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Appendix 1: Basics of Surgical Management in the Care of Necrotizing Fasciitis.

Basics of Surgical Management:

Because early surgical intervention is such an important component of necrotizing fasciitis management, it is important to understand some of the differing priorities amongst treating surgeons. One general consensus is that "surgeons must be bloody, bold, and resolute" when treating this condition (1). Furthermore, Wong *et al.*, elaborates a list of four priorities that every surgeon should have when surgically debriding necrotizing fasciitis: confirmation of the diagnosis (through biopsy and physical findings), delineation of disease extent, complete resection of infected tissue, and post-op wound care (2). With regards to the extent of surgical debridement, the same authors provide a guide to define the extent of dissection necessary. They break the infection into three zones based on skin examination with Zone I being the epicenter of infection (hemorrhagic bullae, necrotic tissue, etc.), Zone II being the distal extent of infection (pain, erythema, soft tissue swelling), and Zone III being the normal surrounding tissue. They, as well as other others, suggest aggressive removal of all necrotic skin/subcutaneous tissue and all effected fascia with a ~5-10mm margin of unaffected margins. Some surgeons define the limit of infected tissue as fascia that can no longer be bluntly dissected by a finger, whereas others use serial intraoperative frozen sections to determine the extent of infection, akin to tumor resection (2-4). The limit is usually between zones II and III. However, some disagree with this extensive of an initial resection and suggest and desire to save as much viable skin as possible. Thus, they advocate for more conservative initial resection with planned return to the OR for additional debridement sometimes as soon as 24 hours after the original operation (2, 5). In general, it is well accepted that necrotizing fasciitis requires multiple debridements (often 3 or more) whether they are planned or dictated by clinical presentation (1).

Finally, wound care after initial surgical debridement is very important since the surgical wounds are almost never primarily closed, due to the frequent need for re-exploration. Some surgeons advocate for the use of non-adherent dressings with antimicrobial agents added (i.e. antibiotic cream, Dakins, active silver dressings). These dressings are then covered with some form of pressure dressing or ACE wrap (2). Other surgeons advocate for the use of negative pressure "wound vacs" over the debrided areas to promote vascularization, tissue granulation, and removal of excess bacteria (1, 6). Others suggest that negative pressure coverage increases the risk of hemorrhage due to the high rates of coagulopathy in these patients. Clearly, treating necrotizing fasciitis is left up to best clinical judgement with early recognition, intervention, and reassessment being paramount.

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Appendix 2: Necrotizing Fasciitis Hijacks the APR.

S. pyogenes, the most common cause of necrotizing fasciitis, is an excellent model for demonstrating how pathogens hijack and evade the body's protective containment mechanisms (1). *S. pyogenes* expresses the virulence factor streptokinase, which constitutively activates plasmin and consequently fibrinolysis (2-4). Plasmin bound to streptokinase is resistant to deactivation and prevents formation of the fibrin/platelet web at the site of infection, allowing *S. pyogenes* to spread through tissues and along fascial planes **(Supplemental Figure 2A)** (5, 6). In fact, murine studies have shown that mice cannot develop necrotizing fasciitis without first receiving humanized plasmin because streptokinase cannot activate murine plasminogen (4, 7). Together, these results emphasize the critical role of plasmin manipulation and the evasion of containment in the pathophysiology of infections such as necrotizing fasciitis (4, 8). Finally, *S. pyogenes* also expresses DNAse B, an enzyme that cleaves DNA and prevents formation of neutrophil extracellular traps **(Supplemental Figure 2B)** (9). Thus, these virulence factors allow *S. pyogenes* to rapidly disseminate through tissues **(Supplemental Figure 2C)**. Using similar pathologic mechanisms, *S. aureus, P. aeruginosa,* and *E. coli* can also manipulate the plasminogen-plasmin system to evade containment and disseminate through tissues **(Table 1)** (10-14).

S. aureus is another pathogen that can hijack the body's containment mechanisms and cause necrotizing fasciitis. Unlike *S. pyogenes*, which activates plasmin to prevent trapping by the fibrin web, *S. aureus* expresses the virulence factors coagulase and von Willebrand binding protein (vWBP) to initially activate fibrin formation (15-18). This abnormal activation of coagulation leads to the formation of a fibrin web that protects the bacteria and prevents host immune cells from clearing the infection, resulting in abscess formation. When the abscess reaches quorum (necessary pathogen density), *S. aureus* expresses the virulence factor staphylokinase, which similarly to streptokinase, activates plasmin to promote fibrinolysis, leading to abscess rupture and bacterial dissemination (19).

In summary, virulence factors acquired by the bacteria causing necrotizing fasciitis, such as streptokinase, DNAse B, VWBP, and staphylokinase, allow for the evasion of bacterial containment mechanisms and the destruction of tissue planes, lead to the characteristic finding of "dishwater fluid" instead of fibrinous pus during surgical debridement of necrotizing fasciitis (**Supplemental Figure 2C**). Importantly, as these pathogens promote fibrinolysis, the coagulation system is constitutively activated in an ineffective attempt to contain the infection, leading to consumption of clotting factors and SIC (20, 21).

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Variable	Result	Score
C-Reactive Protein (CRP) mg/L	<150	0
	≥150	4
White Blood Cell Count (x10^9/L)	<15	0
	15-25	1
	>25	2
Hemoglobin (g/dL)	>13.5	0
	11-13.5	1
	<11	2
Sodium (mmol/L)	≥135	0
	<135	2
Creatinine (mcg/L)	≤141	0
	>141	2
Glucose (mmol/L)	≤10	0
	>10	1

Supplemental Figure 1: LRINEC Score Calculation. A score of > 6 has PPV of 92% of having necrotizing fasciitis. Patients with a LRINEC score of ≥6 should be carefully evaluated for necrotizing fasciitis, per Wong et al. (Wong CH, Khin LW, Heng KS, Tan KC, Low CO. The LRINEC [Laboratory Risk Indicator for Necrotizing Fasciitis] score: a tool for distinguishing necrotizing fasciitis from other soft tissue infections. Crit Care Med. 2004 Jul;32[7]:1535-41).
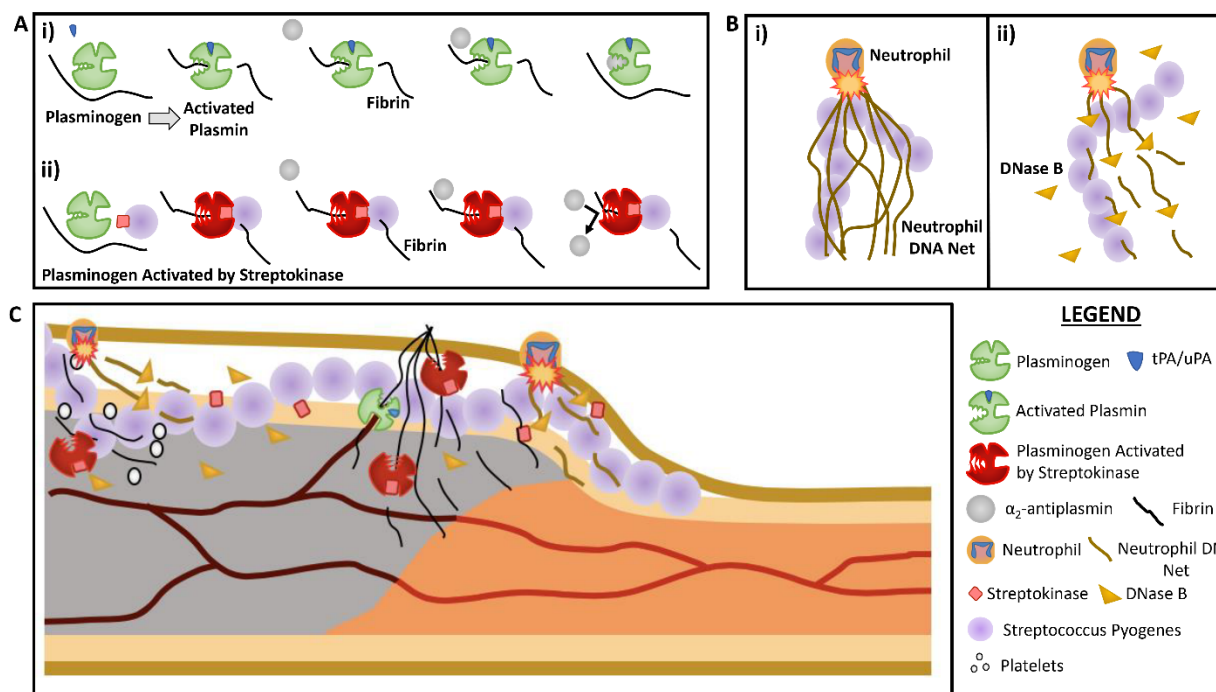
Supplemental Figure 2: Pathologic Molecular Mechanisms Behind Necrotizing Fasciitis. A) Plasmin activation. i) Under physiologic conditions, the body employs tight control over fibrinolysis. Plasminogen is converted into its active form, plasmin, by either tPA (tissue plasminogen activator) or uPA (urokinase-type plasminogen activator) and, once activated, can break down fibrin. After plasmin has completed its job, the body expresses proteins like α_2-antiplasmin, which bind plasmin and inhibit further fibrinolysis. ii) In the setting of NF, *S. pyogenes* expresses streptokinase which activates plasminogen independent of tPA/uPA. Plasminogen activated by streptokinase cannot be inhibited by the body's regulatory mechanisms thereby allowing the bacteria to rapidly degrade clots that the body develops to contain the infection. B) As an additional means to contain bacteria, the body utilizes DNA webs, released by neutrophils (i). However, virulent strains of *S. pyogenes* express the factor, DNase B, which allows it to degrade the DNA webs and further evade containment (ii). C) Together, *S. pyogenes* utilizes these mechanisms to evade containment and rapidly spread under facial planes. The body's repetitive and unsuccessful attempts to contain the bacteria contributes to the consumption of clotting factors that often occurs in the setting of NF.
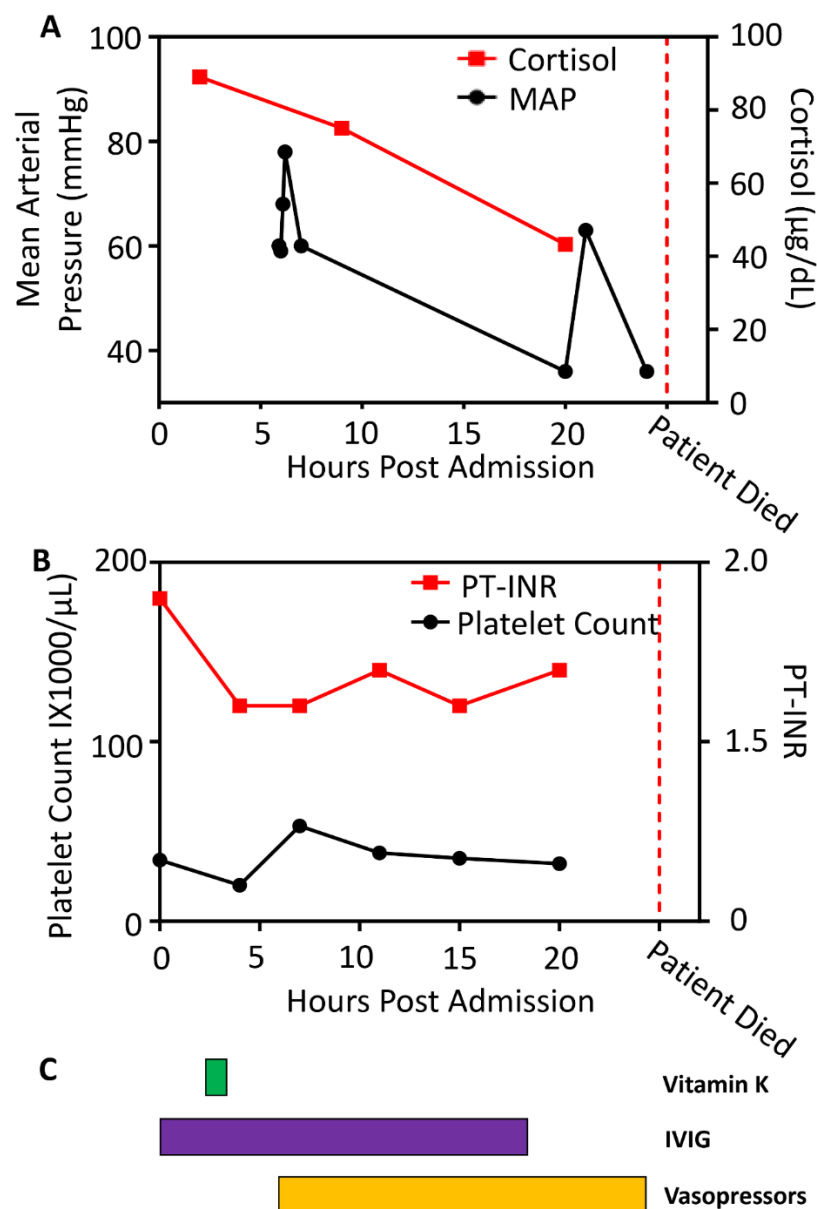
Supplemental Figure 3: Example Patient with Necrotizing Fasciitis Demonstrating Coagulopathy and Decreased Cortisol Levels. Patient was a 17-month-old female that presented initially to a regional hospital with fever, nausea, vomiting, and diarrhea. Physical exam and laboratory values at presentation were unremarkable. The patient was discharged home with supportive care for a presumptive diagnosis of "the flu." The patient's fever persisted over the next 3 days, and on the third day her arm was noted to be swollen with dark discoloration of her fingers and bloody yellow discharge from her antecubital fossa. The patient presented to her primary care physician who immediately referred her to the emergency department. Upon arrival to the emergency department, she was found to be febrile to 101°F and tachycardic. Physical exam revealed a grossly swollen right arm that was mottled, cool to the touch, and exquisitely painful.

Radial and ulnar pulses were absent in the right extremity, but doppler ultrasound did reveal a right brachial pulse. Heparin was administered for suspected thrombosis; however, it was discontinued when the patient was found to have a platelet count of 27,000/µL. Due to concern for sepsis the patient was started on vancomycin and ceftriaxone and was transferred to our tertiary care hospital. Throughout her course of care, vital signs and major coagulation labs were taken during treatment, illustrating the downward course of her disease and attempted efforts at resuscitation. **A)** During the course of her infection, her serum cortisol (red line) trended steadily downward along with her mean arterial pressures (black line). She received a bolus of IV saline, which normalized her blood pressure. However, she had continued respiratory distress and was subsequently intubated. **B)** Once stable, she remained normotensive in the emergency department without pressure support. Her fever increased to 102.5°F, and her coagulopathy worsened with a PT-INR (red line) of 1.9, which remained elevated above 1.6 for the duration of her disease course. To correct her coagulopathy, she was administered vitamin K, fresh frozen plasma, and packed blood cells. Platelet count (black line) was also depressed below 70,000/µL throughout her hospitalization. **C)** During this time, orthopaedics diagnosed the patient with compartment syndrome and had high concern for NF. The patient was taken to the OR for emergent fasciotomy, fascial biopsy, irrigation, and debridement. Fascial biopsy confirmed the diagnosis of NF. Of note, the patient required multiple rounds of calcium and blood products to maintain adequate perfusion pressures throughout the procedure. After the fasciotomy, the vascular status of the patient's arm improved, and her right radial pulse returned. The incisions were left open for a repeat debridement the following morning. Initially, the patient was normotensive upon admission to the ICU, and the team serially monitored serum cortisol to assess for the development of corticosteroid insufficiency (A). Fresh frozen plasma and blood products were continued to achieve a target PT-INR of <1.3 and platelet count of >30,000/µL (a second dose of vitamin K was ordered but not administered). Antibiotics (clindamycin, vancomycin, penicillin G, and ceftriaxone) were continued and IVIG was added to attenuate her inflammatory response. The patient remained hemodynamically stable without the use of vasopressors throughout the night but became hypotensive in the early morning. The decision was made to begin dopamine for pressure support. Repeat evaluation by the orthopaedic surgery team revealed a similar exam without spread of the infection, and they proceeded with the planned debridement. The procedure was completed without complication and intraoperative fascial biopsy displayed no evidence of infection. However, shortly after the debridement, the patient developed abdominal distension concerning for abdominal compartment syndrome. She quickly decompensated and was taken for emergent exploratory laparotomy. Her abdomen was opened, and a silo was placed. After surgery, chest compressions were required for over an hour due to pulseless electrical activity. A rhythm was eventually obtained; however, the patient's blood pressure remained persistently low despite resuscitative efforts. After 3 hours, the patient's parents requested that all lifesaving medical treatment be stopped, and the patient expired. Autopsy revealed that the cause of death was severe sepsis with DIC. Pertinent findings included bilateral subarachnoid hemorrhages, gram-positive cocci in the antecubital fossa and bilateral lungs, and widespread petechiae on the gastrointestinal mucosa. Labs shortly before death revealed a random serum total cortisol of 43.3 µg/dL (drawn at 9:30 am), PT-INR of 1.7, and platelet count of 32,000/µL, and blood and soft tissue cultures revealed Group A streptococcus.
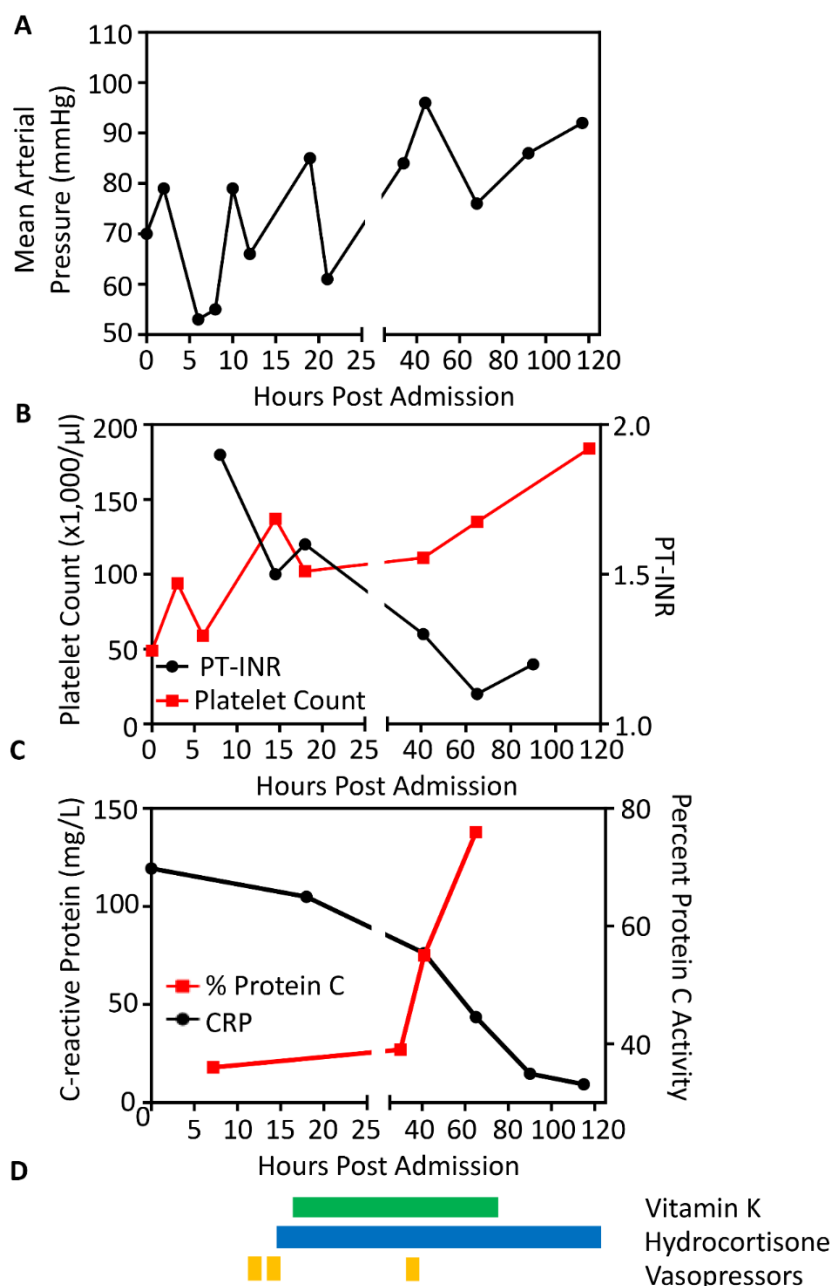
Supplemental Figure 4:
Example Patient with Necrotizing Fasciitis Demonstrating Coagulopathy and Decreased Cortisol Levels with Steroid Administration. Patient was a 12-year-old girl who presented to the emergency department of our tertiary care center, following referral from her primary care physician, three days after falling and scraping her left knee. Over the course of day, the patient's knee became erythematous, painful, and swollen. She developed a subjective fever, rigors, and emesis. In the emergency department, she was found to be febrile to 102.7°F with severe pain radiating from her left knee to her groin on ambulation. An x-ray of the knee was consistent with

soft tissue swelling. Infectious and inflammatory labs were drawn. While waiting for results, the patient became acutely hypotensive to the 90s/30s mm/Hg and developed an erythroderma type rash (A). IV normal saline and epinephrine were administered to normalize and maintain her blood pressure. In addition, vancomycin and clindamycin were initiated out of concern for sepsis. The patient was transferred to the critical care unit. Notable lab results from presentation including a platelet count of 49,000/µL and C-reactive protein (CRP) of 119.4 mg/L (B-D). During this time, orthopaedics evaluated the patient and due to concern for NF, given the rapidly progressing nature, the patient underwent irrigation, debridement, and fascial biopsies of the left knee. Biopsies confirmed the diagnosis of NF and the effected tissue was removed to a point of negative margins. Postoperatively, the patient was started on high-dose hydrocortisone with a loading dose of 160 mg followed by 10 doses of 20 mg q6h (random serum total cortisol prior to the procedure was 7.4 µg/dL) and penicillin G for potential group A streptococcus (D). Coagulation labs were drawn and revealed an elevated PT-INR of 1.9, an elevated fibrinogen of 480 mg/dL, low protein C activity (36%), normal protein S activity, and an elevated D-dimer at 2.38 µg/mL (B-D). Given low protein C activity, there was concern for a persistent consumptive coagulopathy, and vitamin K was administered for a total of 3 doses throughout her stay (D). Following initiation of these therapies, the patient was successfully weaned from pressor support. Her PT-INR, Protein C, D-dimer, Fibrinogen, CRP, and platelets all gradually returned to normal. Steroids were weaned and discontinued. She was discharged home in stable condition on Day 6 with clindamycin monotherapy. Four months following discharge, her only complication was intermittent knee pain.