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MICROBIOLOGICAL PROFILE, ANTIBIOTIC SENSITIVITY AND PROGNOSIS OF PATIENTS WITH FOURNIER'S GANGRENE: A PROSPECTIVE, HOSPITAL BASED STUDY FROM NORTH INDIA

Sanjay Gupta Assistant Professor, Dept of General Surgery, GSVM Medical College, Kanpur.

Ajay Kumar Senior Resident, Dept of General Surgery, GSVM Medical College, Kanpur.

Adiveeth Deb* Junior Resident, Dept of General Surgery, GSVM Medical College, Kanpur.
*Corresponding Author

ABSTRACT **Background:** Fournier's gangrene (FG) is a devastating disease that is characterized by necrotizing fasciitis of the perineal, genital, or perianal region. Broad-spectrum antibiotics are the key component of its treatment. However, there is paucity of data regarding the optimal empirical antibiotic therapy for FG.

Materials and Methods: Data from patients who underwent surgery for FG was retrieved from a prospectively collected departmental FG database. Demographics, clinical characteristics, causative pathogens and drug susceptibility/resistance were evaluated. Outcome was also assessed in terms of mortality.

Results: Fifty patients with a median age of 58.5 (40-83) years were included. The perianal region and scrotum (88%) were the most commonly affected. Diabetes mellitus (DM) was the most common comorbidity (92%). The median time to onset of symptoms was 7 (2-15) days, and the median duration of hospital stay was 22 (4-65) days. Ventilator requirement was required in 15 (30%) patients. The median UFGSI score was 9.5 (3-15). The overall mortality rate was 26%. A positive growth was found in specimen cultures of 48 (96%) patients. The median number of bacterial strains that grew in the cultures was 3 (0-10). Amikacin was the antibiotic with the highest frequency of sensitivity (74%), while the highest resistance was observed against ampicillin-sulbactam (64%). Escherichia coli was the most common microorganism (68%). Acinetobacter baumannii and Klebsiella pneumonia were significantly more common in patients who required mechanical ventilation. The mortality rate was 26%. An Uludag Fournier's Gangrene Severity Index (UFGSI) score of > 9.5 and ventilatory support requirement were factors associated with an increased rate of mortality. Acinetobacter baumannii was the only microorganism which was associated with an increased mortality rate.

Conclusion: Causative pathogens in FG appeared to be shifting; thus, empirical antibiotic treatment for this disease should be modified. We recommend 3rd-generation cephalosporin, metronidazole and amikacin for empirical therapy.

KEYWORDS : Empiric Antimicrobial Therapy, Fournier's Gangrene, Necrotizing Fasciitis

INTRODUCTION:

Fournier's gangrene (FG) is a devastating necrotising disease that affects the perineum and genitourinary regions. The common cause of FG is polymicrobial infections, where the Diabetes Mellitus is an attributing common risk factor **(Shyam and Rapsang 2013)**. Study has shown that males, especially in their 60 to 70s, are more often affected by FG when compared to other populations **(Rodríguez Alonso et al. 2000)**. Aside from diabetes, other risk factors of FG also include chronic alcoholism, renal failure, and obesity **(Montoya Chinchilla et al. 2009).** The majorities of FG studies have shown that early diagnosis and aggressive management of FG are required to significantly improve patient outcome.

MATERIALS AND METHODS:

Prospectively collected data on 50 patients who were treated in our department for FG were evaluated. Patients with a solitary abscess of the perineal-perianal region were not included in the study. Fluid resuscitation began in all these patients at the time of hospital admission, and empirical 3rd generation cephalosporin, metronidazole and amikacin were administered. The patients then underwent radical debridement of devitalized necrotic tissues within the first 12 hours.

The patients were treated with regular cleaning and dressings, and also underwent re-exploration once every 48-72 hours. Debridement was continued whenever felt necessary. Tissue cultures were obtained from the patients during each debridement. Appropriate antibiotic therapy was started based on tissue culture results. Patients with negative results for tissue culture and patients without clinical evidence of infection were discharged home after the defects had healed via gradual tertiary wound closure or skin grafts. Colonizing or contaminating pathogens which were observed in the cultures were not considered to be among the pathogens associated with FG. Demographic data on the cases, co-morbid diseases, time to symptom onset, etiology, ventilator requirement, UFSGI (Uludag Fournier's Gangrene Severity Index) score and mortality were evaluated, and their relationship with causative pathogens, as well as their impact on antibiotic susceptibility and resistance patterns, were investigated.

Statistical analysis was performed using The Statistical Package for Social Sciences (SPSS®) for Windows Version 10.0 (SPSS, Chicago, IL, USA). Data were presented as mean (± standard error) or median (min-max) as necessary. Comparison of the means between the groups for the various variables was performed using the Pearson chi-square test or the Kolmogorov-Smirnov test, whereas comparison of the magnitude of values between the groups was performed using the Mann-Whitney U test. The level of statistical significance was $p<0.05$.

RESULTS:

Table 1. Demographic profile of patients:

A. Age	No. Of Patients	Percentage
Less than 40	0	0
41-45	3	6%
46-50	1	2%
51-55	3	6%
56-60	6	12%
61-65	21	42%
66-70	14	28%
More than 70	2	4%
B. Risk Factors	No. Of Patients	Percentage
1. Diabetes Mellitus	46	92%
2. Obesity	20	40%
3. Hypertension	18	36%
4. Heart Disease	4	8%
5. Alcoholism	8	16%
6. Renal failure	2	4%
7. Urethral Surgery	1	2%
8. Neurogenic bladder	1	2%
9. Corticosteroid Use	6	12%

Table 2: Microbiological profile of patients:

A. Type of infection:	No. Of Patients	Percentage
1. Polymicrobial	40	80%
2. Monomicrobial	8	16%
3. None (Sterile)	2	4%
B. Gram Positive:		
1. Enterococcus sp.	22	44%
2. MRSE	5	10%
3. Streptococcus sp.	8	16%
4. Staphylococcus aureus	6	12%
5.Corynebacterium sp.	1	2%

C. Gram Negative:		
1. Escherichia coli	34	68%
2. Acinetobacter baumannii	17	34%
3. Pseudomonas aeruginosa	15	30%
4. Protesus mirabilis	9	18%
5. Klebsiella pneumoniae	6	12%
D. Fungal:		
1. Candida albicans	10	20%

Table 3: Antibiotic sensitivity profile:

Antibiotic	Sensitive (%)	Resistant (%)
Ampicillin	42	26
Ampicillin-Sulbactam	24	64
Piperacillin-tazobactam	40	14
Cefazolin	22	42
Cefepime	34	28
Imipenem	58	18
Meropenem	56	16
Ciprofloxacin	22	20
Levofloxacin	48	40
Moxifloxacin	26	22
Amikacin	74	16
Vancomycin	52	6
Gentamycin	20	8
Daptomycin	12	8
Tigecycline	68	2
Teicoplanin	28	8
Colymicin	72	2

Of the 50 patients treated for FG in our hospital, the median age was 62.5 (40-83) years. Diabetes mellitus (DM) was the most common comorbidity (92%). The median time to onset of symptoms was 7 (2-15) days, and the median duration of hospital stay was 22 (4-65) days. Ventilator requirement was required in 15 (30%) patients. The median UFGSI score was 9.5 (3-15). The overall mortality rate was 26%. A positive growth was found in the tissues of 48 (96%) patients, whereas no growth was observed in 2 (4%) patients. The median number of bacteria that grew in the cultures was 3 (0-10). The culture was monomicrobial in 16% of patients and polymicrobial in 80% (n=40). Escherichia coli was the most commonly identified microorganism (68%), followed by Enterococcus sp. (44%) and Acinetobacter baumannii (34%) (Table-2). Amikacin was the antibiotic which had the highest frequency of bacterial sensitivity (74%), followed by colimycin (72%), tigecycline (68%) and imipenem (58%). The highest bacterial resistance was observed against ampicillin-sulbactam (64%), followed by ciprofloxacin and levofloxacin (44%) and cefazolin (42%). (Table-3)

Mechanical ventilation support was required in 30% of patients, and the mortality rate was higher in patients who required ventilatory support (p=0.0001). When microorganisms which were isolated from the patients with and without ventilator 5 requirement were compared, Acinetobacter baumannii (p=0.0005) and Klebsiella pneumonia (p=0.0240) were significantly more commonly found in patients who required mechanical ventilation. The mortality rate was 26% (13 patients). A UFGSI score of > 9.5 (p=0.046) and ventilatory support (p=0.0001) were factors associated with an increased rate of mortality. When microorganisms between the patients with and without mortality were compared, Acinetobacter baumannii was the only microorganism which was associated with an increased mortality rate (p=0.0108).

FIGURES:

Figure 1. Extensive Fournier's Gangrene involving the scrotum, peineal region, gluteal region and upper part of thigh.

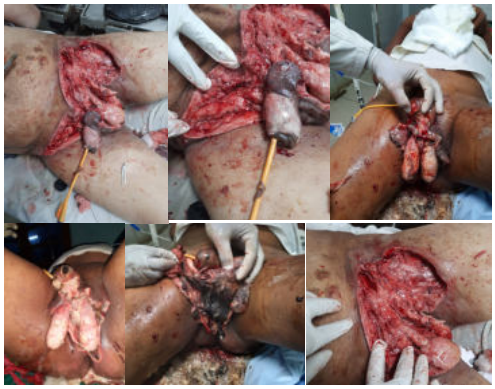

Figure 2. Early surgical debridement and parentral antibiotics form the mainstay of the management of FG.

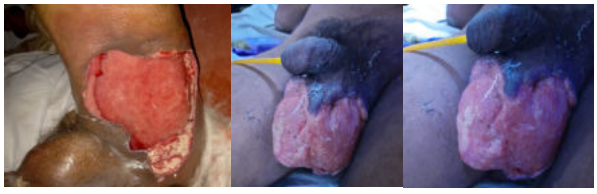

Figure 3. Healthy granulation tissue formed after regular debridement and dressing of the wound.

DISCUSSION:

The present study is the largest study aiming to identify the causative pathogens in FG and their associated patterns of antibiotic susceptibility/resistance. The prevalence of resistant pathogens increased with inappropriate treatment of FG, which was typically a polymicrobial infection related to environmental factors. The median time from symptom presentations to skin gangrenous change is 6 days (**Altarac et al. 2012**). When managing FG patients, this gangrenous tissue requires extensive and repeated debridement (**Sallami et al. 2012**). A positive growth of Klebsiella pneumonia and Acinetobacter baumannii increased in patients who required mechanical ventilation for bacterial pneumonia. The mortality rate was influenced by a UFGSI score > 9.5, ventilator requirement and positive growth of Acinetobacter baumannii.

Although anaerobic culture was not performed in the present study, the median number of microorganisms that grew in the cultures was 3 (0-10). The most common pathogens identified included Escherichia coli, Bacteroides sp., Staphylococcus aureus, Proteus, Streptococcus, Pseudomonas and Enterococci strains [8] . Although Escherichia coli and Enterococci were the most prevalent pathogens identified in the present study, a positive growth of Acinetobacter which has not been reported in the literature, as well as a high rate of Pseudomonas sp., which has rarely been reported, and low rates of Staphylococcus and Streptococci are interesting findings of this study. In particular, the high number of patients who were referred from other medical centers to us might explain the high culture growth rates of Acinetobacter, Pseudomonas and Klebsiella sp., which are resistant and opportunistic pathogens. All these findings suggested that empirical treatment of hospitalized patients with FG should include antimicrobial therapy against these opportunistic pathogens.

Several literatures have shown that patients with diabetes, old age, low blood pressure, high creatine kinase, high lactate, abdominal affection, hemoglobin of less than 10 g/dL, and platelet count of lessthan 150 × 109 /L are associated with poor outcomes (**Martinschek et al. 2012; Ruiz-Tovar et al. 2012**). Many literatures have determined that the risk factors of FG include diabetes mellitus, hypertension, heart disease, smoking, long-term steroid therapy, alcoholism or alcohol abuse, in hot and humid season, and renal failure (**Martinschek et al. 2012; Sallami et al. 2012; Czymek et al. 2010; Mehl et al. 2010; Malik et al. 2010; Ullah and Khan 2009**). Out of the many risk factors, diabetes mellitus is still the highest influencing factor on FG where 43.7% of FG patients are diabetic. A report by **Czymek et. al.** showed that being overweight is also a risk factor of FG, where nearly 40 % of FG patients have body mass indexes (BMIs) of higher than 30 (**Czymek et al. 2010; Mehl et al. 2010**). Although there are several known risk factors that can lead to the development of FG, the clinical onset of FG is still unpredictable.

The most common symptoms of FG are perineal pain and fever that are accompanied by swelling and reddening of perineum or genital area, and the gangreneous change of overlaying skin (**Ruiz-Tovar et al. 2012**). The most common microbiology involved in FG is polymicrobial infection (54%), and the most common found pathogen isolate is Escherichia coli (46.6%). Others contributing pathogen are Streptococcal infection, Bacteroides, Enterobacter, Staphylococcus, Enterococcus, Pseudomonas, Corynebacterium, and Klebsiella pneumoniae (**Rodríguez Alonso et al. 2000; Czymek et al. 2010; Mehl et al. 2010**). Broad-spectrum antibiotic treatment is suggested to adequately cover poly-microbial pathogen, and careful patient monitoring is required to avoid is fungal or hospitalacquired pathogen infection (**Bjurlin et al. 2013**).

The generally accepted and recommended empirical antibiotic therapy includes gentamicin, clindamycin and ampicillin-sulbactam/3rd-generation cephalosporin[6]. However, some studies have recommended metronidazole instead of clindamycin, as well as other aminoglycosides or fluoroquinolone-group antibiotics instead of gentamicin (which is also an aminoglycoside) [6,7] . In our clinical practice, ceftriaxone and a combination of metronidazole and amikacin are used for empirical therapy. Although this is the largest study to investigate antibiotic resistance/susceptibility in FG, the roles of clindamycin/penicillin derivatives in empirical antibiotic treatment should be explored in future studies with larger numbers of patients given the limited number of cases with streptococcal infection in the present study.

Amikacin, which is used in our clinical practice to treat Gram-negative bacterial infections, should routinely be used due to the high susceptibility rates. A high rate of susceptibility to carbapenem antibiotics (imipenem, meropenem) is remarkable. The routine use of ampicillin-sulbactam[6] and fluoroquinolone[7] group antibiotics, which have been recommended for empirical antibiotic therapy, should be reviewed in larger studies given their high rates of bacterial resistance in our study. The positive growth of Acinetobacter baumannii and Klebsiella pneumonia in patients with ventilator-associated pneumonia is consistent with the results of previously reported studies which used relevant methodology [9]. Our study revealed that empirical use of high-susceptibility carbapenem antibiotics (Klebsiella pneumonia) as well as high susceptibility amikacin and colistin (Acinetobacter baumannii) was more appropriate in FG for patients who developed ventilator-associated pneumonia.

While the mortality rate has been reported to be 3-45% in the medical literature [1,2,10,11], the mortality was 26% in the present study. A UFGSI score > 9.5 and ventilator requirement increased mortality. The increased rate of ventilator-associated mortality can be explained by development of ventilator-associated pneumonia, which was diagnosed by a significant growth of Klebsiella pneumonia and Acinetobacter baumannii [9,12]. In the present study, Acinetobacter baumannii was the only pathogen which was associated with an enhanced mortality rate in FG. Given the increased prevalence of Acinetobacter baumannii in recent years, there may also be an increasing prevalence of Acinetobacter baumannii in FG. The high rate of Acinetobacter among the causative pathogens of FG in our study in patients with a history of hospitalization is particularly striking. Although no study has specifically examined the relationship between FG and Acinetobacter baumannii, the fact that a positive growth of Acinetobacter baumannii enhanced ventilator-associated mortality has also been reported in a meta-analysis by Siempos et al. [13] which showed the mortality rate in ventilator-associated pneumonia caused by Acinetobacter baumannii to range between 30% and 70% [9,12,13]. The prospectively collected data stored in our departmental FG database is the major strength of the present study. The major limitations are unavailability of anaerobic culture data for technical reasons and retrospective design of the study. In conclusion, antibiotic therapy for treatment of FG should be modified based on culture and antibiogram results. It is important to make alterations in empirical therapy based on changes in bacterial flora and relationship between poor prognostic factors and mortality and causative pathogens in FG. Institutes should evaluate their own culture results and choose their best empirical antimicrobial therapy regimen. Based on the findings of this study, larger further studies are necessary to find out the most accurate empirical antibiotherapy for FG.

A study from Spain (n = 51) showed that the survivors of FG are 13.5 years younger than those who have died (60 versus 73.5, p = 0.02) (**Luján Marco et al. 2010**). In a 2012 report from Turkey (n = 52), the non-survivors group are older in age than survivors (62 versus 55 years old). In our study, the results also showed that the older patients age had higher rates of mortality. This result is concurrent with in the other previous studies, where increased age was shown to be related to higher mortality rate (**Martinschek et al. 2012; Roghmann et al. 2012**). Although FG is rare, its rapid progression can lead to life-threatening conditions that require early surgical intervention and parenteral antibiotics to improve patient outcomes (**Morua et al. 2009**).

CONCLUSION:

Fournier's gangrene (FG) is a rare emergent condition that affects the perineum and urogenital region. The clinical course of FG is fulminant and serious regardless of parenteral antibiotic treatment. The mortality rate of FG remains high and can be considered as a surgical emergency. Due to its high mortality rate and rapid progress, FG must be diagnosed and managed promptly in clinical settings. The reduction of obesity, alcohol consumption, tobacco use is helpful in reducing the possible risk of FG. Furthermore, older patients with genital or perineal pain should be examined for crepitus of skin. Finally, when a patient is diagnosed with FG, swift consultation with surgeons for early debridement and administration of broad-spectrum antibiotics are required in order to save the patient's life.

All institutes should evaluate their own culture results and then choose the best empirical antimicrobial therapy regimen. Future large studies are necessary to find out the most accurate empirical antibiotic therapy for FG.

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