

***Escherichia coli* producer of extended-spectrum beta-lactamases as causative agent of Fournier gangrene of urogenital origin associated with higher mortality**

***Escherichia coli* productora de betalactamasas de espectro extendido como agente causal de gangrena de Fournier de origen urogenital asociada a mayor mortalidad**

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Abstract

Background: Fournier gangrene (FG) is a necrotizing fasciitis that endangers the patient's life. The objective of this study was to determine the etiology and impact of the agent isolated on wound and urine culture. **Method:** We performed a retrospective analysis within a cohort of 66 patients with FG of urogenital origin. The measured qualitative values were expressed as frequency and Percentage and compared with the chi square test and Fisher's test. The difference was considered statistically significant at $p < 0.05$. **Results:** Patients who died had more frequent cultures of urine and wound positive for extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli*: urine, survivors 14.5% vs. deaths 44.4%; wound, 20.8% vs. 66.6% ($p < 0.001$). **Conclusions:** During the integral evaluation of the patient with FG it is essential to perform the urine and surgical wound cultures in order to initiate the antibiotic management directed at an early stage. Patients with GF who die present a greater number of cultures positive for *E. coli* ESBL.

KEY WORDS: Fournier gangrene. Mortality. Urinary tract infection. *Escherichia coli* ESBL.

Resumen

Antecedentes: La gangrena de Fournier (GF) es una fascitis necrotizante que pone en peligro la vida del paciente. El objetivo de este trabajo fue determinar la etiología y el impacto del agente aislado en el cultivo de la herida y de orina. **Método:** Se llevó a cabo un análisis retrospectivo de una cohorte de 66 pacientes con GF de origen urogenital. Los valores cualitativos medidos se expresaron como frecuencia y porcentaje, y se compararon con la prueba de ji al cuadrado y la prueba de Fisher. La diferencia se consideró estadísticamente significativa con $p < 0.05$. **Resultados:** Los pacientes que murieron presentaban con mayor frecuencia cultivos de orina y herida positivos para *Escherichia coli* productora de betalactamasas de espectro extendido (BLEE): orina, sobrevivientes 14.5% vs. muertes 44.4%; herida, sobrevivientes 20.8% vs. muertes 66.6% ($p < 0.001$). **Conclusiones:** Durante la valoración integral del paciente con GF es fundamental realizar cultivos de orina y de herida con el fin de iniciar el manejo antibiótico dirigido de manera temprana. Los pacientes con GF que mueren presentan mayor número de cultivos positivos para *E. coli* BLEE.

PALABRAS CLAVE: Gangrena de Fournier. Mortalidad. Infección de vías urinarias. *Escherichia coli* BLEE.

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Introduction

Fournier's gangrene (FG) is a necrotizing fasciitis that puts patient's life in danger. It occurs mainly in patients with a certain degree of immunosuppression¹⁻⁵. It has an incidence of 1.6 per 100,000 population, and mainly affects males, although there are cases reported in females. The main risk factors for developing it are diabetes mellitus, obesity, chronic alcoholism, kidney failure, liver failure, smoking, cancer and human immunodeficiency virus infection.⁶ Mortality in the first presented series was 88%, although in the most modern ones it ranges from 7.5 to 16%^{7,8}. The main causative agents are anaerobic organisms (54%), *Escherichia coli* (46.6%) and streptococci (36.8%).^{8,9}

The purpose of this work was to determine the etiology and impact of the agent isolated in wound and urine cultures of patients diagnosed with FG treated at *Hospital General de Mexico Dr. Eduardo Liceaga*.

Method

The patient information needed for analysis was collected at *Hospital General de Mexico Dr. Eduardo Liceaga*. Patient records consistent with this diagnosis in the period encompassed from January 2011 to December 2017 were searched in the medical records department. One-hundred and twenty records of patients diagnosed with FG of urogenital origin as a reason for discharge were assessed. Fifty-four patients were excluded for not meeting the diagnostic criteria (scrotal abscesses, inguinal abscesses, acute and chronic prostatitis). Sixty-six patients who were clinically diagnosed, who were managed by the urology department, who underwent extensive surgical debridement and who were administered broad-spectrum antibiotic therapy were included.

A retrospective analysis of this cohort of patients with urological-origin FG was carried out. Analyzed variables were the microorganism that developed in urine and wound cultures, and the selected antibiotic therapy, with a comparison being made between the group of survivors (n = 48) and those who died (n = 18). Sixty-six patients were assessed, which were included for statistical analysis.

Statistical analysis was carried out using the Statistics for Social Sciences (SPSS) package for Windows, version 20.0.

Qualitative measured values were expressed as frequency and percentage, and were compared with the chi-square test and Fisher's test. The difference was considered statistically significant with a p-value < 0.05, with a 95% confidence interval.

Results

Total population consisted of 66 patients, out of which there were 48 survivors and 18 deaths (27.7%), with an average age of 59.5 years, average weight of 76.5 kg and average body mass index of 27.7. Regarding the necrotizing fasciitis extent, 28% had penile-scrotal, 53% perineal and 16% inguino-abdominal involvement. There was a history of diagnosis or criteria consistent with type 2 diabetes mellitus diagnosis in 56.7% of patients, and 22.4% had a history of hypertension. Alcoholism was positive in 44.8% of patients.

Leukocytosis with neutrophilia predominated in the blood count; an average white blood cell (WBC) count of 23/mm³ was found (standard deviation [SD]: 7.4), 89% (SD: 6) of neutrophils and 5% (SD: 2) of lymphocytes. Average hemoglobin level was 12.9 (SD: 3) and 50% of patients had anemia. Platelet count average was 254/mm³ (SD: 18). When blood chemistry was analyzed, we found that glucose average value was 253 mg/dL (SD: 50), for creatinine it was 2.54 mg/dL (SD: 1.6), for urea 124 mg/dL (SD: 68), sodium 131 mEq/L (SD: 5), potassium 4.8 mEq/L (SD: 1), calcium 8 mEq/L (SD: 0.82), bicarbonate 16.8 (SD: 5), albumin 1.9 g/dL (SD: 0.5) and cholesterol 114 U/L (SD: 26). International Normalized Ratio (INR) was on average 1.5 (SD: 1.6) (Table 1).

Urine culture was found to be positive in 68.7% (n = 45). *Candida albicans* was isolated in 17.9% (n = 12) and gram-negative organisms in 17.9% (n = 12), followed by *E. coli* in 13.4% (n = 9) and extended-spectrum beta-lactamase (ESBL)-producing *E. coli* in 9% (n = 6); polymicrobial origin was found in 9% (n = 6). When the analysis of the wound cultures was performed, a larger variety of microorganisms was found. The main agent isolated from wounds was ESBL-producing *E. coli*, which was found in 32.8% (n = 22) of patients, followed by *E. coli* and gram-negative organisms, each one with 13.4% (n = 9), the *C. albicans* + *E. coli* binomial with 6% (n = 4), and *Acinetobacter baumannii*, *C. albicans*, *Enterococcus faecalis*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Staphylococcus hominis* and hemolytic staphylococci, each with 4.5% (n = 3). Four patients showed no

Table 1. Description of variables within the population, in means and percentages

Variable	Total (n = 66)	Variable	Total (n = 66)
WBC (mm ³)	23 (7.4)	Diabetes (%)	56.7 (38)
Neutrophils (%)	89 (6)	Hypertension (%)	22.4 (15)
Lymphocytes	5 (2)	Alcoholism (%)	44.8 (30)
Hemoglobin (mm ³)	12.9 (3)	Triggering factors (%)	
		Catheter > 1 year	15 (10)
		Orchepididymitis	13.6 (9)
		Urethral lithiasis	4.5 (3)
		History of TURP	4.5 (3)
		Urethral stricture	3 (2)
Hematocrit (mm ³)	254 (18)	Risk factors (%)	
		CKD	15.5 (10)
		Cirrhosis	12.2 (8)
		COPD	7.5 (5)
Platelets (mm ³)	254 (8)	UTI (%)	85 (57)
Glucose (mg/dL)	253 (50)	IPSS (%)	
		Mild	25.4 (17)
		Moderate	55.2 (37)
		Severe	17.9 (12)
Creatinine (mg/dL)	2.54 (1.6)	Sepsis (%)	80.30 (53)
Urea (mg/dL)	124 (68)	Severe sepsis (%)	9 (6)
Sodium (mEq/L)	131 (5)	Suprapubic cystostomy (%)	58.2 (39)
Potassium (mEq/l)	4.8 (1)	CONUT score (%)	
		Mild	52.2 (5)
		Moderate	37.3 (25)
		Severe	9% (6)
Calcium (mEq/L)	8 (82)	ICU admission	35.8% (24)
Bicarbonate (mmol/L)	16.8 (5)	Hemodialysis	22% (15)
Albumin (g/dL)	1.9 (.5)	INR	1.5 (1.6)
Cholesterol (U/L)	114 (26)	BMI (SD)	27.7 (6)

BMI: body mass index; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; ICU: intensive care unit; INR: International Normalized Ratio; IPSS: international prostate symptom score; SD: standard deviation; TURP: transurethral resection of the prostate; UTI: urinary tract infection.

development in the wound culture. Table 2 shows the comparison of microorganisms isolated in urine and blood between the groups of survivors and deceased subjects. When the statistical analysis was performed, the patients who died were found to have urine and wound ESBL-producing *E. coli*-positive cultures more often: urine, survivors 14.5% vs. deceased subjects 44.4%; wound, survivors 20.8% vs. deceased subjects 66.6% ($p < 0.001$).

Antibiotic management was based on ertapenem in 47.6% of cases ($n = 32$), imipenem in 17.9% ($n = 12$),

imipenem with vancomycin in 14.9% ($n = 10$), ertapenem with vancomycin in 9% ($n = 6$), and piperacillin-tazobactam and vancomycin in 9% ($n = 6$).

Discussion

There are many studies in the literature that have sought to find the factors associated with higher mortality in FG-diagnosed patients, but none has analyzed the impact of microbiology in the disease evolution. Subjecting the patients to vacuum-assisted closure therapy has been found to significantly decrease mortality⁹. Another factor associated with higher mortality is the percentage of body surface area involved, especially when it is larger than 3.25%¹⁰.

Both clinical and laboratory abnormal values, including heart rate, temperature, blood pressure, respiratory rate, WBC count, serum urea, serum creatinine, serum bicarbonate, serum lactate, serum calcium, serum sodium, serum potassium and serum albumin have been associated with mortality in FG¹¹⁻¹⁵.

As for the microorganism isolated in patients with FG, there is a large number of works that have reported their findings. Yilmazlar et al.¹⁶ found that the most commonly isolated agent in their patients was *E. coli* (64%), which is very similar to the findings of this work, where *E. coli* was the most commonly isolated microorganism (26.8%).

In the 1980s, necrotizing fasciitis was thought to be an infection caused by streptococci, but a higher relationship between a polymicrobial origin and FG was later observed. Patients with FG have been shown to have an average of four different microorganisms in cultures, with the most common being streptococci, staphylococci, *E. coli* and *P. aeruginosa*, which is very similar to those reported in this work (9% staphylococci, 26.8% *E. coli* and 4.5% *P. aeruginosa*); no cases of streptococci isolates were found. Our microbiology laboratory did not report more than one bacterial strain present in each culture¹⁷⁻¹⁹.

A study of a series of 43 patients reported that the most common bacterial microorganisms found in wounds were *E. coli* (48.8%), *Pseudomonas* spp. (20.9%), *Enterococcus* spp. (18.6%), *Staphylococcus* spp. (13.9%), *Streptococcus* spp. (11.6%), *Proteus* spp. (11.6%), *Acinetobacter* spp. (9.3%), *Bacteroides* spp. (9.3%) and *Klebsiella pneumoniae* (4.6%); no analysis was carried out on the relationship between morbidity and mortality and the agent isolated in the culture²⁰.

Table 2. Microorganism isolates in urine and wound cultures from patients with Fournier gangrene and comparison between survivors and deceased subjects

Positive culture	Urine (%) (n = 66)	S (%) (n = 48)	D (%) (n = 18)	Wound (n = 66)	S (%) (n = 48)	D (%) (n = 18)
<i>C. albicans</i>	17.9 (n = 12)	16.6 (n = 8)	22.2 (n = 4)	0	0	0
Gram-negative	17.9 (n = 12)	20.8 (n = 10)	11.1 (n = 2)	13.4 (n = 9)	16.6 (n = 8)	5.5 (n = 1)
<i>E. coli</i>	13.4 (n = 9)	14.5 (n = 7)	11.1 (n = 2)	13.4 (n = 9)	16.6 (n = 8)	5.5 (n = 1)
ESBL-producing <i>E. coli</i>	13.4 (n = 9)*	2 (n = 1)	44.4 (n = 8)	32.8 (n = 22)*	20.83 (n = 10)	66.6 (n = 12)
Polymicrobial	9 (n = 6)	8.3 (n = 4)	11.1 (n = 2)	0	0	0
<i>E. coli</i> + <i>C. albicans</i>	0	0	0	6 (n = 4)	6.25 (n = 3)	5.5 (n = 1)
<i>A. baumannii</i>	0	0	0	4.5 (n = 3)	6.25 (n = 3)	0
<i>E. faecalis</i>	0	0	0	4.5 (n = 3)	6.25 (n = 3)	0
<i>P. mirabilis</i>	0	0	0	4.5 (n = 3)	6.25 (n = 2)	5.5 (n = 1)
<i>P. aeruginosa</i>	0	0	0	4.5 (n = 3)	2.08 (n = 1)	11.1 (n = 2)
<i>S. hominis</i>	0	0	0	4.5 (n = 3)	6.25 (n = 3)	0
Hemolytic staphylococci	0	0	0	4.5 (n = 3)	6.25 (n = 3)	0
No development	27.2 (n = 18)	37.5 (n = 18)	0	6.6 (n = 4)	8.3 (n = 4)	0

*Statistically significant (p<0.05).

D: deceased subjects; S: survivors.

Bacterial isolates from FG patients usually represent urogenital or anorectal region normal flora, such as enteric strains (*E. coli*, *Klebsiella* spp., *Proteus* spp.), gram-positive cocci (staphylococci, streptococci, enterococci) and anaerobic bacteria (*Clostridium* spp., *Bacteroides* spp., *Fusobacterium*)^{21,22}. Paty and Smith²³ reported *E. coli*, *Bacteroides* spp. and streptococci as the most commonly isolated bacteria. Palmer et al.²⁴ reported that *E. coli* and streptococci strains predominated, while *Bacteroides* spp. strains grew less commonly in samples of patients with FG. Ulug et al.²⁵ found that *E. coli* and *P. aeruginosa* were the most commonly isolated bacteria from patients with FG. Ayan et al.²⁶ found *E. coli* (58%) and *Staphylococcus aureus* (36%) to be FG most common etiologic agents. In one study that included 15 cases²⁷, gram-negative bacilli, *E. coli* and *Acinetobacter* spp. were the most common microorganisms.

Recently, community-acquired methicillin-resistant *S. aureus* has emerged as a cause of FG with a severe and even fulminant clinical course²⁷. Poor hygiene and local trauma predispose to the development of FG, given that bacteria have access to the deepest tissues. Synergy between anaerobic bacteria is claimed to contribute to FG pathogenesis. These bacteria secrete multiple toxins and enzymes that make the tissue to rapidly become necrotized (e.g., hyaluronidase, streptokinase, collagenase); in addition, they predispose to the formation of thrombi in blood vessels and to serious cardiovascular insufficiency^{28,29}.

In our work, a large number of patients with FG was found to have positive cultures for ESBL-producing *E. coli*, which is a finding that has not been previously reported in the literature. When making the comparison between patients who survived and those who died, the latter had a larger number of positive

cultures for this microorganism, with the difference being statistically significant.

Conclusion

During the comprehensive assessment of the patient with FG, it is essential to carry out urine and surgical wound cultures in order to start targeted antibiotic management in an early manner. Patients with FG who die have a higher number of ESBL-producing *E. coli*-positive cultures.

Conflicts of interest

The authors of this work have no conflicts of interest.

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