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MINIREVIEW

Fournier's Gangrene – Current Concepts

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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.

Key words: 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; Mallikarjuna *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

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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 underreported 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; Gołąb *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 Drożdż, 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; Gołąb *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; Yeniyol *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 leukocyte 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).

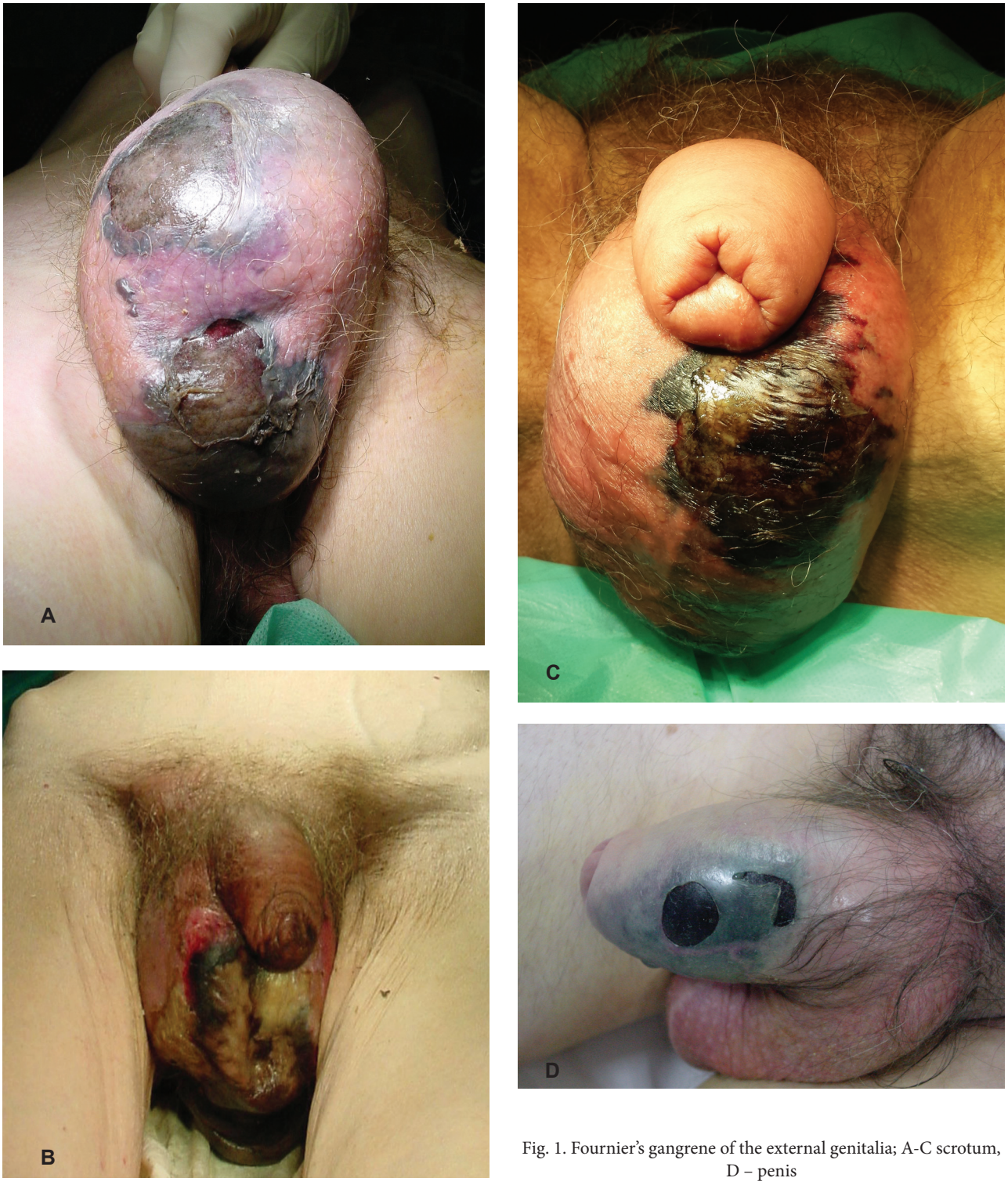

Fig. 1. Fournier's gangrene of the external genitalia; A-C scrotum, D – penis

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., *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 vasoconstriction, and increased intracellular antibiotics transportation (*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; Gołąb *et al*., 2001; Grabe *et al*., 2011; Kara *et al*., 2009; Kuzaka *et al*., 1998; Pawłowski *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.*, 1990; 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 (Mallikarjuna *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 *Enterobacteriaceae* family and strictly anaerobic bacteria (Pais *et al.*, 2013). Combined antibiotic therapy is advocated to cover this broad spectrum of microorganisms (Gołąb *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 Mallikarjuna *et al.* underline that triple antibiotic combined with radical debridement is the mainstay of treatment of FG (Mallikarjuna *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 (Mallikarjuna *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 (Mallikarjuna *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 Mallikarjuna *et al.* (Mallikarjuna *et al.*, 2012).

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