous Pressure (CVP) ranged from 17 to 19. However, he continued to require Dopamine for hemodynamic support.

**Table 1** Positive findings in the lab work

Lab Data	
WBC	9.8
Hemoglobin	18.4
Hematocrit	53.0%
Neutrophils	92%
Platelets	216
Lactate	33
S Creatinine	1.5
U/A	Negative

Upon arrival in the ICU, patient remained stable overnight and his lactate level dropped to 1.5. However he became hypotensive the following morning. He was intubated and norepinephrine and vasopressin infusions were started to keep mean arterial pressure above 65 mmHg. On physical examination, erythema was noted extending approximately 4 cm on each side of the incision, with crepitus which extended beyond the erythema. A similar 5 x 6 cm lesion was noted on the right thigh. At this time, a STAT call was made to the pathology lab for evaluation of the surgical specimen. Microscopy revealed Gram positive cocci and bacilli with spores. At this point, the diagnosis of gas gangrene with *Clostridium perfringens* was entertained.<sup>1,2</sup> His antibiotics were switched to clindamycin, vancomycin and primaxin. He had documented allergy to penicillin.

In light of the new diagnosis and the hemodynamic instability, the patient was taken to the operating room for wide debridement and excision. His procedure went uneventfully. Patient returned to the surgical ICU but remained acidotic with a base deficit. Over the next six hours, his pressor requirements began to increase. Spreading erythema and crepitus beyond the margins of erythema prompted another emergent debridement and irrigation. Patient returned to the ICU but remained in critical condition. He was taken to the operating

room the same day again for the same scenario. However, the patient became unstable the next morning with a drop in the urine output (UOP) and elevation in liver enzymes and troponin. At this point he had had four surgeries in a period of 48 hours. His abdomen again showed spreading erythema. A STAT echo cardiogram showed severe right sided heart failure.

At this point, a decision was made not to do any further debridement. Dobutamine was added for heart failure with little improvement in his hemodynamics. His arterial blood gas (ABG) at the time was pH 7.28/pCO<sub>2</sub> 30/pO<sub>2</sub> 80/HCO<sub>3</sub> 14/BE<sub>-</sub>12. Instead we decided to give high dose IVIG to neutralize the exotoxins.<sup>3</sup> He was given 3G/KG IVIG over 12 hours. We marked the areas of erythema and crepitus sites and closely monitored the patient via serial exams. No further spread was noted over the next 12 hours. We then inserted a Swan Ganz catheter to better monitor his cardiac output. His swan data were consistent with cor pulmonale. His figures are displayed in Table 2.

**Table 2** Swan Ganz catheter data were consistent with cor pulmonale

Lab Data	
CVP	37
PAS	66
PAD	45
CI	1.6
PCWP	24
Mixed Venous sPO <sub>2</sub>	46%

We replaced dobutamine with Milrinone with elevation of cardiac output to 6.1 with the bolus of 50 µg/kg/min. CI remained >2.6 with a maintenance dose of 0.375µg/kg/min. His mixed venous blood gas increased to 81%. We stopped infusion of all intravenous fluids in the next 48 hours. The patient cleared his acidosis and his BE was reduced by 50%. He was weaned off all his pressors 48 hours after administration of IVIG and was extubated a day later. The remainder of his ICU stay was fairly uneventful. He went to the operating room multiple times for exploratory laparotomies and change of vacuum dressings, all with no complications. There was no evidence of persistent infection on naked eye examination. Specimens sent to the lab for cultures were negative for bacteria or spores. He was eventually discharged to a rehab facility on hospital day 65. His final cultures grew only anaerobic Gram positive bacilli which confirmed our preliminary diagnosis of Type III necrotizing fasciitis (Table 3).<sup>4</sup>

**Table 3** Features of type III necrotizing fasciitis

Features of Type III Necrotizing Fasciitis
Rapid progression upto 2 cm an hour
Muted host response
Deep penetrating wound
Crush Injury
Intestinal surgery
Obstetric Complication i.e. PROM
Heroine Injections

## Discussion

Necrotizing fasciitis remains a serious illness with a mortality rate ranging between 30 to 60%. Its treatment is challenging, antibiotics and surgical treatment remain the mainstay of treatment. But clinical course frequently gets complicated with severe or recurrent sepsis, wounds involving large surface area, non-healing, fistula formation due to bowel adherence and contamination of the wound with bowel contents or other body fluids. They have a prolonged need for

mechanical ventilation and tend to have longer ICU stays. Severity of illness is high in infections caused by clostridia due to their ability to produce exotoxins. Alpha toxin is a zinc metalloproteinase which causes vascular leak, hemolysis, thrombocytopenia and liver damage. Theta toxin is an oxygen labile toxin causing leukostasis, thrombosis, decreased tissue perfusion and tissue hypoxia. Both toxins caused profound bradycardia when purified toxins were injected in experimental animals. Both Alpha and Theta toxins reduce cardiac output by myocardial suppression. The combination of reduced cardiac output and vascular leak leads to profound shock, in addition to the above mentioned toxins, Clostridia also produce lecithinases and Phospholipase which play key role in cell destruction and tissue necrosis by destroying lecithin (phosphatidylcholine) and phospholipids in cell membranes (Table 4). There are small series of case reports as well as clinical trials reporting the use of IVIG in a variety of clinical settings. FDA has approved it for use in idiopathic thrombocytopenic purpura, primary immune deficiency, B-cell CLL and as prophylaxis in stem cell recipients. It is also used in toxic shock syndrome caused by Group A *Streptococcus* and *Staphylococcus* as well as in recurrent *C. difficile* colitis.<sup>4-7</sup> Tetanus immunoglobulin (TIG) is used in non-immunized adults who sustain high risk or contaminated wounds. Specific immunoglobulins are also used in hepatitis A and B. However, clinical data for IVIG use in sepsis has been conflicting or equivocal at best.

**Table 4** Clostridial exotoxin

Clostridial Exotoxin	
α-toxin	Hemolysis and Decreased Inotropy
θ-toxin <sup>5</sup>	Hemolysis and Direct Vascular Injury
κ-toxin	Collagenase <sup>6</sup>
γ-toxin	Hyaluronidase

IVIG exhibits contrasting properties depending on its concentration and dose. At low doses it is primarily pro-inflammatory and activates complement. At high doses it is anti-inflammatory. Proposed mechanisms include scavenging of active complement fragments (C3b, C4b, C3a, C5a) which prevents further immune damage. IVIG has both monomeric and dimeric components in dynamic equilibrium. Electron microscopic images show that dimeric IVIG exhibits greater activity against bacterial toxins [8]. Dimeric IgG fractions from large donor pools are rich in antibodies with certain specificities, which explain their ability to neutralize circulating super antigens and microbial exotoxins. Other postulated mechanisms include activation of leukocytes and modulation of cytokines (Table 5).

**Table 5** Postulated mechanisms of actions for IVIG

Postulated Mechanisms of Actions for IVIG
Scavenging of Active Complement Fragments
Binding of Super antigens Neutralization of Microbial Exotoxins
Cytokine Modulation
Leukocyte Activation

## Conclusion

We chose to give high dose IVIG in hope of achieving a higher concentration of dimeric IVIG in the recipient. Our patient had worsening signs and symptoms in spite of being on clindamycin. This is the first reported case of IVIG use in *Clostridium perfringens* necrotizing fasciitis.<sup>9</sup> Adverse effects associated with IVIG include fever, headaches, and rash as well as high cost of treatment with a decreased supply. We stress the importance of recognizing circulatory overload posed by IVIG especially in the setting of decreased inotropy seen with clostridial soft tissue infections.<sup>10,11</sup>

## Acknowledgments

None.

## Conflicts of Interest

None.

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