Ahvaz Jundishapur University of Medical Sciences
Faculty of Medicine
Thesis for Doctoral Degree in General Medicine

Title:
Investigating the prognostic factors in predicting the need for multiple debridement and mortality in Fournier’s gangrene 1383-1395

Supervisors:
Dr: Dinyar Khazaeli
Dr: Mohamad Reza Dadfar

Author:
Elham Eskandari

Registration No:B-93/009

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Place of Research:
Ahvaz Imam Khomeini, Golestan Hospital

Author:
Elham Eskandari

Supervisors:
Dr. Dinyar Khazaei

Dr. Mohamad Reza Dadfar

Registration No:B-93/009
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استاد راهنما

۱. جان آقای دکتر خزاعی

هیات داوران

۱. جان آقای دکتر مصباح

۲. جان آقای دکتر حسینی

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<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abstract</td>
<td>1</td>
</tr>
<tr>
<td>Chapter One</td>
<td>3</td>
</tr>
<tr>
<td>Introduction</td>
<td>4</td>
</tr>
<tr>
<td>Overview</td>
<td>6</td>
</tr>
<tr>
<td>Chapter Two</td>
<td>30</td>
</tr>
<tr>
<td>Materials and Methods</td>
<td>30</td>
</tr>
<tr>
<td>Objective and Hypothesis</td>
<td>31</td>
</tr>
<tr>
<td>Method and sampling plan</td>
<td>34</td>
</tr>
<tr>
<td>Chapter Three</td>
<td>38</td>
</tr>
<tr>
<td>Results</td>
<td>38</td>
</tr>
<tr>
<td>Chapter Four</td>
<td>57</td>
</tr>
<tr>
<td>Discussion</td>
<td>57</td>
</tr>
<tr>
<td>Chapter Five</td>
<td>63</td>
</tr>
<tr>
<td>References</td>
<td>64</td>
</tr>
</tbody>
</table>
Abstract

Introduction: Fournier’s gangrene is a rare but life-threatening fulminant disease. Owing to small study cohorts, the published literature is limited. The aim of this study was to investigate the prognostic factors in predicting the need for multiple debridement and mortality in Fournier’s gangrene.

Methods

This retrospective study reviewed 85 cases of Fournier’s gangrene during last 12 years from 2004 to 2016. The information regarding these patients were collected through medical records from two tertiary hospitals of Imam Khomeini and Golestan affiliated to Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran. The data such as demographic, gender, blood tests, history, site of beginning, comorbidities were collected. The outcome was divided into two categories of survival and death.

Results

Of the 85 patients evaluated, 12 (14.1%) died and 73 (85.9%) survived. Of 85 cases, 5 (5.9%) were female, while 80 (94.1%) were male. The mean age of patients was 57.79±17.3 years (range: 18-87 yr). There was no significant difference in mean age between survivors and non-survived (P value=0.1). The mean length of hospital days was 8.92±7.12 days (1-38 days). According to the history of all patients, we found that swilling, pain, diabetes mellitus, drug use, fever, smoking, HTN, CVD and chills had highest prevalence.
Conclusion

In summary, older patients with comorbidity of HTN are at higher risk of experiencing mortality.

Keywords: Fournier’s gangrene, comorbidity, mortality, hypertension.
Chapter One

Introduction
1.1. Introduction

Necrotizing soft tissue infection is a potentially fatal infection involving skin and subcutaneous tissue (1). It is usually accompanied by the systemic inflammatory response syndrome (SIRS) and needs prolonged treatment (2). Necrotizing fasciitis (NF) is characterized by widespread necrosis of the subcutaneous tissue and fasciae. However, NF as a soft tissue infection typically does not cause myonecrosis, but invades the deep fascia (3).

When NF happens in the genitalia and perineum it was called as Fournier’s Gangrene. Its rapid and destructive course is caused by polymicrobial infectious organisms (1,2). Monomicrobial infection is usually associated with immunocompromised patients (cancer, diabetes mellitus, vascular insufficiencies, and organ transplantation or alcohol abusers) (4). Many aerobic and anaerobic pathogens may be involved, including Bacteroides, Clostridium, Enterobacteriaceae, Proteus, Pseudomonas, and Klebsiella, but group A hemolytic streptococcus and Staphylococcus aureus, alone or in synergism, are the initiating infecting bacteria (5). Typical sites of the infection are the extremities, abdomen, and perineum (1). In most NSTI cases anaerobic bacteria are present, usually in combination with aerobic gram-negative organisms. They proliferate in an environment of local tissue hypoxia. Because of lower oxidation-reduction potential, they produce gases such as hydrogen, nitrogen, hydrogen sulfide and methane, which accumulate in soft tissue spaces because
of reduced solubility in water (6). Clinical findings may include swelling, pain, fever, erythema, induration, crepitations, sloughing off of the skin, or a blistering and purulent collection. The need for more rapid and scientific methods of NF diagnosis led to the development of a clinical scoring systems, like the LRINEC scoring system (The Laboratory Risk Indicator for Necrotizing Fasciitis) or the APACHE II scoring system (The Acute Physiology and Chronic Health Evaluation) (6, 7). The patient must be admitted to an ICU, where start IV therapy and immediate and aggressive surgical debridement must be performed (8).

Some prognostic factors have been investigated regarding predicting the patients with higher risk of multiple tissue debridement and mortality including WBC > 15000, positive CRP, diabetes mellitus, immunosuppression, alcoholism, peripheral vascular disease, IV drug abuse, hypertension, corticosteroids, HIV, GI malignance, malnutrition, major trauma, surgery, renal insufficiency and obesity (9). The aim of this study was to investigate the prognostic factors in predicting the need for multiple debridement and mortality in Fournier’s gangrene.

1.2. Overview
1.2.1. Systemic Inflammatory Response Syndrome

1.2.1.1. Background

In 1992, the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) introduced definitions for systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, septic shock, and multiple organ dysfunction syndromes (MODS) (10). The idea behind defining SIRS was to define a clinical response to a nonspecific insult of either infectious or noninfectious origin. SIRS is defined as 2 or more of the following variables:

- Fever of more than 38°C (100.4°F) or less than 36°C (96.8°F)
- Heart rate of more than 90 beats per minute
- Respiratory rate of more than 20 breaths per minute or arterial carbon dioxide tension (PaCO₂) of less than 32 mm Hg
- Abnormal white blood cell count (>12,000/µL or < 4,000/µL or >10% immature forms)

SIRS is nonspecific and can be caused by ischemia, inflammation, trauma, infection, or several insults combined. Thus, SIRS is not always related to infection.

Infection is defined as "a microbial phenomenon characterized by an inflammatory response to the microorganisms or the invasion of normally sterile tissue by those organisms." (11, 12)
1.2.1.2. Definition

Necrotizing soft tissue infection (Necrotizing fasciitis)

Necrotizing fasciitis is a rapidly progressive inflammatory infection of the fascia, with secondary necrosis of the subcutaneous tissues. The speed of spread is directly proportional to the thickness of the subcutaneous layer. Necrotizing fasciitis moves along the fascial plane.

Necrotizing fasciitis has also been referred to as hemolytic streptococcal gangrene, Melaney ulcer, acute dermal gangrene, hospital gangrene, supportive fasciitis, and synergistic necrotizing cellulitis. Fournier gangrene is a form of necrotizing fasciitis that is localized to the scrotum and perineal area(13).

Necrotizing fasciitis may occur as a complication of a variety of surgical procedures or medical conditions, including cardiac catheterization(10), vein sclerotherapy, and diagnostic laparoscopy(14), among others (15-18). It may also be idiopathic, as in scrotal or penile necrotizing fasciitis.

The causative bacteria may be aerobic, anaerobic, or mixed flora(18). A few distinct necrotizing fasciitis syndromes should be recognized. The 3 most important are as follows:

- Type I, or polymicrobial
- Type II, or group A streptococcal
- Type III gas gangrene, or clostridial myonecrosis
A variant of necrotizing fasciitis type I is saltwater necrotizing fasciitis, in which an apparently minor skin wound is contaminated with saltwater containing a *Vibrio* species. Because of the presence of gas-forming organisms, subcutaneous air is classically described in necrotizing fasciitis. This may be seen only on radiographs or not at all(19).

1.2.1.3. Prevalence

The frequency of necrotizing fasciitis has been on the rise because of an increase in immunocompromised patients with diabetes mellitus, cancer, alcoholism, vascular insufficiencies, organ transplants, HIV infection, or neutropenia. Since 1883, more than 500 cases of necrotizing fasciitis have been reported in the literature. There may be an increased incidence in African and Asian countries; however, because of the lack of recorded cases, the true incidence is not known(20).

The mean age of a patient with necrotizing fasciitis is 38-44 years. This disease rarely occurs in children. Pediatric cases have been reported from resource-poor nations where poor hygiene is prevalent. The male-to-female ratio is 2-3:1. These infections can be difficult to recognize in their early stages, but they rapidly progress. They require aggressive treatment to combat the associated high morbidity and mortality(21).
Necrotizing soft tissue infection is a rare but very severe type of bacterial infection. It can destroy the muscles, skin, and underlying tissue. The word "necrotizing" refers to something that causes body tissue to die(21).

1.2.1.4. Causes

Many different types of bacteria can cause this infection. A very severe and usually deadly form of necrotizing soft tissue infection is due to *Streptococcus pyogenes*, which is sometimes called "flesh-eating bacteria."

Necrotizing soft tissue infection develops when the bacteria enters the body, usually through a minor cut or scrape. The bacteria begins to grow and release harmful substances (toxins) that kill tissue and affect blood flow to the area. As the tissue dies, the bacteria enters the blood and rapidly spreads throughout the body(22).

1.2.1.5. Symptoms and exams

Symptoms include:

- Small, red, painful lump or bump on the skin

- Changes to a very painful bruise-like area and grows rapidly, sometimes in less than an hour, The center may become black and die, The skin may break open and ooze fluid

Other symptoms can include:

- Feeling ill

- Fever
- Sweating
- Chills
- Nausea
- Dizziness
- Weakness
  - Shock(16, 23)

Exams and Tests

- Tests that may be done include:
  - CT scan
  - Blood tests
  - Skin tissue biopsy

1.2.1.6. Treatment

Immediate treatment is needed to prevent death. Treatment includes:

Powerful, broad-spectrum antibiotics given immediately through a vein (IV)

Surgery to drain the sore and remove dead tissue

Special medicines called donor immunoglobulins (antibodies) to help fight the infection in some cases.

Other treatments may include:

Skin grafts after the infection goes away to help the skin heal and look better

Amputation if the disease spreads through an arm or leg 100% oxygen at high pressure (hyperbaric oxygen therapy) for certain types of bacterial infections(19)
1.2.1.7. Prevention

Always the skin should be cleaned thoroughly after a cut, scrape, or other skin injury. (24)

1.2.2. Fournier gangrene

1.2.2.1. Definition

Fournier gangrene is an acute necrotic infection of the scrotum; penis; or perineum. It is characterized by scrotum pain and redness with rapid progression to gangrene and sloughing of tissue. Fournier gangrene is usually secondary to perirectal or periurethral infections associated with local trauma, operative procedures, or urinary tract disease. (25)

Since 1950, more than 1,800 cases for study have been reported in English language medical literature. This disease occurs worldwide and, although it is recognized more frequently among male adults, has been identified also among women and children. Treatment usually consists of the surgical removal (debridement) of extensive areas of dead tissue (necrosis, necrotic) and the administration of broad-spectrum intravenous antibiotics. Surgical reconstruction may follow where necessary. (26)

1.2.2.2. Signs & Symptoms
Symptoms include fever, general discomfort (malaise), moderate to severe pain and swelling in the genital and anal areas (perineal) followed by rankness and smell of the affected tissues (fetid suppuration) leading to full blown (fulminating) gangrene. Rubbing the affected area yields the distinct sounds (crepitus) of gas in the wound and of tissues moving against one another (palpable crepitus). In severe cases, the death of tissue can extend to parts of the thighs, through the abdominal wall and up to the chest wall.

This disease is commonly found in conjunction with other disorders (comorbidity), especially those that weaken the immune system. Some disorders that increase the predisposition to Fournier gangrene are diabetes mellitus, profound obesity, cirrhosis, interference with the blood supply to the pelvis, and various malignancies(1).

1.2.2.3. Causes

Portals of entry for the bacteria, fungi, and/or viruses responsible for a particular case of Fournier gangrene are generally colorectal, urogenital or cutaneous in origin. Anorectal abscesses, urinary tract infections, surgical instrumentation and other contributing factors have all been implicated. Some cases continue to be of unknown cause (idiopathic). Why this process occasionally develops in individuals with common ailments is still not understood.

There are many ways for the virulent microorganism to gain access to the host, where the compromised immunological system is unable to prevent the infection from taking hold. The virulence of the resulting disorder is thought to
be enhanced by the toxins and enzymes produced by the combination of microorganisms (synergy)(27).

1.2.2.4. Affected Populations

The mean age of presentation is about 50 years, but the range of patient ages in reported cases is from eight days to 90 years. Fournier gangrene is diagnosed more frequently among males. It may be that the high male to female ratio in the diagnosis is the result of the lack of recognition of this entity among women by physicians. It is believed that the male to female proportion may be anywhere from 5:1 to 10:1(28).

1.2.2.5. Related Disorders

Symptoms of the following disorders can be similar to those of Fournier gangrene. Comparisons may be useful for a differential diagnosis.

1. Epididymitis is inflammation of the long, tightly coiled tube behind each testicle (epididymis) that carries sperm from the testicle to the spermatic duct. Affected individuals usually have painful swelling of the one epididymitis and the associated testicle. In some cases, the second testicle may also be tender. In addition, affected individuals have fever, painful swelling and redness (erythema) of the scrotum, and/or inflammation of the tube from which urine is carried from the bladder (urethritis). The two main forms of epididymitis are the sexually-transmitted form and the nonspecific bacterial form.
Hydrocele is a fluid-filled sack along the spermatic cord within the scrotum. Hydroceles are common in the newborn infant. They may be unilateral or bilateral and result when there is failure of the tract through which the testis descends from the abdomen into the scrotum to close. Peritoneal fluid drains