Fournier’s Gangrene – Current Concepts

MARTA WRÓBLEWSKA¹, BOLESŁAW KUZAKA²*, TOMASZ BORKOWSKI¹, PIOTR KUZAKA¹, DARIUSZ KAVECKI¹ and PIOTR RADZISZEWSKI¹

¹Institute of Haematology and Transfusion Medicine, Warsaw, Poland
²Department of General, Oncological and Functional Urology, Medical University of Warsaw, Poland
³Department of Urology, Teaching Postgraduate Hospital Czerniakowska 231, Warsaw, Poland

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Abstract

Fournier's gangrene (FG) is a rapidly progressive form of infective necrotising fasciitis of the perineal, genital, or perianal regions, leading to thrombosis of the small subcutaneous vessels and necrosis of the overlying skin. It is believed that the occurrence of the disease in women is underreported and may be unrecognised by some clinicians. Fournier's gangrene is a life-threatening condition, constituting an urological emergency. Many patients with Fournier's gangrene have medical or surgical conditions, which are predisposing factors to this disease or its more severe or fatal course. These comprise diabetes mellitus, hypertension, alcoholism and advanced age. Recent reports in the literature point to changes in the epidemiology of FG, comprising an increasing age of patients. Several authors reported that the mean age of FG patients is at present 53–55 years. Prognosis in FG patients is based on FGSI (Fournier’s gangrene severity index) score. Despite the progress in medical care for FG patients, the mortality rate reported in the literature remains high – most often 20–40%, but ranges from 4% to 80%. The most common isolates cultured from FG lesions are both Gram-positive and Gram-negative, as well as strictly anaerobic bacteria. Recently community-acquired methicillin-resistant Staphylococcus aureus (CA-MRSA) has emerged as an etiological agent of FG with severe clinical course and even fulminant sepsis. Rarely FG may have a fungal etiology, being caused by yeast-like fungi Candida spp. or by moulds. Antibiotics should be administered parenterally and in doses high enough to reach an effective concentration in the infected tissues.

Keywords: Fournier's gangrene, necrotising fasciitis, Fournier's gangrene severity index score

Introduction

Fournier’s gangrene (FG) is a rapidly progressive form of infective necrotising fasciitis of the perineal, genital, or perianal regions, leading to thrombosis of the small subcutaneous vessels and necrosis of the overlying skin (Ahmadnia et al., 2009; Champion, 2007; Jeong et al., 2005; Smith et al., 1998). It is a life-threatening condition, constituting an urological emergency (Capitan Manjon et al., 2003; Malikarjuna et al., 2012).

FG was first described by Baurienne in 1764, however it was named after Jean-Alfred Fournier – a French venerologist, who reported it in 1883 as a rapidly progressive or fulminant genital gangrene in otherwise healthy young men, with a sudden onset and no apparent cause or specific etiology (Baurienne, 1764; Fournier, 1883). Silva et al. claim that the epidemiology and clinical course of FG have changed from its original description, with a higher median age of the patients and more insidious onset of the disease recorded in recent studies (EAU; Silva et al., 2002). Apart from the genital region, FG may also affect the perineum and abdominal wall (Ahmadnia et al., 2009; Capitan Manjon et al., 2003; Saijo et al., 1990). However, according to the reports in the literature, recently its clinical course tends to be less fulminant and its etiology is now very often identified (Pais et al., 2013).

Epidemiology

Incidence. The condition is relatively rare, with an estimated overall incidence of 1.6/100000 males (Sorensen et al., 2009). In a large study comprising 1680 hospitalised patients the overall incidence was the highest in men aged 50 to 79 years and amounted to 3.3/100000 (Sorensen et al., 2009). In a study by Sorensen et al. patients with FG constituted less than 0.02% of hospitalised patients (Sorensen et al., 2009).

Sex and age. The disease typically affects and predominates in males, but rarely FG is diagnosed also in
women (Eke, 2000; Sarvestani et al., 2013; Silva et al., 2002). Sporadic cases of FG have been also described in babies and children (Abubakar et al., 2009; Adams et al., 1990). In a study by Kuo et al. women accounted for 5 out of 44 patients with FG (11.4%), while Sorensen et al. studied a group of 1680 FG patients, among whom only 39 were women (2.3%) (Kuo et al., 2007; Sorensen et al., 2009). Kim claims that the male-to-female ratio is mostly approximately 10:1 (Kim, 2011). Eke postulates that the occurrence of the disease in women is under-reported and may be unrecognised by some clinicians (Eke and Raphael, 2011).

In contrast to the original publication, recent reports in the literature point to changes in the epidemiology of FG, comprising an increasing age of patients. Several authors reported that the mean age of FG patients is at present 53–55 years (range 23–81) (Benjelloun et al., 2013; Clayton et al., 1990; Kara et al., 2009; Kuo et al., 2007). In a study by Sarvestani et al. the mean age was 44.6 years (Sarvestani et al., 2013). In several other studies the mean age of patients with FG was just over 60 years (Ahmadnia et al., 2009; Montoya Chinchilla et al., 2009; Silva et al., 2002).

**Risk factors.** Many patients with Fournier’s gangrene have medical or surgical conditions, which are predisposing factors to this disease or its more severe or fatal course. These include diabetes mellitus, hypertension, alcoholism and advanced age (Ayan et al., 2005; Clayton et al., 1990; Eke and Raphael, 2011; EAU; Ferreira et al., 2007; Goľab et al., 2001; Kim, 2011; Mallikarjuna et al., 2012; Silva et al., 2002). Patients with poor general health are particularly prone to FG. This includes malnutrition or obesity, chronic renal failure, chronic liver disease, malignancies and other conditions causing immunosuppression (Ahmadnia et al., 2009; Bednarek and Droźdż, 2008; Capitan Manjon et al., 2003; Kara et al., 2009; Kuo et al., 2007; Mallikarjuna et al., 2012; Silva et al., 2002; Tahmaz et al., 2006). Diabetes mellitus was present in 56% of FG patients (Ulug et al., 2009). In a group of 41 FG patients studied by Ayan et al. diabetics constituted over 40%, while in a study of 60 FG patients by Silva et al. – 42% were diabetics (Ayan et al., 2005; Silva et al., 2002). All twenty FG patients examined by Montoya Chinchilla et al. were diabetics (Montoya Chinchilla et al., 2009). Alcoholism is present in 25–50% of FG patients (Clayton et al., 1990). Palmer speculated that a generally debilitated state of the patients favours infectious gangrenous process and influences their survival (Palmer et al., 1995). In a study by Kuo et al. liver cirrhosis was highly related to mortality (Kuo et al., 2007).

FG is also more often seen in patients with long-term bladder catheterisation (who frequently remove the catheter by themselves), urethral stricture, local trauma or perianal disease. FG very often originates from urogenital or anorectal diseases which have not been treated properly (Montoya Chinchilla et al., 2009; Silva et al., 2002). Perianal disease was present in 60% of FG patients (Ulug et al., 2009). In a study by Kuo et al. over 50% of FG cases originated from colorectal area, while 25% – from urological region (Kuo et al., 2007). Some cases are idiopathic, with no cause identified.

Kim reports that in men the risk of perineal infection may be increased by anal intercourse (blunt trauma to the area, spread of anorectal microbes), while in women FG may follow septic abortions, hysterectomy, episiotomy, vulvar or Bartholin gland abscesses (Kim et al., 2011). In children strangulated inguinal hernia, circumcision, omphalitis, insect bites, trauma, urethral instrumentation, peri-rectal abscesses, systemic infections and burns have been linked to the disease (Eke and Raphael, 2011). Poor perineal hygiene or the presence of chronically indwelling catheters, such as in paraplegic patients, poses an increased risk of the disease (Kim et al., 2011).

**Length of hospitalization.** The development of clinical symptoms of FG usually lasts several days and the duration of hospital stay ranges from several to over 50 days (Capitan Manjon et al., 2003; Ersay et al., 2007; Kuo et al., 2007; Montoya Chinchilla et al., 2009; Silva et al., 2002; Tahmaz et al., 2006). In a study by Ferreira et al. the mean hospital stay of 43 patients exceeded 73 days (Ferreira et al., 2007). Ersay et al. found that FG patients who required repeated debridement had a significantly longer duration of hospital stay (Ersay et al., 2007). In this study comprising 70 patients the median hospitalization time was 26.0 days for survivors compared to 8.0 days for non-survivors (Ersay et al., 2007). In another study the mean duration of hospital stay was 31.54 days and 12.8 days, comparing survivors and non-survivors, respectively (Ulug et al., 2009).

**Mortality.** Despite the progress in medical care for FG patients, the mortality rate reported in the literature remains high – most often 20–40%, but ranges from 4% to 80% (Benjelloun et al., 2013; Capitan Manjon et al., 2003; Champion, 2007; Clayton et al., 1990; Eke, 2000; Ersay et al., 2007; Goľab et al., 2001; Jeong et al., 2005; Kara et al., 2009; Kuo et al., 2007; Laor et al., 1995; Mallikarjuna et al., 2012; Palmer et al., 2005; Pawlowski et al., 2004; Silva et al., 2002; Smith et al., 1998; Sohu et al., 2013; Tahmaz et al., 2006; Thwaini et al., 2006; Tuncel et al., 2006; Ulug et al., 2009; Yeniyl et al., 2004). Sorensen et al. reported an overall population-based fatality rate of 7.5%, in a group of 1680 patients, which was lower than reported from tertiary care hospitals (Sorensen et al., 2009). Also in a study by Montoya Chinchilla et al. the mortality rate was 10% (Montoya Chinchilla et al., 2009). Eke claims that the mortality
rate due to FG is related to the patient’s condition at presentation (Eke et al., 2000). Mortality among children with FG appears to be lower than reported in adults (Adams et al., 1990).

The most common causes of death are sepsis and ARDS (acute respiratory distress syndrome), disseminated intravascular coagulopathy, septic shock, acute kidney failure, hepatic failure and multiple organ failure (Jeong et al., 2005; Kuo et al., 2007; Tahmaz et al., 2006). Recently Sohu et al. reported that increased heart and respiratory rates, elevated serum creatinine, pre-existing kidney disease, and higher extent of affected body surface as well as severe sepsis on admission and hypotension were associated with higher mortality (Sohu et al., 2013). Several authors point to the early diagnosis of FG as a means to improve patients’ survival rate (Kuo et al., 2007; Sarvestani et al., 2013; Sohu et al., 2013).

Clayton et al. reported that survivors of FG were significantly younger than those who died – 52 versus 69 years, respectively (Clayton et al., 1990). Laor also reported younger age of survivors (Laor et al., 1995). However, in a study by Ulug et al. the mean age of survivors was 53.95 ± 21.49 years, compared to 57.20 ± 12.94 years in non-survivors, with the difference being not statistically significant (Ulug et al., 2009). Other researchers also found no statistically significant difference in the age of survivors and non-survivors (Ersay et al., 2007; Tuncel et al., 2006; Yeniyol et al., 2004).

**Prognostic scores.** Neoplasm, permanent urethral catheterisation or immunosuppression are factors associated with worse prognosis (Capitan Manjon et al., 2003). At present prognosis in FG patients is based on FGSI (Fournier’s gangrene severity index) score, reported by Laor et al. (Laor et al., 1995). The median FGSI score was higher in nonsurvivors (22) compared to survivors (12) (Sohu et al., 2013). Mallikarjuna et al. postulate that early diagnosis using Laboratory Risk Indicator for Necrotizing Fasciitis score and stratification of patients into high risk category using FGSI score help in early initiation of treatment (Mallikarjuna et al., 2012).

Laor et al. stated that deviation from homeostasis at presentation with FG is the most important general parameter that predicts outcome and recommended the use of FGSI score for evaluation of therapy and reporting results. The FGSI score comprises nine parameters, such as body temperature, heart rate, respiratory rate, serum level of sodium, potassium, creatinine and bicarbonate, as well as hematocrit value and leucocyte count (Laor et al., 1995). Each parameter is graded from 0 to 4 and summed up to obtain the FGSI score. It was concluded that a score > 9 was associated with a 75% probability of death of a patient, while a score of ≤ 9 corresponded to a 78% probability of survival (Laor et al., 1995).

Yeniyol et al. confirmed FGSI usefulness as a prognostic index in FG patients – score for survivors was 3.0 ± 1.8, compared to 12 ± 2.4 for non-survivors (Yeniyol et al., 2004). Ulug et al. retrospectively assessed the FGSI score in a group of 27 patients and also concluded that it should be used in a clinical evaluation of FG patients (Ulug et al., 2009). They found a mean FGSI score at admission of 5.04 ± 2.49 for survivors compared with 13.6 ± 4.61 for non-survivors. Similarly Ersay et al. reported the clinical usefulness of FGSI score (4.66 ± 2.31 for survivors and 11.56 ± 2.68 in non-survivors) (Ersay et al., 2007). Similar findings were reported by several authors (Chawla et al., 2003; Erol et al., 2009; Sarvestani et al., 2013). However, Tuncel et al. reported no correlation between the FGSI and the disease severity or the patient’s survival (scores 2.0 and 4.0 for survivors and non-survivors, respectively) (Tuncel et al., 2006).

Ahmadnia et al. proposed new prognostic criteria for predicting survival in FG (based on 71 patients), comprising shorter time between the onset of the symptoms and hospitalisation, less tissue necrosis, laboratory parameters (higher albumin and calcium values, lower urea level) and lower number of required debridements (Ahmadnia et al., 2009).

**Clinical symptoms and pathophysiology**

The clinical symptoms of Fournier’s gangrene typically include a sudden intense pain in the scrotum, prostration, pallor, and fever (Mallikarjuna et al., 2012). At first only the scrotum is involved, but infection can quickly spread to the penis and perineal tissues, and also along the anterior abdominal wall, up to the clavicle (Saijo et al., 1990). In a study by Ferreira et al. comprising 43 cases of FG the most often affected regions were the scrotum (93.3% of cases), the penis (46.5% of cases), and the perineum or perianal region (37.2% of cases) (Ferreira et al., 2007).

Redness of the skin is one of the early symptoms of this condition, followed by swelling of the tissues, which in turn may lead to the feeling of tightness in the genitalia and perineal region. Scrotal swelling, fever and pain are the most common symptoms of FG, however in some cases (up to 40%) the presentation is more insidious (EAU, Mallikarjuna et al., 2012). The symptoms usually persist from 2 days to over a week.

The underlying process involves cell necrosis, inflammation and swelling (Fig. 1 A–D). Crepitus of the inflamed tissue is a common feature of the disease due to the presence of gas forming anaerobic microorganisms (Mallikarjuna et al., 2012). It should be noted that the degree of internal necrosis is often much greater than suggested by the external clinical signs (EAU).
**Etiology**

Fournier's gangrene is classified as type 1 necrotising fasciitis of polymicrobial etiology (EAU). Kim reports an average of 4 isolates per case (Kim *et al.*, 2011). The most common isolates cultured from FG lesions comprise both Gram-positive and Gram-negative, as well as strictly anaerobic bacteria. Rarely FG may have fungal etiology, being caused by yeast-like fungi *Candida* spp. or by moulds (Johnin *et al.*, 2000, Kumar *et al.*, 2011, Rutchik and Sanders, 2003).

Bacteria isolated from FG patients usually represent the normal flora of the urogenital or anorectal region, such as enteric rods (*Escherichia coli*, *Klebsiella* spp., *Proteus* spp.), Gram-positive cocci (staphylococci, streptococci, enterococci) and obligate anaerobic bacteria (*Clostridium* spp., *Bacteroides* spp., *Fusobacterium* spp.).

Fig. 1. Fournier’s gangrene of the external genitalia; A–C scrotum, D – penis
spp., Peptococcus spp., Peptostreptococcus spp.) (EAU, Eke and Raphael, 2011; Ersay et al., 2007; Jeong et al., 2005; Kim, 2011; Kuo et al., 2007; Paty and Smith, 1992). Paty and Smith reported E. coli, Bacteroides and streptococci as the most often isolated bacteria (Paty and Smith, 1992). In a study by Palmer predominated strains of E. coli and streptococci, while strains of Bacteroides spp. were less commonly cultured from patients with FG (Palmer et al., 1995). Ulug et al. found E. coli and Pseudomonas aeruginosa as the bacteria most commonly isolated from FG patients (Ulug et al., 2009). Ayan et al. found E. coli (58%) and S. aureus (36%) as the most common etiological agents of FG (Ayan et al., 2005). In a study comprising 15 cases, the most common isolates were Gram-negative bacilli – E. coli and Acinetobacter spp. (Kara et al., 2009).

Recently community-acquired methicillin-resistant S. aureus (CA-MRSA) has emerged as an etiological agent of FG with severe clinical course and even fulminant sepsis (Burton et al., 2008; Kalorin et al., 2007).

Poor hygiene and local trauma predispose to FG as bacteria gain access to deeper tissues (Ayan et al., 2005). It is claimed that synergy between aerobic and anaerobic bacteria contributes to the pathogenesis of FG (Champion, 2007; Ersay et al., 2007). These bacteria secrete many toxins and enzymes that cause tissue necrosis (e.g. hyaluronidase, streptokinase, collagenase), formation of thrombi in the blood vessels and severe cardiovascular impairment (Champion, 2007; EAU; Smith et al., 1998). Subsequent inflammatory reaction of the host contributes to multi-organ failure and death if not treated adequately.

Biochemical markers

Apart from clinical symptoms, the biochemical markers may aid the clinician in risk stratification and prediction of mortality (Mallikarjuna et al., 2012; Ahmadnia et al., 2009). Laboratory tests such as serum urea and creatinine (higher values in non-survivors), as well as sodium and potassium levels (lower values in non-survivors) may have prognostic value (Clayton et al., 1990; Jeong et al., 2005; Laor et al., 1995; Ulug et al., 2009). However, Tuncel et al. found no statistically significant differences in these values in a group of 20 FG patients (Tuncel et al., 2006). Instead, they indicated the significance of albumin and alkaline phosphatase levels in samples taken on admission to the hospital (Kuo et al., 2007; Tuncel et al., 2006). Other biochemical markers useful in FG patients are increased serum lactate and calcium and low bicarbonate or magnesium levels (Erol et al., 2009; Mallikarjuna et al., 2012).

Wong et al. proposed another score – the Laboratory Risk Indicator for Necrotising Fasciitis (LRINEC) – based on biochemical and haematologic changes, which may help detect even clinically early cases of necrotising fasciitis (Wong et al., 2004).

Imaging studies (e.g. radiology, ultrasonography and computed tomography) used for diagnosis of FG are beyond the scope of this publication and have been recently revised by Mallikarjuna et al. (Mallikarjuna et al., 2012).

Treatment

FG remains a urological emergency. The mainstay of its treatment is early radical debridement of necrotic tissues, drainage and antimicrobial therapy, as well as haemodynamic stabilisation of the patient. Patients with Fournier’s gangrene have to be treated aggressively as soon as possible to decrease their mortality, as it can be fatal in up to 80% of cases. It has been confirmed that delayed and/or inadequate surgery results in higher mortality (EAU).

Apart from surgical debridement and antibiotic treatment, hyperbaric oxygen (HBO) is recommended by some authors as an additional therapy of FG patients, however it may not delay surgical debridement of necrotic tissue (reviewed by Ayan et al., 2005; Mallikarjuna et al., 2012; Pais et al., 2013). It is believed that HBO therapy inhibits the growth of anaerobic bacteria in the affected tissues (particularly if clostridia are involved), prevents further extension of tissue necrosis and reduces systemic toxicity (Pais et al., 2013). Further benefits of hyperbaric oxygen include improvement in neutrophil phagocytic function, increased fibroblast proliferation and angiogenesis, reduction of edema by vasodilatation, and increased intracellular antibiotics transport (e.g. aminoglycosides) (Capelli-Schellpfeffer & Gerber, 1999). However the benefit of HBO therapy in FG remains uncertain (EAU, Grabe et al., 2011).

It is very important to adequately manage the comorbid conditions (e.g. diabetes, alcoholism, etc.) and perform aggressive resuscitation to maintain function of the organs in anticipation of surgery as failure to do so may increase the risk of patient’s death (Pais et al., 2013). Tetanus prophylaxis is advocated in cases with soft-tissue injury (Kim, 2011; Pais et al., 2013). The effect of administration of pooled immunoglobulins to FG patients remains to be clarified (EAU).

Surgery. Surgical debridement of the lesions and drainage must be performed early in the course of the disease and aggressively, with extensive excision of the necrotic tissue (Capitan Manjon et al., 2003; Gölb et al., 2001; Grabe et al., 2011; Kara et al., 2009; Kuzaka et al., 1998; Pawlowski et al., 2004; Silva et al., 2002; Sugihara et al., 2012; Thwaini et al., 2006). It is underlined that also tissues with doubtful viability should be
excised as leaving an infected tissue unoperated can cause greater necrosis of the genitalia and spread of the infection to other areas of the body (Pais et al., 2013; Tahmaz et al., 2006). Radical surgery, which comprises complete removal of necrotic tissue in the affected area, may be sufficient in many patients to treat the infection. Some patients require repeated surgical debridement, however it does not correspond to the disease’s outcome (Chawla et al., 2003; Clayton et al., 1999; Kuo et al., 2007; Malkowski et al., 2006a, 2006b; Palmer et al., 1995; Ulug et al., 2009). However Ersay et al. found that the FGSI score corresponded to the number of debridements among the survivors (Ersay et al., 2007). It is estimated that multiple surgical debridement is often required, with an average of 3.5 procedures required per patient (Chawla et al., 2003).

There are advances in management of Fournier gangrene, including use of vacuum-assisted closure (VAC) system dressing with negative pressure, which speeds healing of the lesions and minimises skin defects (Malikarjuna et al., 2012).

Surgery in FG patients – apart from the removal of the necrotic tissue – may also comprise orchiectomy, colostomy and percutaneous suprapubic cystostomy, however it is rarely required (Ayan et al., 2005; Ersay et al., 2007; Kuo et al., 2007; Silva et al., 2002). Disfiguring surgery and sexual dysfunction resulting from it may cause psychosocial problems in many FG patients, therefore they often require reconstructive surgery of the genitalia and extensive skin grafting (Champion, 2007; Silva et al., 2002).

**Antibiotic therapy.** Administration of broad spectrum antibiotic therapy is indicated early in the course of the disease (Grabe et al., 2011; Kuo et al., 2007; Kuzaka et al., 1998; Pais et al., 2013). As indicated above, the antibiotic spectrum should cover staphylococci, streptococci, Gram-negative rods of the Entero bacteriaceae family and strictly anaerobic bacteria (Pais et al., 2013). Combined antibiotic therapy is advocated to cover this broad spectrum of microorganisms (Golab et al., 2001; Kara et al., 2009; Pais et al., 2013). Antibiotics should be administered parenterally and in doses high enough to reach an effective concentration in the infected tissues (EAU).

It is recommended therefore to administer a broad-spectrum penicillin or third generation cephalosporin and an aminoglycoside (e.g. gentamicin), plus metronidazole or clindamycin, while awaiting the results of microbiological cultures (Ayan et al., 2005; Eke and Raphael, 2011; Pais et al., 2013). Pais et al. suggest using a combination of ciprofloxacin and clindamycin in empiric therapy of FG (Pais et al., 2013). Another option is to use a β-lactam/ β-lactamase inhibitor in combination with an aminoglycoside and metronidazole or clindamycin (Pais et al., 2013). Clindamycin may be particularly effective as it suppresses toxin production and modulates cytokine release. In a recent review Malikarjuna et al. underline that triple antibiotic combined with radical debridement is the mainstay of treatment of FG (Malikarjuna et al., 2012). Some newer guidelines recommend the use of carbapenems or piperacillin-tazobactam. In the case of patients infected with methicillin-resistant *S. aureus* (MRSA) vancomycin should be used.

Other therapeutic options include the use of linezolid, daptomycin or tigecycline, particularly in previously hospitalised patients receiving prolonged antibiotic therapy (Malikarjuna et al., 2012). Samet et al. reported a successful treatment of FG with tigecycline (Samet et al., 2009).

In the rare case of detection of fungi in the direct stain of the tissue, amphotericin B or caspofungin should be added to the empiric regimen (Pais et al., 2013).

**Topical therapy.** Several substances applied topically may aid tissue healing in patients with FG (Malikarjuna et al., 2012; Smith et al., 1998). These therapies include application of honey (contains enzymes which digest necrotic tissues and phenolic acid with antibacterial activity), irrigation of wounds with 0.025% sodium hypochlorite or enzymatic debridement of the wounds by application of lyophilised collagenase. These and other measures have been recently reviewed by Malikarjuna et al. (Malikarjuna et al., 2012).

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**Literature**


