SURGICAL INFECTIONS

EDITED BY: Evangelos P. Misiakos and Konstantinos George Tsalis
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frontiers Research Topics

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SURGICAL INFECTIONS

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Surgical infections are caused by the breakdown of the equilibrium existing between organisms and the host. This may occur after a breach in a protective surface, as occurs after surgical trauma, changes in host resistance, or particular characteristics of the organism. The possible outcomes are abscess formation, local spread with/without tissue death, distant spread or resolution.

A surgical infection is an infection requiring operative treatment (excision or drainage), and occupies an unvascularized space in tissue, or may occur in an operated site. Common examples of the former group are furuncles and carbuncles, hollow viscus inflammations, such as appendicitis, cholecystitis, and most abscesses. The latter group comprises all surgical site infections.

This Research Topic provides comprehensive information on the biology, mechanisms, prevention and treatment of surgery-related infections.

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EDITORIAL
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Check for updates

Editorial: Surgical Infections

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Keywords: surgical infections, bacteria, culture, necrosis, surgery

Editorial on the Research Topic

Surgical Infections

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Surgical infections represent a common and serious problem in everyday clinical practice. Surgical site infections, after elective or emergency gastrointestinal or vascular operations, is a commonly encountered problem associated with considerable morbidity and mortality in the surgical patient (1, 2). In addition, idiopathic necrotic infections, such as necrotizing fasciitis, carry high mortality rates if surgery is delayed (3). Therefore, we decided to create a Research Topic dealing with this peculiar clinical problem. Since this is just the beginning, the published articles, so far, cannot cover all aspects of this Topic, i.e., biology, mechanisms, prevention and treatment of surgery-related infections. This Research Topic contains articles, originating from Greece, which cover several aspects of surgical infections.

The first article is a commentary on the article (4). In this commentery, titled "Commentary: Evidence for Replacement of an Infected Synthetic by a Biological Mesh in Abdominal Wall Hernia Repair" and written by Tampaki et al., 2017, the authors state that the use of biological mesh in difficult hernias with infected mesh seems to be of clinical benefit. However, the increased expenses associated with its use cannot be fully justified, as there is not sufficient evidence from randomized trials proving their advantages.

The second article is also a commentary but on (5). This commentary titled, "Commentary: Hernia, Mesh, and Topical Antibiotics, Especially Gentamycin: Seeking the Evidence for the Perfect Outcome…" is also written by Tampaki et al., 2017, from the Univerity of Athens. The aim of this paper is to study the impact of prophylactic use of topical antibiotics, especially gentamycin, in hernia repair with mesh. The authors agree with Dr. Kulacoglou that gentamycin empirically used as monotherapy in hernia repair with mesh may be beneficial in patients with compromised immune status, such as advanced age, chemotherapy, comorbidities, long duration of operation, etc. They conclude that prophylactic use of antibiotics in the nosocomial environment may help reducing surgical site infections in clean surgeries, such as hernia repair with mesh, but one should take into account the existing increased antibiotic resistance rates.

In the third paper, "Fournier's Gangrene: Lessons Learned from Multimodal and Multidisciplinary Management of Perineal Necrotizing Fasciitis" by Ioannidis et al., 2017, the authors present their experience in the management of a potentially lethal disease, Fournier's gangrene, in a University Surgical Depertment, in Thessaloniki, Greece. They analyze the clinical, laboratory data, comorbidities, bacterial cultures, management, complications, and clinical outcome of 20 patients who had been treated surgically in their center for perineal necrotizing fasciitis. They also underline the importance of aggressive surgical debridement in the management of this challenging condition.

In the fourth paper, "Aortic Graft Infection: Graphene Shows the Way to an Infection-Resistant Vascular Graft" by Patelis et al., 2017, from the University of Athens, the authors analyze the unique characteristics of graphene, a two-dimensional material used in aortic reconstruction. Due to its bacteriostatic and bactericidal effects, graphene may resolve the problem of aortic graft infections in the future. Indeed, graphene and its derivatives could potentially lead the way to the production of infection-resistant or bactericidal graft materials, which can be used in aortic reconstruction or other types of arterial repair, in order to avoid the development of graft infection.

The fifth paper titled "Simultaneous Hepatic and Mesenteric Hydatid Disease—A Case Report" by Paramythiotis et al., 2017, from Thessaloniki, Greece, describes a case of a 39 year old man with intermittent abdominal pain. Abdominal CT revealed three calcified lesions, one in the liver, one adjacent to an ileal loop, and one close to the urinary bladder. Hydatid cysts in two organs may coexist in 5–13% of cases; however, a hydatid cyst in the mesentery is extremely rare. The hepatic hydatid cyst was treated with evacuation and drainage, whereas the other two ones were excised. In conclusion, hydatid cysts should be excised when feasible, or at least they should be evacuated and drained.

The sixth paper is entitled "Incidence and Risk Factors for Organ/Space Infection after Radiofrequency-Assisted Hepatectomy or Ablation of Liver Tumors in a Single Center: More than Meets the Eye" by Karavokyros et al., 2017, from Laikon General Hospital, Athens, Greece. In this paper the authors investigate the possible risk factors for the development of organ/space infection after liver tumor resection or radiofrequency ablation, with emphasis in secondary blood stream infections. The incidence of surgical/site infections after these procedures was calculated as 16%. Admission to the ICU was found to be a statistically significant factor predisposing to the development of postoperative infections. The authors concluded that patients with compromised physical condition, or comorbidities are at greatest risk for developing postoperative infections.

The last paper entitled "Early Diagnosis and Surgical Treatment for Necrotizing Fasciitis: A Multicenter Study" by Misiakos et al., 2017, presents a retrospective study including 62 patients treated surgically in four University Surgical Departments in Athens, Greece. This devastating infection involved the perineum in 46.8% of cases, the lower limbs in 35.55% of cases, the upper limbs and axillary region in 8.1% of cases. Septic shock occurred in 12.9% of cases and correlated strongly with mortality. The overall mortality rate was 17.7% in this series. The authors concluded that repeat surgical debridement and meticulous perioperative management is the mainstay of treatment in this potentially lethal condition.

We believe that this is a promising beginning with the above excellent papers in this topic. We encourage the admission of new papers from other countries in this field.

AUTHOR CONTRIBUTIONS

Both authors discussed the articles presented in the Research Topic "Surgical Infections" and prepared the manuscript.

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GENERAL COMMENTARY
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Commentary: Evidence for Replacement of an Infected Synthetic by a Biological Mesh in Abdominal Wall Hernia Repair

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Keywords: hernia, mesh infection, biological mesh, mesh replacement, mesh complication

A commentary on

Evidence for Replacement of an Infected Synthetic by a Biological Mesh in Abdominal Wall Hernia Repair
by Montgomery A, Kallinowski F, Köckerling F. Front Surg (2016) 2:67. doi: 10.3389/fsurg.2015.00067

It was a pleasure to go through the manuscript by Montgomery et al. because it provides stimulating arguments in favor of using biologic meshes and replacing infected synthetic ones in difficult abdominal wall reconstruction (AWR), whereas it brings up excellent discussion topics on the subject (1).

First, we certainly agree that biologic meshes are being used with increased frequency in many fields and, indeed, the outcomes are perceived to be better than those for traditional polymer-based prosthetic mesh replacement materials. However, we believe that the use of biological grafts increased rapidly without clear clinical evidence of efficacy and, therefore, we would like to highlight that selection of the proper implant is always crucial along with careful consideration of patient characteristics related to prosthetic will as this could effectively lead us to decreased complication rates, readmissions, and number of postoperative visits.

Interestingly, the same side of the coin as suggested above is being presented in recent clinical reports focusing on the successful use of light weighted, macroporous synthetic meshes in contaminated ventral hernia reconstructions, showing that in contaminations with *Staphylococcus aureus* and *Escherichia coli*, the biologic meshes proved to be less resistant compared to reduced-weight synthetics and, therefore, raising the question whether biologics should be questioned in contaminated ventral hernia reconstruction (2).

Furthermore, a highly anticipated multicenter prospective double-blinded randomized controlled trial by Rosen et al. examining material safety, efficacy, and cost effectiveness wants to demonstrate that the use of a macroporous light-weight polypropylene mesh is much more cost effective in comparison to the use of a biologic mesh (3). As suggested above, with currently >200 meshes being commercially available in the United States, it is significant to highlight strength and weaknesses of materials used and always explore possibilities of combining them so as to take advantage of their benefits. As far as synthetic meshes are concerned, tensile strength, porosity, elasticity, and fabrication method are significant. Excessive tensile strength leads often to inflammation, material contraction, and further postoperative pain, whereas the various pore sizes influence the meshes

Abbreviations: AWR, abdominal wall reconstruction; BMI, body mass index; SSIs, surgical site infections.

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incorporation into the surrounding tissues. Additionally, knitting materials are more porous and flexible, while weaving materials appear stronger. Permanent meshes have demonstrated higher infection and fistula rates, increased recurrence rates, and even cases of small bowel obstruction, while expanded meshes primarily used in vascular grafts and in abdominal surgeries present higher hernia recurrence rates and shrinkage in size. A combination of the above create "composite" meshes, approved for clinical use, while lastly absorbable meshes degrade fully and can be used in contaminated fields (4).

On the other hand, the collagen matrix of biological grafts acts regeneratively promoting new collagen deposition, impacting a better biocompatibility and immunogenic ability and leading to decreased infection resistance. As a consequence, excessive scaring and graft encapsulation can be avoided. Moreover, the chemically cross-linked collagen matrix can resist degradation for several years from various enzymes like collagenases. Although in case studies where infection occurred, a graft removal was seldom necessary (5), follow-up studies showed a high incidence of laxity, eventration, and recurrent herniation with the authors highlighting again the insufficiency of high-quality evidence regarding biological mesh use in ventral hernia repair (5).

Indisputably, both biologic and synthetic materials present with advantages and disadvantages. In an attempt to overcome them, both have been lately combined into the release of a hybrid mesh appearing very promising as it is expected the biologic component to protect the synthetic one from infections leading to a biologic component replacement and the final synthetic mesh incorporation into the tissue host, with a diminished risk of fistulization (5).

The latest COBRA study showed a significant advantage of biosynthetic absorbable meshes related to long-term recurrence and quality of life in patients with more complex situations of ventral hernia repair, presenting their use as a good alternative over biologic and permanent synthetic mesh use (6). The above also highlights that besides material use, other factors related to mesh complications play a vital role including the various surgical techniques used, which influence long-term results, several patient and technical factors. More specifically, while it is known that permanent synthetic meshes are related to higher infection rates, therefore, contraindicating their use in contaminated fields, a recent meta-analysis showed that an overall infection rate reaching up to 5% combined with certain patient risk factors such as smoking, American Society of Anesthesiologists score >3, and emergency operation, worsened the chances of infection (7). Moreover, the impact of demographics such as patients body mass index as well as certain risk factors such as hernia grade, hernia size, and past bariatric surgery have been shown as predictive factors of recurrence (8). The above emphasizes the absolute necessity of proper implant selection along with careful consideration of patient characteristics related to prosthetic will.

In the latest retrospective review by Chamieh et al., the authors concluded that synthetic meshes are not inferior to biologic meshes when working on similar cohort patients in contaminated fields. More specifically, patients length of stay was 4 days longer concerning biological meshes, whereas re-admission rates were 52.9% in the biologic group versus a 45.8% in the synthetic group. Surgical site infections and recurrence with re-admitions were less frequent for biological meshes (38.9 versus 55.6%, respectively). The overall infection rate was more frequent in the biologic group showing, however, a less frequent microbiology of Gram-positive bacteria (50 and 29.2% for synthetic versus 39 and 63%, respectively) (9).

Concluding, based on a late systematic review regarding costs and efficacy of biologic mesh implants in AWR, their expense cannot be fully justified, whereas the evidence remains insufficient to determine a favorable correlation between cost and clinical benefits of the biological materials (10). Therefore, we believe that until high-level of evidence coming from randomized clinical trials demonstrates superiority of biological materials, the expense associated with their use cannot be confirmed and, therefore, it is highly risky to suggest the superiority and selection of these materials given their cost, and their preference over synthetic meshes in difficult AWR.

AUTHOR CONTRIBUTIONS

ECT conceived of the idea and drafted the manuscript. AT helped draft the manuscript. KK and GK helped to revise the manuscript. All authors read and approved the final manuscript.

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GENERAL COMMENTARY
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Commentary: Hernia, Mesh, and Topical Antibiotics, Especially Gentamycin: Seeking the Evidence for the Perfect Outcome…

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A commentary on

Hernia, Mesh, and Topical Antibiotics, Especially Gentamycin: Seeking the Evidence for the Perfect Outcome…
by Kulacoglou H. Front Surg (2014) 1:53. doi: 10.3389/fsurg.2014.00053

It was a pleasure to go through the manuscript by Hacan Kulacoglou (1) published in Frontiers in Surgery, which focuses on topical antibiotic prophylaxis use especially gentamycin in clean surgeries such as in inguinal hernia mesh reconstructions, as he brings up excellent discussion topics.

Indisputably there are benefits in using antibiotics topically rather than orally or intravenously, reducing the chances of bacterial resistance and presumably the risk of having a surgical site infection (SSI), however leading to unwanted effects development, with the most common being contact dermatitis (2).

It has been suggested that gentamycin, topically or parenterally administered (1), is effective especially against Gram-negative bacteria; however, its use as empirical monotherapy or in combination with other antibiotics in clean surgeries has not been officially comparatively evaluated. Antibiotic choice, duration, dose, dosing interval, and first dose timing in contaminated but also in clean fields appear significant and would rather depend on the antibiotic's adverse effect profile, drug interactions, and the probability of bacterial resistance, especially given the emergence of bacterial resistance to third-generation cephalosporins, causing great concerns.

Although antibiotic prophylaxis is not mandatory in clean, elective operations, regular use of implants, accounting a 90% of inguinal hernia repairs, creates controversies (2). The European Hernia Society (3) does not suggest routine antibiotic prophylaxis. However, it is recommended where patient-related or procedure-related risks exist, as also Mazaki et al. indicated in a randomized controlled trial, showing that prophylaxis use proves to have effect on SSI prevention (4). Interestingly, mesh use in inguinal hernia reconstructive surgeries does not necessarily lead to greater wound infection risk (5). Latest data concerning wound infections regarding open mesh contrarily to non-mesh techniques used in inguinal hernia reconstructive surgeries suggest that deep infections surface rare and do not necessarily lead to mesh removal when mono- or multifilament mesh fabrics are applied along with drainage. Furthermore, the majority of RCTs are against using prophylaxis

Abbreviations: SSI, surgical site infection; SENIC, Study of the Efficacy of Nosocomial Infection Control; NNIS, National Nosocomial Infection Surveillance; EARS-NET, European Antimicrobial Resistance Surveillance Network; EHS, Environmental, Health, and Safety.

in hernia repair procedures, whereas benefits in low-risk patients seem scarce (6, 7).

According to the Environmental, Health, and Safety guidelines, prophylaxis in clean operative procedures is not required. However, risk factors presented including the patient's age, immunosuppression status, co-morbidities, long operation duration, and drainage use are an exception (8). Further classification of the patients in low-risk and high-risk groups for SSIs seems mandatory. According to the most widely known risk indexes Study of the Efficacy of Nosocomial Infection Control and National Nosocomial Infection Surveillance evaluating the SSI rates, significant risk factors related to high SSI rates include abdominal operation processes, a more than 2-h procedure, wounds classified as dirty/infected or contaminated and patients being operated with more than three discharge diagnoses (9). Another significant issue underlined is the accurate and adequate estimation of SSI rates which can lead to significant bias and false results according to different definitions given concerning the SSIs, their time of occurrence, the patients follow-up and the study designs. The above moves the focus away from examining the most significant factors related to SSIs, which are the surgical microenvironment and the level of a country's health service (9). By all means, an SSI rate of above or below 5% in many centers should not be objectively judged and implementations should be determined according to standard criteria.

Several surveys from England emphasize the surgeon's preference in using antibiotic prophylaxis also in low-risk patients regarding hernia repair procedures despite the lack of adequate clinical evidence (10). The first study on aminoglycoside resistance in Upper Egypt showed that implementation of newer aminoglycosides in terms of more resistant bacteria eradication could help in mixed infections, with aminoglycosides and b-lactams acting synergistically, whereas among the regimens tested, gentamicin and amoxicillin combination has proven the least productive. They also concluded that the high resistance rates to aminoglycosides could be reduced by imposing efficient infection control policies. Among different nations, extremely high resistance to gentamicin (94.5%) in Turkey versus (32.6%) India was observed, whereas the most common resistant phenotype in Greece was that of kanamycin–neomycin (11), which may be attributed to deviations and variances in aminoglycoside treatment regimens. Resistance rates also rise varying widely between European countries. Reporting resistance rates to third-generation cephalosporins reached up between 20 and 30% in 2012 with a documented increase in aminoglycoside resistance rates (12).

The above highlights the vital importance of evaluating the surgical microenvironment and the level of a country's health service as the most significant factors related to SSI rates. When examining antibiotic prophylaxis in clean surgeries, issues such as bacterial resistance development should be determined after taking into consideration annual updates from the European Antimicrobial Resistance Surveillance Network and reports on health cost increase per country, as such changes in resistance are always indicative of valuable trends.

Worth mentioning is that increased incidences of adverse effects have been recorded when adding aminoglycosides to b-lactams versus b-lactam monotherapy (13). Fruitful implementation of infection control measures will reduce the problem of bacterial resistance decreasing the length of hospital stay, treatment costs, and mortality rates. Therefore, as there is no system to regularly monitor antibiotic resistance or the treatment efficacy in the community, providing data that would help guide empirical antibiotic therapy also in the case of clean surgeries, clinically applying empirical combination antibiotic regimens in clean surgeries is a matter of great importance and has to be examined with caution.

AUTHOR CONTRIBUTIONS

ECT conceived of the idea and wrote the manuscript. AT helped to draft the manuscript. KK and GK helped to revise the manuscript. All authors read and approved the final manuscript.

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ORIGINAL RESEARCH
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Fournier's Gangrene: Lessons Learned from Multimodal and Multidisciplinary Management of Perineal Necrotizing Fasciitis

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Background: Fournier's gangrene (FG) is a rapidly evolving necrotizing fasciitis of the perineum and the genital area, the scrotum as it most commonly affects man in the vast majority of cases. It is polymicrobial in origin, due to the synergistic action of anaerobes and aerobes and has a very high mortality. There are many predisposing factors including diabetes mellitus, alcoholism, immunosuppression, renal, and hepatic disease. The prognosis of the disease depends on a lot of factors including but not limited to patient age, disease extent, and comorbidities. The purpose of the study is to describe the experience of a general surgery department in the management of FG, to present the multimodal and multidisciplinary treatment of the disease, to identify predictors of mortality, and to make general surgeons familiar with the disease.

Methods: The current retrospective study is presenting the experience of our general surgery department in the management of FG during the last 20 years. The clinical presentation and demographics of the patients were recorded. Also we recorded the laboratory data, the comorbidities, the etiology, and microbiology and the therapeutic interventions performed, and we calculated the various severity indexes. Patients were divided to survivors and non-survivors, and all the collected data were statistically analyzed to assess mortality factors using univariate and then multivariate analysis.

Results: In our series, we treated a total of 24 patients with a mean age 58.9 years including 20 males (83.4%) and 4 females (16.6%). In most patients, a delay between disease onset and seeking of medical help was noted. Comorbidities were present in almost all patients (87.5%). All patients were submitted to extensive surgical debridements and received broad-spectrum antibiotics until microbiological culture results were received. Regarding all the collected data, there was no statistically significant difference between survivors and non-survivors except the presence of malignancy in non-survivors ($p = 0.036$) and the lower hemoglobin ($p < 0.001$) and hematocrit ($p = 0.002$) in non-survivors. However, multivariate analysis did not reveal any predictor of mortality.

Conclusion: Early diagnosis, aggressive thorough surgical treatment, and administration of the proper antibiotic treatment comprise the cornerstone for the outcome of this disease. In small populations like in the present study, it is difficult to recognize any predictors of mortality and even the severity indexes, which take into account a lot of data cannot predict mortality.

Keywords: necrosis, perianal, perineum, polymicrobial, scrotum, surgical debridement

INTRODUCTION

Fournier's gangrene (FG) is a surgical and urological emergency as it is a life threatening, potentially lethal, polymicrobial necrotizing fasciitis of the perineal and genital region affecting mainly males, but it can also present in females too (1–5). While this condition was known and has been described in sporadic case reports by the late eighteenth century (4, 6–17) it was only by the end of the nineteenth century that Jean Alfred Fournier provided a case series with a detailed description of the disease (13). However, until today, despite the fact, that in many circumstances the disease is treated by general surgeons and not by urologists, the description and analysis of FG is missing in most of the surgical textbooks. The purpose of the current retrospective study is to describe the experience of a general surgery department in the management of FG, to present the multimodal and multidisciplinary treatment of the disease, to identify, if possible predictors of mortality, including demographic, clinical, laboratory, etiological, microbiological, and surgical factors and also comorbidities and comorbidity and disease severity indexes, and finally to make general surgeons familiar with the disease.

MATERIALS AND METHODS

Study Design

For the current retrospective study, the surgical and hospitalization records of our department from 1st January 1997 to 31st December 2016 were reviewed, searching for patients who have been diagnosed with FG or perineal gangrene or necrotizing fasciitis of the perineum. Ethical approval was not required for this study in accordance with the national and institutional guidelines. The diagnosis was based either on clinical examination, which revealed perineal skin necrosis or crepitus of the perineum, and/or on imaging studies revealing the presence of air in the perineal area. The final diagnosis of FG was established in all cases during surgery when the gray black, foul smelling gangrenous tissue was revealed.

The data recorded included demographics, clinical findings, medical history and comorbidities, laboratory findings, etiology and extent of the disease, therapeutic interventions, disease severity indexes, morbidity, mortality, and hospitalization. The outcome parameters of the study were in hospital mortality (defined as death from any cause during hospitalization), 30- and 90-day mortality (defined as death from any cause during the first 30 and 90 days after the procedure, respectively).

Demographic Findings

The demographics data that were recorded regarding each patient included gender and age.

Clinical Findings

The recorded clinical findings were as follows: symptoms, duration of symptoms prior to seeking medical treatment in the emergency department (ED), physical examination findings, vital signs {blood pressure (systolic, diastolic, and mean), heart rate [beats per minutes (bpm)], respiratory rate [breaths per minute (brpm)], and temperature}, presence of sepsis, severe sepsis, or septic shock. {Sepsis was defined as systemic inflammatory response syndrome (SIRS) in combination with a microbiologically or clinically documented infection. SIRS was defined as presence of at least two of the following criteria: temperature >38°C or <36°C, white blood cells (WBCs) >12,000/mm^3, <4,000/mm^3 or >10% of immature forms heart rate >90 bpm, respiratory rate >20 bpm or $PaCO_2$ <32 mmHg. Severe sepsis was defined as sepsis along with tissue hypoperfusion (lactic acidosis with lactate >3 mmol/L) or hypotension (systolic blood pressure <90 or mean blood pressure <70 mmHg or a drop in systolic pressure ≥40 mmHg from normal) or organ dysfunction (18). Organ dysfunction variables were as follows: liver dysfunction [total bilirubin >2 mg/dL, activated partial thromboplastin time (aPPT) >60 s, or international normalized ratio (INR) >1.5], pulmonary dysfunction (arterial hypoxemia with PaO_2/FiO_2 <300), and renal dysfunction (diuresis <0.5 mL/kg/h for at least 2 h, creatinine >2 mg/dL, or an increase of >0.5 mg/dL), hematologic dysfunction (platelets <100,000/mm^3), neurological dysfunction (disturbance of consciousness), cardiovascular dysfunction (hypotension in need of dopamine ≥5 μg/kg per minute or norepinephrine at any dose) (18, 19). Septic shock was defined as the presence of severe sepsis with hypotension despite adequate fluid resuscitation.}

Medical History and Comorbidities

Past medical and surgical history was recorded, and the comorbidities considered were as follow: pulmonary disease, renal disease, heart disease, liver disease, diabetes mellitus, hypertension, hyperlipidemia, malignancy, peripheral vascular disease, psychiatric disease, obesity, and immunosuppression. Also smoking and alcoholism were recorded. Pulmonary disease was defined as either emphysema or chronic obstructive pulmonary disease. Renal disease was defined as serum creatinine >1.7 mg/dL (20). Heart disease was considered as presence of any of the following: angina pectoris, past myocardial infraction, coronary disease, coronary artery bypass graft surgery, signs of myocardial ischemia on the electrocardiogram, valvular heart disease, heart failure, and atrial fibrillation (20). Liver disease was defined as the presence of any of the following: chronic hepatitis B or C, liver cirrhosis (21). Diabetes mellitus was considered present if the patient had a fasting blood glucose >126 mg/dL or was on antidiabetic treatment with diet, oral drugs or insulin. Hypertension was defined as SP >150 mmHg or DP >90 mmHg or if the patient was receiving antihypertensive treatment (20). Hyperlipidemia was defined as total cholesterol levels ≥200 mg/dL, LDL levels ≥100 mg/dL, or the patient was under medical treatment. Malignancy was considered present if the patient had any active solid or hematologic malignancy. Peripheral vascular disease was considered present if the patient had a history rest pain, of claudication, or ischemic gangrene, or if he had undergone a previous intervention surgical or percutaneous (22), or as an ankle brachial index of less than 0.9. Psychiatric disease was considered present if the patient had depression, bipolar disorder, schizophrenia or if he was receiving drugs (23, 24). Obesity was defined as body mass index (BMI) >30. Immunosuppression was defined as leukopenia, chronic immunosuppressive treatment or any active solid or hematologic malignancy (25). Patients were defined as smokers if they had been smoking at least 10 cigarettes per day, until admission or if there was a history of at least 20 years of nicotine use given up not more than 10 years ago. Alcoholism was defined as the presence of either alcohol dependence or alcohol abuse. Also the Charlson comorbidity index (CCI) and the Age Adjusted Charlson comorbidity index (AACCI) were calculated.

Laboratory Findings

The laboratory tests studied were hemoglobin, hematocrit, platelet count (PLT), WBC, glucose, serum creatinine, serum urea, serum total protein, serum albumin, serum globulin, liver function tests [including total bilirubin, gamma-glutamyl transferase, alkaline phosphatase, alanine transaminase (ALT-SGPT), and aspartate transaminase (AST-SGOT)], sodium (Na^+), potassium (K^+), calcium (Ca), lactate dehydrogenase, creatine kinase, coagulation tests [prothrombin time, international normalized ratio (INR), and aPPT], cholesterol levels, C-reactive protein (CRP), and gas analysis (including $PaCO_2$, PaO_2, bicarbonate, lactic acid, and pH).

Etiology and Extent

Furthermore, the etiology of FG and microbiological test results (Gram positive, Gram negative, anaerobic) were recorded. The extent of FG indicating the affected body surface was assessed using modified body surface area nomograms used routinely to calculate the extent of burn injuries (26) according to which the perineum, scrotum, and penis account for 1% each and each ischiorectal fossa for 2.5% (18).

Therapeutic Interventions

Antibiotics regimen administrated, the time interval from hospital admission to surgical treatment, the type and extent of surgery, need for colostomy and type of colostomy, need for urostomy, the use of a rectal diversion system, duration of surgery, number of surgical debridements performed, perioperative transfusion and use of vasoactive drugs was also recorded. Also, the use of hyperbaric oxygen and vacuum-assisted closure (VAC) were recorded. We also recorded the type of wound healing either as healing by secondary intention or by reconstruction with a skin graft performed by a plastic surgeon.

Disease Severity Indexes

We calculated also the acute physiology and chronic health evaluation II severity score (APACHE II), the Fournier's Gangrene Severity Index (FGSI) score, which has been created by Laor and colleagues in 1995 by modifying the APACHE II score (26). The nine parameters studied are heart rate, respiratory rate, temperature, hematocrit, leukocyte count, serum sodium, potassium, creatinine, and bicarbonate levels, and the deviation from normal is graded in a scale from 0 to 4 to a maximum of 36 points. The values are added to calculate the FGSI score (26). Moreover, we also calculated the Uludag FGSI that also takes into account age and dissemination to a maximum of 43 points (18). Finally, we calculated the laboratory risk indicator for necrotizing fasciitis (LRINEC) which is based on the values of CRP, WBC, hemoglobin, serum sodium, serum creatinine and plasma glucose (11).

Morbidity, Mortality, and Hospitalization

In addition, complications and morbidity, the intensive care unit (ICU) stay, total hospitalization time, hospitalization in the surgical department, and hospitalization in plastic surgery department, and mortality were recorded.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences for windows version 20.0. The measured quantitative values were checked for normality. Values with normal distribution were expressed as mean ± SD and compared with parametric independent samples *t*-test, while values without normal distribution were expressed as median and interquartile range and compared to a non-parametric Mann–Whitney test. The measured qualitative values were expressed as frequency and percentage and compared with the chi-square test and Fisher's exact test. Values found significant in the univariate analysis were used for multivariate analysis with a binary logistic regression model. The difference was considered statistically significant at $p < 0.05$ as the confidence interval was 95%.

RESULTS

During the last 20 years a total of 24 patients were diagnosed and treated in our surgical department with the diagnosis of FG. The mean age was 58.9 ± 11.3 years (45–79 years), while 20 (83.3%) patients were males and 4 (16.7%) were females. The median time between disease onset to hospital admission was 2 days. Clinically the majority of patients (21 patients—87.5%) presented with local signs of inflammation in the perineal area including pain, heat, erythema, and local edema. The presence of local abscess was evident in eight patients (33.3%). Skin necrosis was present in 13 patients (54.2%), 3 (12.5%) of whom had a foul smelling local discharge, while crepitation was also present in 5 patients (20.8%). The disease involved the scrotum in males and the genital region in females in 19 cases (79.2%), the perineum in 22 cases (91.7%) and the perianal region in 13 cases (54.2%) (**Figure 1**). Most patients (18 patients—75%) were febrile, tachycardic with increased respiratory rate fulfilling the criteria of SIRS and sepsis (all patients were considered to have a clinically documented infection), nine patients (37.5%) presented with severe sepsis, and three patients (12.5%) with septic shock. There was no statistically significant difference between survivors and non-survivors regarding the demographics and clinical presentation of the disease (**Table 1**).

Neutrophilic leukocytosis was evident in the majority of patients (22 of 24—91.6%) while inflammation indicators (CRP) were increased in 23 patients (95.8%). The other laboratory test results did not differ significantly among survivors and non-survivors except from hematocrit and hemoglobin which were statistically significant lower in non-survivors (**Table 2**).

Regarding comorbidities, three patients (12.5%) had no comorbidities, while seven patients (29.1%) presented with diabetes mellitus, of whom one patient (4.2%) was diagnosed

FIGURE 1 | Skin necrosis of the scrotum **(A)**, scrotum, perineal and perianal region **(B)** in males and of the genital, and perineal region **(C)** in a female.

TABLE 1 | Patient demographics and clinical presentation.

Variable	Total	Non-survivors	Survivors	*p*
Age (years)	58.9 ± 11.3	57.4 ± 10.9	58.8 ± 11.9	0.749
Male/female	20/4	4/1 (80%/20%)	16/3	0.822
HR (bpm)	93.1 ± 16.3	97 ± 18.2	93.3 ± 15.6	0.554
RR (brpm)	20.9 ± 5	23.6 ± 6.4	20 ± 4.6	0.168
SAP (mmHg)	103.1 ± 18.9	98 ± 19.2	104.3 ± 19.7	0.503
DAP (mmHg)	62.1 ± 11.7	60.3 ± 12	66 ± 11.4	0.412
MAP (mmHg)	78.8 ± 11.1	77 ± 11.9	82 ± 7.6	0.474
Temperature (°C)	37.9 ± 1.1	38.2 ± 1.3	37.9 ± 1.1	0.563
Diuresis (cc)	1,586 ± 593	1,400 ± 612	1,660 ± 611	0.436
Time from symptoms to emergency department (days)	2 (1)	3 (1.5)	2 (1)	0.410
Body surface (%)	3 (2)	3 (1.5)	3 (3)	0.528
Sepsis	18 (75%)	4 (80%)	14 (73.7%)	0.772
Severe sepsis	9 (37.5%)	2 (40%)	7 (36.8%)	0.897
Septic shock	3 (12.5%)	1 (20%)	2 (10.5%)	0.521

during hospitalization. Also, seven patients had hyperlipidemia (29.1%), and six patients had peripheral vascular disease (25%). Hypertension was evident in six patients (25%), heart disease in five patients (20.8%), obesity in five patients (20.8%), pulmonary disease in four patients (16.6%), and immunosuppression in four patients (16.7%). Two patients (8.3%) presented with renal failure, two patients with liver disease (8.3%), two patients with malignancy (8.3%), and two patients with psychiatric disease (8.3%). Nine patients (37.5%) were smokers while five patients (20.8%) were alcoholics. The median BMI of the patients was 27. The median score in CCI was 2, and the median score in age-adjusted CCI was 3. With the exception of malignancy that was statistically significant more common in non-survivors than survivors ($p = 0.036$), there was no other statistically significant difference in comorbidities between non-survivors and survivors (**Table 3**). Regarding the history of surgical or urologic intervention, one patient had an inguinal hernia surgery, two patients had appendectomy, one patient had surgery of anal fissure, one patient had hemorrhoidectomy, one patient had been submitted to total mesorectal excision, and one patient had transurethral prostatectomy.

Pelvic X-ray was performed in all patients and revealed the presence of air in soft tissues in 18 of them (75%) (**Figure 2**). Perineal and scrotum ultrasound was performed in one patient (4.2%) showing diffuse marked thickening of skin with multiple echogenic foci with associated dirty shadowing which was consistent with the presence of gas. Pelvic CT was performed in four patients (16.7%), and pelvic MRI in one patient (4.2%), who in fact presented to the ED with an MRI already performed previously, revealing extended local inflammation, soft tissue thickening, stranding of fat surrounding the involved structures and the presence of soft tissue air.

The initial infection origin in 10 patients (41.6%) was colorectal, of whom one patient had local recurrence of rectal cancer. Five patients (20.8%) presented with local skin infection or perineal abscess, while in four patients (16.7%) the initial port of entry was the urogenital tract. Three patients (12.5%) presented with local trauma in the area while two patients (8.3%) had idiopathic Fournier gangrene. The most common isolated bacteria were Gram negative and especially *Escherichia coli* in 11 patients (45.8%), followed in frequency by *Klebsiella pneumoniae* in three patients (12.5%), *Pseudomonas aeruginosa* in three patients (12.5%), *Acinetobacter baumannii* in two patients (8.3%), *Proteus mirabilis* in two patients (8.3%), and *Providencia stuartii* in one patient (4.2%). In same patients more than 1 g negative bacteria were present. Microbial cultures revealed also Gram positive bacteria and specifically *Staphylococcus aureus* in three patients (12.5%), *Staphylococcus epidermidis* in one patient (4.2%), *Streptococcus* species in two patients (8.3%), and *Enterococcus* species in two patients (8.3%). The anaerobe bacteria isolated from the microbial cultures were *Bacteroides* species in 11 patients (45.8%) and *Enterobacter* species in five patients (20.8%). Thirteen patients (54.1%) had a polymicrobial infection isolating more than one type of bacteria. There was statistically significant difference between survivors and non-survivors regarding the etiology and microbiology of the disease (**Table 4**).

TABLE 2 | Laboratory tests.

Variable	Total	Non-survivors	Survivors	*p*
Hemoglobin (g/dL)	11.5 ± 1.4	9.8 ± 0.9	12 ± 1.1	<0.001
Hematocrit (%)	33.9 ± 4.8	28.5 ± 3.8	35.3 ± 3.7	0.002
PLT (K/μL)	226,000 (222,500)	149,000 (294,500)	226,000 (229,000)	0.506
White blood cell (total/mm^3)	15,000 (8,360)	17,600 (16,860)	14,700 (9,700)	0.619
Glucose (mg/dL)	100 (115)	120 (105)	100 (120)	0.618
Creatinine (mg/dL)	0.75 (0.6)	1.29 (1.2)	0.75 (0.61)	0.135
Urea (mg/dL)	33 (13.5)	40 (71.5)	32 (14)	0.198
Total protein (g/dL)	4.85 ± 0.49	4.86 ± 0.58	4.8 ± 0.47	0.965
Albumin (g/dL)	2.44 ± 0.29	2.41 ± 0.27	2.44 ± 0.31	0.777
Globulin (g/dL)	2.63 ± 0.32	2.65 ± 0.36	2.62 ± 0.33	0.910
Bilirubin (mg/dL)	0.84 (0.62)	0.88 (8.16)	0.84 (0.6)	0.934
Gamma-glutamyl transferase (U/L)	50 (37)	50 (42)	30 (38)	0.9
Alkaline phosphatase (U/L)	99 (50)	95 (401)	99 (50)	0.77
ALT (U/L)	24 (13)	20 (9.5)	26 (15)	0.868
AST (IU/L)	26 (14)	23 (70)	29 (12)	0.934
Na^+ (mmol/L)	136 (7)	131 (7)	138 (6)	0.183
K^+ (mmol/L)	3.9 (0.3)	4 (0.72)	3.9 (0.3)	0.707
Ca (mg/dL)	9.2 (1.3)	9.1 (0.9)	9.6 (1.7)	0.465
Lactate dehydrogenase (U/L)	169 (140)	138 (137.5)	177 (136)	0.77
Creatine kinase (U/L)	64 (62)	50 (118)	64 (46)	0.967
Prothrombin time (s)	14.8 ± 2.9	17.1 ± 4.9	14.2 ± 2.5	0.251
Activated partial thromboplastin time (s)	32 (2)	32 (0.95)	32 (3)	0.523
International normalized ratio	1.25 ± 0.24	1.43 ± 0.4	1.2 ± 0.13	0.255
Cholesterol (mg/dL)	210 (70)	210 (65)	225 (60)	0.803
C-reactive protein (mg/dL)	3.2 (1.9)	3.0 (2.1)	3.2 (1.6)	0.298
$PaCO_2$ (mmHg)	32.5 ± 5.8	29.4 ± 5.1	32.9 ± 5.5	0.182
PaO_2 (mmHg)	97.2 (19)	92.1 (7.3)	100 (18.9)	0.143
Bicarbonate (mmol/L)	21.2 ± 1.9	20.8 ± 1.3	21.5 ± 2	0.595
Lactic acid (mmol/L)	1.36 ± 0.46	1.36 ± 0.53	1.35 ± 0.46	0.992
pH	7.36 ± 0.09	7.35 ± 0.15	7.37 ± 0.08	0.717

TABLE 3 | Comorbidities.

Variable	Total (24)	Non-survivors (5)	Survivors (19)	*p*
Pulmonary disease	4 (16.6%)	2 (40%)	2 (10.5%)	0.179
Renal disease	2 (8.3%)	1 (20%)	1 (5.2%)	0.380
Heart disease	5 (20.8%)	1 (20%)	4 (21.0%)	0.959
Liver disease	2 (8.3%)	0(0%)	2 (10.5%)	0.449
Diabetes mellitus	7 (29.1%)	2 (40%)	5 (26.3%)	0.608
Hypertension	6 (25%)	1 (20%)	5 (26.3%)	0.772
Hyperlipidemia	7 (29.1%)	1 (20%)	6 (31.5%)	0.612
Malignancy	2 (8.3%)	2 (40%)	0 (0%)	0.036
Peripheral vascular disease	6 (25%)	1 (20%)	5 (26.3%)	0.772
Psychiatric disease	2 (8.3%)	1 (20%)	1 (5.2%)	0.380
Obesity	5 (20.8%)	1 (20%)	4 (21.0%)	0.959
Immunosuppression	4 (16.6%)	2 (40%)	2 (10.5%)	0.179
Smoking	9 (37.5%)	1 (20%)	8 (42.1%)	0.615
Alcoholism	5 (20.8%)	0 (0%)	5 (26.3%)	0.544
Charlson Comorbidity Index	2 (1.5)	3 (3.5)	2 (2)	0.084
Age Adjusted Charlson Comorbidity Index	3 (1)	3 (2)	3 (1)	0.156
Body mass index (kg/cm^2)	27 (9.5)	29 (24.5)	26 (10)	0.482

The administered empirical antibiotic regimens were penicillin-type antibiotics (piperacillin with tazobactam) in 12 patients, third-generation cephalosporins (cefotaxime, ceftriaxone, ceftazidime) in 6 patients (25%), carbapenems (imipenem/cilastatin, meropenem) in 3 patients (12.5%), and quinolones

FIGURE 2 | Pelvic X-ray showing the presence of air in the soft tissue.

TABLE 4 | Etiology and microbiology.

Variable	Total (24)	Non-survivors (5)	Survivors (19)	p
Trauma	3 (12.5%)	1 (20%)	2 (10.5%)	0.521
Urogenital	4 (16.6%)	1 (20%)	3(15.7%)	0.822
Skin infection–abscess	5 (20.8%)	1 (20%)	4 (21.0%)	0.959
Idiopathic	2 (8.3%)	0 (0%)	2 (10.5%)	0.449
Colorectal	10 (41.6%)	2 (40%)	8 (42.1%)	0.668
Gram (−)	17 (70.8%)	4 (80%)	13 (68.4%)	0.612
Gram (+)	6 (25%)	1 (20%)	5 (26.3%)	0.772
Anaerobes	11 (45.8%)	2 (40%)	9 (47.4%)	0.769
Polymicrobial infection	13 (54.1%)	3(60%)	10 (52.6%)	0.769

(ciprofloxacin) in 3 patients (12.5%). In these antibiotic regimens, aminoglycosides (amikacin or gentamicin) were added in eight patients. Metronidazole was added in 20 patients (83.3%), clindamycin in 4 patients (16.7%), and antibiotics for Gram-positive bacteria (linezolid, daptomycin, and teicoplanin) were added in 4 patients (16.7%). Antibiotics regiments were changed according to culture susceptibility tests. The median duration of antibiotic administration was 16 days.

The median time from admission to surgery was 4 h with the exception of one patient who has been admitted to the internal medicine department for unknown fever investigation, and the diagnosis was delayed for 48 h and the median surgical time was 55 min. Surgical debridement in all cases involved the perineal and scrotum area in males and the perineal and genital region in females, and in 11 patients (45.8%) involved the perianal area. The median Body surface affected by FG was 3%, and there was no statistically significant difference between non-survivors and survivors. Extensive and aggressive surgical debridement, with resection of necrotic or infected tissue and tissue of doubtful viability until viable tissue was encountered, was necessary in all patients (**Figure 3**). Four of the patients (16.7%) were submitted during the initial operation to loop colostomy, three of whom (12.5%) were submitted to sigmoidostomy and one patient (4.2%) to transverse colostomy. During operation, the median blood transfusion was 1 U of (red blood cells) RBC per patient, and seven patients needed vasoactive drugs. Rectal diversion device was used in two patients (8.3%) (**Figure 4**), while none of the patients needed urostomy. Thirteen patients were submitted to only one surgical debridement while seven patients (29.1%) were submitted to two surgical debridements and four patients (16.7%) had more than two surgical debridements. Following extended surgical debridement the surgical wounds were washed daily with plenty of hydrogen peroxide and povidone iodine, until the development of granulomatosis (**Figure 5**). Hyperbaric oxygen therapy was employed for three patients (12.5%), and VAC therapy in one patient (4.2%). There was statistically significant difference between survivors and non-survivors regarding the demographics and clinical presentation of the disease (**Table 5**).

Histopathological analysis revealed ulceration of the epidermis, the presence of neutrophilic exudate, thrombosed vessels, and necrosis, and abscessation of the subcutaneous fat tissue (**Figure 6**).

FIGURE 3 | Extended surgical debridement of the scrotal, perineal, and perianal area.

FIGURE 4 | Rectal diversion device.

The median prognostic severity index scores were 10 for APACHE II, 5 for FGSI, 6 for Uludag FGSI, and 5 for LRINEC and presented no statistically significant difference among survivors and non-survivors (**Table 6**).

Regarding morbidity and complications, besides severe sepsis and septic shock, four patients were diagnosed with pneumonia, three patients developed multiple organ dysfunction syndrome (MODS), three patients with bacteremia, two patients with acute renal failure, one patient with pulmonary embolism, one patient with deep vein thrombosis, one patient with ischemic myocardium, one patient with pulmonary edema.

From the 19 patients who survived wound healing was achieved by secondary intension in 14 patients (73.7%) and by reconstruction from plastic surgeons with a skin draft in 5 patients (26.3%) (**Figure 7**).

The median period of hospitalization, including the hospitalization in general surgery department, ICU, and plastic surgery department, was 27 days, 40 days in survivors, and 3 days in non-survivors, with the difference being statistically significant ($p = 0.008$). The difference in days of hospitalization is due to the fact that in non-survivors the death occurred early, during the first day of patient hospitalization. The median stay in the surgical department was 16 days, 25 for survivors and 3 for non-survivors. For the nine patients (37.5%) transferred following surgery to the ICU, the median ICU stay was 2 days while the median ICU for the all the patients was 0 days; however, some patients were in ICU for up to 27 days. For the patients submitted to skin graft, the median stay in the plastic surgery department was 24 days.

FIGURE 5 | Granulomatosis of the surgical wounds following extended surgical debridement and daily dressing changes of the scrotum, perineal, and perianal region **(A)**, of the scrotum and perineum **(B)**, and of the scrotum and left inguinal region **(C)**.

Regarding non-survivors all the patients died during hospitalization and earlier than 30 days hospitalization. So the in hospital, 30 and 90 days mortality rate was the same and was 20.83% (5 of 24 patients). The cause of death was severe sepsis and septic shock in three patients. One patient died from massive pulmonary embolism, and one patient died from generalized carcinomatosis, cancerous cachexia, and MODS.

Univariate analysis revealed as significant predictors of mortality, the presence of malignancy, low hematocrit, and low hemoglobin. However, in multivariate analysis, none of these was significant.

DISCUSSION

In 1883, a French dermatologist and venereologist, Jean Alfred Fournier, described a life threatening clinical condition characterized by progressive necrotizing fasciitis of the male genitourinary tract (1–14, 16–18, 26–36). This condition was officially named as FG despite the fact that it has been originally described by Baurienne in 1764, by Pouteau in 1783, by Jones in 1871, and

TABLE 5 | Intervention and hospitalization.

Variable	Total (24)	Non-survivors (5)	Survivors (19)	*p*
Time from emergency department to OR (h)	4 (2)	3 (2)	4 (2.75)	0.086
Surgical time (min)	55 (21.5)	60 (27.5)	55 (27)	0.647
Number of surgical debridements	1 (1)	2 (2)	1.5 (1)	0.631
Transfusion (RBC)	1 (2)	1 (2)	1 (2)	0.405
Vasoactive drugs	7 (29.1%)	2(40%)	5 (26.3%)	0.608
Colostomy	4(16.7%)	1	3	0.822
Rectal diversion	2(8.3%)	0	2	0.449
Urostomy	0 (0%)	0	0	1
Hyperbaric oxygen	3 (12.5%)	0	3	0.342
Vacuum-assisted closure	1	0	1	0.600
Total hospitalization (days)	27(38.5)	3 (16.5)	40 (39)	0.008
Intensive care unit stay (days)	0 (1.5)	0 (1.5)	0 (2)	0.961
Surgical department stay (days)	16 (34.5)	3 (18)	25 (34)	0.075

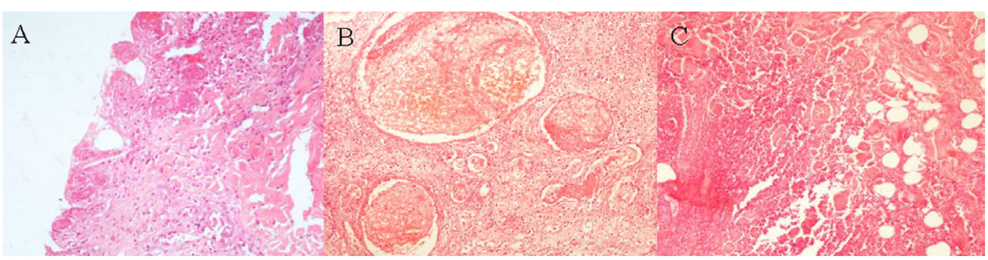

FIGURE 6 | Histopathologic findings in Fournier's gangrene revealing neutrophilic exudate and epidermis necrosis **(A)**, thrombosis of vessels **(B)**, and abscessation and necrosis of subcutaneous fat tissue **(C)** (hematoxylin and eosin staining ×200).

TABLE 6 | Severity index and prognostic scores.

Variable	Total	Non-survivors	Survivors	p
APACHE II	10 (3.5)	14 (12)	10 (2)	0.142
FGSI	5 (5)	5 (9)	2 (4)	0.179
Uludag FGSI	6 (9)	9 (6)	5 (3)	0.062
LRINEC	5 (4)	7 (4.5)	5 (4)	0.145

FIGURE 7 | Skin graft reconstruction immediately after surgery **(A)**, long-term result after skin graft **(B)**, and wound healing by secondary intention **(C)**. The patients are in accordance with **Figure 5**.

later by Avicenna in 1877 (4, 6–17). According to Fournier, the disease is characterized by an abrupt onset of painful scrotal swelling and a rapid progression to gangrene in otherwise healthy men without any obvious or definite cause (3, 4, 7, 8, 10, 11, 13, 14, 17, 26, 32, 36). Many different terms including idiopathic gangrene of the scrotum, periurethral phlegmon, streptococcal scrotal gangrene, gangrenous erysipelas of the scrotum, and synergistic necrotizing cellulitis have been used to describe this clinical entity over the years (8, 9, 11–13). The term "necrotizing fasciitis" was first used by Wilson in 1952 for the description of inflammation of soft tissue occurring in superficial and deep fascia regardless of location (8). Initially, the term "Fournier gangrene" was used for the idiopathic gangrene of genitals of men; however, later this term began to be used for all almost the necrotic inflammations of the region (14, 16).

In the past, Fournier gangrene typically affected predominately male patients and developed rapidly, but nowadays it has been reported to be diagnosed in people of all ages, from newborn babies to the very elderly (4, 28). FG is a rare condition and affects around 1:7,500 (12, 33). While, Fournier' gangrene is still considered by many a disease that affects only males, it is nowadays evident that females can be affected too and develop necrotizing fasciitis of the perineum and genitalia, although in many cases it was not termed FG, and that may be a reason why the disease in females is under recognized (8). However, most of the studies reveal a male predominance (male:female is 10:1) with a mean age of 50 years although high incidence of disease presentation in female patients with an increased percentage of 30% or even 47.7% have been reported (5, 11–13, 16, 17, 37, 38). Male predominance exists perhaps due to easier drainage of the female perineum via the vaginal route (17). While, disease predominance is affected by gender, mortality is not and males and females present with similar prognosis. However, despite the fact that the disease is less common in females, yet it is often more extensive, because of the female pelvic anatomic feature (39). In our series, there was an increased incidence of female patients (16.7%) possibly due to the fact that patients were treated by a general surgery department and not by a urology department. While the reported mortality rate of the disease was high between 30 and 50% (36), unfortunately even in our days and despite the development of modern medical therapies the mortality remains high reported in a range from 7 to 33% (32). In our series mortality was within the reported range in literature as it was 20.83%.

Fournier's gangrene is an infection caused by aerobic and anaerobic bacteria, usually acting synergistically that spread along the subcutaneous and fascial planes across the perineum, scrotum and sometimes beyond these tissues leading to thrombosis of subcutaneous vasculature and skin necrosis (4, 7, 10). This typical clinical picture of gangrene generally starts in the scrotal region and rapidly spreads to the penis, perineum, and inner thighs (4). The disease most usually present with rapid onset followed by a fulminant progression, and rarely with an insidious onset followed by slow course (9). The local signs are those of inflammation including pain, heat, erythema and edema involving the scrotum in up to 93.3% the penis in 46.5% and the perineum and perianal region in 37.2% (40). However, in the present study, possibly due to the fact the data come from a general surgery department and not from a urology department, perineal and perianal involved was high (91.7 and 54.2%, respectively), and penis involvement was noted only in one patient (4.2%). Local inflammation signs were present in the majority of patients, but crepitus only in five of them (20.8%), which is accordance with the literature as crepitus can be found in 19–64% of cases (32, 37). Also, as the disease progresses, necrosis of the overlying tissue may become evident (9, 32, 40). Moreover, systemic signs, including fever, tachycardia and tachypnea, are usually present, and the diagnosis of SIRS can be made in up to 84.7% of cases (9, 18, 32, 40), as in our series were it was evident in 75% of cases, in whom the diagnosis of sepsis was established as all the patients were considered to have a clinically documented infection. In some cases, sepsis can progress to severe sepsis and even septic shock (37.5 and 12.5% in the current study, respectively). Laboratory studies usually reveal leukocytosis, thrombocytopenia, anemia, which are caused from sepsis (32). Anemia is a result of thrombosis, ecchymosis and decreased erythrocyte production leading to reduced functioning erythrocyte mass (32). In the present study, while the median hematocrit and hemoglobin was decreased, anemia was more evident in the non-survivors group and univariate analysis showed that it statistically significant affected mortality. Besides the complete blood cell count, biochemical studies should be performed including electrolytes, glucose levels, urea and creatinine, arterial blood gas to access pH, and coagulation studies (40). In various studies, variable laboratory data have been associated with mortality such as creatinine, calcium, lactate, and bicarbonate (40); however, in our series, possibly to the small sample, none of them differed statistically significant between survivors and non-survivors.

Imaging modalities can aid to confirm the diagnosis in ambiguous cases, reveal the underlying etiology and estimate the extent of the disease (13, 32, 40). Radiographs may demonstrate the presence of soft tissue air, even before it is evident in clinical examination (32, 40). It has been reported that it has a sensitivity of 90–100% in revealing soft tissue air in diabetics with necrotizing fasciitis, while clinical examination showed gas only in 19–64% of the patients (32, 40). However, in our case series gas in the soft tissue was present in 75% of the cases, which is in agreement with the fact that the absence of air in the soft tissue in the pelvic X-ray does not rule out the diagnosis of FG. In these cases, other imaging modalities including ultrasound, computed tomography, and magnetic resonance imaging can establish the diagnosis, by demonstrating the presence of air in the subcutaneous or soft tissue of the scrotum and the perineum along with soft tissue inflammation and thickening (9, 32, 40). Furthermore, these modalities can provide useful information in evaluating the extent of FG, and also they can reveal the underlying etiology of the disease (32). In the current study, one patient has been submitted to MRI before hospital admission, which confirmed the diagnosis by revealing the characteristic findings of FG, demonstrating that MRI, while due to extended time of the exam and increased cost is not an examination of choice, can establish the diagnosis of the disease.

In patients developing FG, there are frequently a number of comorbidities (1, 3–5, 7–18, 26, 29–36). Diabetes mellitus, alcoholism, immunosuppression, chemotherapy, chronic corticosteroid use, HIV, leukemia, cardiac disorders, systemic lupus erythematosus, obesity, liver disease, Crohn's disease, and kidney failure are some of the comorbid risk factors for the development of FG (1, 3–5, 7–18, 26, 29–36). Diabetes mellitus is present in 20–70% of patients with Fournier gangrene (9, 11). Diabetes mellitus was also noted in increased frequency in our series (29.2%). However, despite the fact that various comorbidities have been associated with mortality (11, 18, 33), in the present study the only comorbid condition associated statistically significant with mortality was the presence of malignancy either solid or hematologic ($p = 0.038$). Also, to evaluate comorbid conditions in total and to strengthen their effect, the following clinical scores were calculated: CCI and Age-Adjusted CCI (AA-CCI) (41–43). CCI has been developed to predict mortality and measure 1-year mortality risk by assessing comorbidities and the burden of disease (41–43). The AA-CCI score, in which age is being considered an independent factor of mortality, can be generated by adding additional points for age (41–43). CCI and AA-CCI have been used as predictors of mortality in FG (18).

There are three routes that can be followed by the infection in FG (33). First, bacteria in the lower urinary tract can move to the paraurethral gland and corpus spongiosum and through the Buck's fascia the infection can extend to Dartos, Colles', and Scarpa fascia (7, 33). The infecting bacteria probably pass through Buck's fascia of the penis and spread along the Dartos fascia of the scrotum and penis, Colles' fascia of the perineum, and Scarpa's fascia of the anterior abdominal wall (3, 7, 11, 26, 33). The second route for the infection begins around the rectum and spreads directly to the scrotum and testis through Colles' fascia (3, 7, 33). As a third route, we can list the bacteria that are present on the skin and can penetrate the subcutaneous tissue with trauma (7, 33). The testicles are protected from the inflammation due to their unique vasculature from the testicular artery. So the suspected source of sepsis in Fournier gangrene can be idiopathic, colorectal, urogenital, dermatological, and of course traumatic (5, 8, 9, 11, 33). The commonest causes of FG are urogenital (urethral stricture, indwelling catheter, traumatic catheterization, prostatic biopsy, vasectomy, and perineal trauma), anorectal (perianal abscess, rectal biopsy, anal dilatation, hemorrhoidectomy, rectosigmoid malignancy, appendicitis, and diverticulitis), and gynecological (infected Bartholin's gland, septic abortion, episiotomy wound, coital injury, genital mutilation) (5, 8, 9, 11, 33). Local trauma, extension of a urinary tract, and a perianal infection are the most common initial ports of entry (11). In the current study, the most common etiology was colorectal followed in frequency by cutaneous infections and abscesses and by urogenital. As in other series, so in ours etiology was not correlated with mortality (18).

All of the abovementioned factors in association with some bacterial species can easily be the start of a polymicrobial severe subcutaneous infection that begins adjacent to the portal of entry, which may be urethral, rectal or cutaneous (1, 3–18, 26, 29, 32–34, 44). Localized cellulitis progresses to a diffuse inflammatory reaction involving deep fascial planes. This bacterial infection results in microthrombosis of the small cutaneous and subcutaneous vessels leading to the development of gangrene of the overlying skin (1, 3, 5–9, 11–13, 16–18, 26, 29, 32–34, 44). Small subcutaneous vessels thrombosis and subsequent tissue necrosis have as a result low oxygen concentrations which lead to anaerobe growth (5). Moreover, these anaerobes and aerobes by acting synergistically produce multiple enzymes like heparinase, collagenase, hyaluronidase, streptodornase, and streptokinase, which cause tissue destruction (5, 9). The rate of fascial necrosis has been documented to be approximately as much as 2–3 cm/h (12, 32). This progression of tissue necrosis results from the endarteritis caused by the spread of the microorganisms (4, 7). These microorganisms in association with local edema, hypoxia caused by difficulty in local blood supply, which favors the development of anaerobic bacteria, produce hydrogen and nitrogen that accumulate in tissues causing crepitation and leading to a rapidly evolving necrotizing fasciitis of the scrotal soft tissue and of the perineum (4, 7). The responsible bacterial strains consist of both Gram-negative and -positive aerobic and anaerobic species, but anaerobes were identified less frequently: *E. coli*, *P. aeruginosa*, *Proteus*, *Klebsiella*, *Streptococcus* species, *S. aureus*, *Enterococcus*, *Clostridia*, *Bacteroides*, and less commonly MRSA and *Candida* in patients who were hospitalized for a longer time (1, 3–5, 7–13, 26, 29). In the current study, also more infections were polymicrobial, and the most commonly isolated bacteria were Gram negative, and specifically *E. coli*, then anaerobic bacteria, and finally Gram positive, but the type of bacteria did not affect mortality.

The cornerstones of therapy are the early recognition, rigorous hemodynamic support, aggressive resuscitation and intravenous hydration, urgent and aggressive surgical debridement of all necrotic areas, and antibiotics (12, 29, 45). The key to the treatment of Fournier gangrene is early and aggressive surgical debridement of the necrotic tissue, empirical broad-spectrum antibiotic therapy (third-generation cephalosporin, penicillin, and metronidazole) along with treatment of the predisposing conditions (13, 14, 26). Surgical debridement must aim in resecting all necrotic and infected tissue, and an aggressive approach should be adopted (14). While the time interval from disease onset to surgery, and especially the delay from hospital admission to surgery may be an important prognostic factor regarding mortality, not all studies have corroborated that (37, 46), as in the present series were there was statistical significant difference between survivors and non-survivors. Moreover, the extent of the disease, which is directly related to the extent of surgical debridement has also been correlated to mortality, once again not to be confirmed by other studies (46, 47) as in our series were the body surface involved by FG was not statistically significant related to mortality. Furthermore, regarding the number of surgical debridements performed in each patient, the data is still controversial as some studies found it to be a significant parameter of mortality, while others not (29, 46, 47), as we in our series.

Furthermore, protective colostomy, although still controversial, in some series has been considered important to achieve rapid healing because it eliminates fecal contamination (14). Recent studies have shown significantly lower mortality in the patient groups with protective colostomy compared with them without colostomy (15, 28, 29). This can easily be explained as the wound in the acute inflammatory phase can stay clean, and fecal diversion can prevent any further infection spread in the area (28). Moreover, the colostomy can affect the rapid improvement of nutritional status which is very important for containing inflammation, through the early enteral nutrition (15). A loop colostomy is always preferred instead of an intestinal stoma because of the formed and solid stools that are easily restricted, and there are fewer possibilities for contamination to the surrounding skin (15). However, it is claimed that even if destruction of the perirectal area occurs colostomy is never necessary (14). In our series we did not find any significant difference in survival in patients with and without colostomy. Moreover, in some cases a rectal diversion device can be used instead of colostomy to prevent fecal contamination of the wound (40).

In addition, the hyperbaric oxygenation helps marginally viable tissues survive. Its anti-inflammatory properties prevent ischemia, edema, reperfusion injury, and further complications of hypoxic tissues (13, 40). The debate regarding hyperbaric oxygen and mortality is still ongoing as there are data both showing reduced mortality and other showing no association between hyperbaric oxygen and mortality, as was the case in the current study (7). With the recent advent of the VAC system dressing, there seems to be a dramatic improvement with minimizing skin defects and speeding tissue healing (9). VAC is a wound care system based on the negative pressure vacuuming and has been used with great success to care many different types of wounds (2). VAC therapy involves the application of a sterile open-cell foam sponge to the wound, adding transparent adhesive drapes and a non-collapsible tube, which helps the connection to a portable pump that provides negative pressure to this air-tight environment of the wound (2, 11). VAC application promotes blood flow and creates a perfect environment for wound healing. VAC therapy reduces tissue edema and excess fluid, increases oxygen and defender wound cells (2). A negative pressure value of 125 mmHg was therefore selected for use in our study. In the current study mortality rates were not influenced by rectal diversion, hyperbaric oxygen treatment or VAC therapy. Regarding, urinary diversion, while urostomy may be suggested in some cases, satisfactory diversion can be achieved by urinary catheterization (13, 40) as in the current study.

The final goal in treating a patient with FG after the patient has recovered is the reconstruction of the extended defects caused by the aggressive surgical debridement, once granulation tissue has formed (45). A lot of methods have been described including healing by secondary intention, delayed primary closure, loose wound approximation, skin graft, and flaps (13, 30, 40). While secondary intention has been proposed for small wounds confined to the scrotum (13, 30, 40) and can lead to prolonged hospitalization, and deformity due to contracture we have successfully employed this method in our series in the management of more extended wounds. For larger defects either flap reconstruction or split thickness skin graft can be used (13, 30, 40). Skin graft is a simple procedure that can be done in one stage with a good cosmetic and functional result (13, 30, 40), as in the present series were this technique was employed in five patients by plastic surgeons.

For the prediction of mortality in FG that is to validated indexes the FGSI score and the Uludag FGSI. Also, for the same reason, the acute physiology, age, and chronic health evaluation II severity score (APACHE II) has been used along with the laboratory risk indicator for necrotizing fasciitis (LRINEC). The FGSI score, has been created in 1995 by Laor et al. by modifying the APACHE II score (26). There are nine parameters studied: heart rate, respiratory rate, temperature, hematocrit, leukocyte count, serum sodium, potassium, creatinine, and bicarbonate levels, and the deviation from normal is graded in a scale from 0 to 4 to a maximum of 36 points. The values are added to calculate the FGSI score (26). While its predictive value have been validated in a lot of series (18), and a cutoff point of 9 seems to provide a good discriminatory capacity regarding mortality, in our study due to the small sample, we did not find any statistically significant difference regarding the FGSI in survivors and non-survivors. The newer and novel Uludag FGSI, which was created by Yilmazar et al. in 2010, also takes into account age and disease dissemination to a maximum of 43 points (18). In contrast with FGSI, which accounts only for the patient's acute physiologic status, APACHE II evaluates the patients both acute and chronic health status to predict mortality in severely ill patients with critical systemic disease (48). It has been used both for necrotizing fasciitis in general (48) and for FG specifically, in which a cutoff value of 20 has been proposed (45). Finally, the laboratory risk indicator for necrotizing fasciitis (LRINEC) that is based on the values of CRP, WBC, hemoglobin, serum sodium, serum creatinine, and plasma glucose has also been employed in an attempt to predict mortality for necrotizing fasciitis in any part of the body but also for the perineum (FG) (11, 49). A value of LRINEC <6 is related to low risk of mortality and ≥ 9 with a high risk, while a value in between with a moderate risk (49). In our case series, we could not find any statistically significant difference neither for APACHE II nor for LRINEC score between survivors and non-survivors. Possibly, our relatively low mortality rate can be in part attributed to the low median score of all the prognostic indicators, which were 5 for FGSI, 6 for UFGSI, 10 for APACHE II, and 5 for LRINEC.

Fournier's gangrene represents a severe disease with increased morbidity and mortality. Morbidity rates as high as 80% have been reported with mean hospital stay of 31–35 days (10). The median hospital stay in our in our series was 27 for all patients, but 40 for survivors only. Regarding morbidity, there is still an ongoing debate about the incidence of incontinence following aggressive surgery. Aggressive surgery is mainly related to increased rate of secondary wound infection and the need for skin grafts to achieve wound healing (11). Fecal incontinence is not a commonly reported complication of aggressive debridement as muscle involvement is rarely present (7). Very few studies report long-term outcomes in patients with FG, and most of them focus on chronic pain, disfigurement and sexual dysfunction leading also to psychosocial problems of these patients (9, 50). While fecal incontinence may present simultaneously with the disease onset in patients with an extensively damaged anal sphincter in up to 40% who would require a stoma, following stoma closure no morbidity was recorded (38). Fecal incontinence seems to be temporary and may affect some of the patients (9).

In conclusion, FG remains a surgical and urological emergency with increased morbidity and mortality even nowadays and the general surgeon must be familiar with it, as its early recognition and aggressive surgical treatment, along with antibiotic therapy and rigorous resuscitation, are the basis of this severe condition's successful management.

ETHICS STATEMENT

Due to the retrospective nature of the study and as there was no research intervention, the current study was exempt from this requirement.

AUTHOR CONTRIBUTIONS

OI: study design, study supervision, data collection, analysis, interpretation, introduction, methodology, results, and discussion sections, and critical revision for important intellectual content. LK: data collection, introduction, methodology, results, and discussion sections. DT: data collection, analysis, interpretation, methodology and results sections. IS, AC, AG, and IV: data collection, analysis, interpretation, methods and results sections. SS, NS, and SP: data collection, methods and results sections. GP, MP, EK, and IM: study conception and design, data collection, methodology, results, and discussion sections. KT: study conception and design, study supervision, introduction, methodology, results, and discussion sections, and critical revision for important intellectual content.

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Aortic Graft Infection: Graphene Shows the Way to an Infection-Resistant Vascular Graft

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Aortic graft infection is a potentially lethal complication of open and endovascular repair of aortic aneurysms. Graphene is the only existing two-dimensional material, and its unique structure gives graphene and its derivatives a plethora of original characteristics. Among other characteristics, graphene demonstrates bacteriostatic and bactericidal effects that could potentially resolve the problem of graft infection in the future. Data already exist in literature supporting this antibacterial effect of graphene oxide and reduced graphene oxide. Combining these materials with other substances enhances the antibacterial effect. Additionally, it looks feasible to expect antibiotic-delivering graphene-based graft materials in the future. Based on already published data, we could conclude that regarding graphene and its derivatives, the blessing of bactericidal effect comes with the curse of human cells toxicity. Therefore, it is important to find a fine balance between the desired antibacterial and the adverse cytotoxic effect before graphene is used in graft materials for humans.

Keywords: graphene, aortic aneurysm, graft survival, infection, bacterial infections

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Prosthetic graft infection is a grave and frequently lethal complication of both open and endovascular repair of aortic aneurysms (AA). Despite its relatively low overall incidence, the absolute numbers of graft infection are rising, as the use of synthetic grafts (Dacron, PTFE, or nylon) has become an everyday occurrence in both elective and emergency AA repair, with a reported graft infection incidence of 0.2 to as high as 6% in EVAR cases (1–4). Overall morbidity and mortality rates are high, and in cases of patients' readmission due to aortic graft infection, in-hospital mortality can be 18% or higher (5, 6). Additionally, bacterial resistance to antibiotics is an evolving problem that could bring medicine and humanity back into the pre-antibiotic era if it remains unsolved (7).

Treatment of aortic graft infection varies from conservative treatment with long-term antibiotic administration to graft excision combined with a bypass procedure. The latter could be either extra-anatomical or follows the natural anatomic course of the aorta, but both approaches are linked to significant morbidity, mortality, and procedure-related complications. The *in situ* reconstruction of the aorta using either cryopreserved allografts or autologous veins is a similarly disabling method of aortic reconstruction after infected graft excision (8). As a result, our surgical attempts to resolve a case of aortic graft infection often bring our patient to worse status than before. The father of medicine, Hippocrates, stated that prevention is better than cure; therefore, the need for infection-resistant graft materials is essential in order to avoid the devastation of aortic graft infection and the patient disabling nature of existing treatment strategies.

Creating an infection-resistant material has been in the scope of biomedical engineering for a period of time, but focus has been concentrated on how an infection can be fought after it had occurred. Antibiotic-soaked and silver-containing grafts have already been used for AA repair after graft infection. Despite these grafts being a useful tool in the vascular surgery armament, the final outcomes of their use in real practice are ambiguous (9, 10). Other approaches, such as the use of bio-absorbable antibiotic-impregnated beads, have also been suggested as a potential solution to the problem of aortic graft infections (11).

Newly developed materials may cover the need for new infection-resistant graft materials. One of these futuristic supermaterials that have already found its place in many health-related applications is graphene. Graphene is the only two-dimensional material, with each graphene layer being 1 atom or 0.345-nm thick (12). Graphene demonstrates a number of unique characteristics, and its promising future applications have awarded its creators, Andre Geim and Konstantin Novoselov, the 2010 Nobel Prize in Physics. Graphene is approximately more than 300-fold stronger than structural steel or Kevlar, 1,000-fold lighter than paper and almost as flexible as PTFE. These impressing characteristics are the result of the graphene's structure as a carbon allotrope with sp2-bonded carbon atoms arranged in a sheet-like structure.

Graphene sheets are produced in a number of different methods, the most common of which are mechanical or thermal exfoliation, chemical vapor deposition (CVD), and epitaxial growth (12). Further post-processing of graphene sheets produce its derivatives, such as graphene oxide (GO) and reduced graphene oxide (rGO). Each of these methods and final products has slightly different characteristics and properties. Only graphene products of the highest quality demonstrate the abovementioned properties. These pristine graphene sheets are products of CVD, which at present renders the production expensive, but the price of graphene derivatives is constantly decreasing as production methods are optimized (13–15).

In existing literature, pristine graphene sheets have already been reported to have bacteriostatic and bactericidal properties. These two properties are of great interest for bioengineers committed to improve the graft materials of today to become less prone to bacterial infection. In a recent detailed review of graphene's future in the grafts materials engineering, it seems that despite existing data supporting these beneficial properties of graphene, not all publications agree to the extent and efficacy of these (12). In this review, it has been reported that the surface of the graphene sheet plays a major role on the bactericidal action of this material. If the material is produced by vacuum filtration and the material particles lied flat on the surface, the bactericidal effect was minimum or none (16, 17). On the other hand, rGO with sharper particles' edges demonstrated a significant bactericidal effect on *S. aureus* and *E. coli* bacteria (18–20). The mechanism behind this interaction of surface and bacteria is probably the bacterial membrane damage by the graphene edges and the efflux of cytoplasm. This proposed mechanism is also supported by the increased bactericidal effect of graphene on bacteria with thinner peptidoglycan membrane layer (21). At present, further mechanisms of actions on molecular level are also being considered, especially when combined materials are used (22–24).

In addition to the nature of the material surface, binding other molecules to graphene can also affect its bactericidal or bacteriostatic effect. Silver particles, platinum particles, chitosan, polyvinyl-*N*-carbazole, lactoferrin, diazonium salt, poly-L-lysine, and polyhexamethylene guanidine hydrochloride are a few of the substances used to increase the bactericidal and bacteriostatic effects of graphene sheets (12, 25–27). The results of these combined materials depend not only on the graphene derivative used (mainly GO or rGO) but also on the studied bacteria that show different interaction with these modified graphene surface. Endovascular materials are usually primarily contaminated and infected with *S. aureus* and *S. epidermidis*, although secondary hematogenic contamination with Gram-negative bacteria is also possible. rGO shows the strongest antibacterial effect toward both Gram-positive and Gram-negative bacteria, but in order to achieve the best possible antibacterial effect against the usual bacteria involved, further studies have to examine various combinations of graphene and other substances, although some evidence already exist (18).

Graphene has been used as a delivery agent for medication since 2008 (28). Since then graphene and its derivatives have been used in delivering a wide range of medication (29–33). In one case, graphene sheets were modified to deliver medication at a concentration controlled through electric pulses (34). Taking all these under consideration, it is not fiction to believe that in the future a graphene-based stent-graft could release antibiotics into the blood stream and/or the surrounding vessel wall when specific bacteria react with the graphene surface. This futuristic model would fight bacteria whenever that is necessary without contributing to bacteria multidrug resistance and by delivering the antibiotic directly to the affected tissues, thus minimizing systemic side effects.

Infection-resistant graphene-based graft materials could be constructed today with the already existing knowledge and technology. In the near future, these same graft materials could go a step further and evolve into infection fighting antibiotic-delivery agents. Unfortunately, before we see these steps ahead of current bioengineering, the question of biocompatibility and biotoxicity should be resolved (35). Graphene and its derivatives have been found to be toxic to certain lines of eukaryotic cells, and toxicity levels are analog to the bactericidal effect (24, 36, 37). From already published data, we could conclude that regarding graphene and its derivatives the blessing of bactericidal effect comes with the curse of human cells toxicity. Wrapping graphene particles within other structures or biofilms could resolve the problem of biotoxicity to some extent, but it would also affect its bactericidal effect (12, 38).

Graphene and its derivatives could potentially lead the way to new and truly infection-resistant or bactericidal graft materials that can be primarily used in aortic or other arterial repair in order to avoid the occurrence of graft infection, not fighting an already-occurring infection. A proper animal model and *in vivo* studies by a multidisciplinary team of bioengineers and vascular surgeons are necessary in order to research the potential role of graphene and its derivatives in building infection-resistant aortic grafts and provide the necessary data on patency, biotoxicity, and biocompatibility. These future materials would further reduce the incidence of graft infection that remains a lethal complication of open and endovascular aortic repair.

AUTHOR CONTRIBUTIONS

NP—conception, data collection, literature review, manuscript writing, and critical appraisal. DS—data collection and critical appraisal. TL—conception and critical appraisal. CK—conception, manuscript writing, and critical appraisal. All the authors have accepted the final version of the manuscript.

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Simultaneous Hepatic and Mesenteric Hydatid Disease—A Case Report

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Introduction: Hydatid cysts most commonly present in the liver and the lungs; however, they can appear more rarely in other locations, such as the mesentery, with a rather unclear mechanism of manifestation. Herein, we present a case of simultaneous presence of hydatid cysts in the liver and the mesentery of a young man.

Case report: A 39-year-old man was referred to our Department for further investigation of intermittent abdominal pain, especially in the right upper quadrant, and abdominal distension. Abdominal CT imaging revealed three calcified lesions, one in the liver, a similar adjacent to an ileal loop and one close to the urinary bladder, while antibody control was positive for echinococcal infection. The lesions were excised and the patient was discharged on the seventh post-operative day in good general condition. Post-operative control after 6 months did not show any signs of recurrence.

Conclusion: Simultaneous presence of hydatid cysts in two organs occurs in 5–13% of cases. Presence in the mesentery is extremely rare, although, should be included in the classic differential diagnosis, especially in endemic areas.

Keywords: hydatid cyst, liver diseases, mesentery, drainage cysts, excision surgery, parasitic diseases

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BACKGROUND

Hydatid disease, also referred as echinococcosis, is a chronic, cyst-forming, parasitic helminthic disease.

Three forms of echinococcosis are recognized clinically: cystic echinococcosis caused by *Echinococcus granulosus*, alveolar echinococcosis caused by *Echinococcus multilocularis*, and polycystic echinococcosis caused by *Echinococcus vogeli* or *Echinococcus oligarthrus* (1, 2).

The adult *E. granulosus* resides in the small bowel of the definitive hosts, namely the dogs or other canids. Gravid proglottids release eggs in the feces which, after ingestion by an intermediate host (sheep, goat, swine, cattle, horses, and camel), hatch in the small bowel. These eggs release an oncosphere that penetrates the intestinal wall and migrates through the circulatory system into various organs, especially the liver and lungs (3), but also in more uncommon locations.

In community-based studies, the reported prevalence of cystic echinococcosis ranges from 1 to 7%, while the females and the older population show a greater prevalence than males and other age groups (4).

In most cases, *echinococcosis* is asymptomatic due to the slow growth and development of the cysts. However, the symptoms depending on the size and location of these lesions (5).

Diagnosis of hydatid cyst is achieved by combination of serological tests and imaging, while history of exposure is also important. Imaging findings vary depending on the stage of the cyst (5). In 2001, World Health Organization (WHO) developed a cystic echinococcosis (CE) classification system, in order to deciding the appropriate management worldwide. This system is based on ultrasound imaging findings of cysts. Classical imaging may consist of ultrasound examination, computed tomography (CT), and magnetic resonance imaging (MRI). Calcification of the cysts can be present in 30% of all cases at the time of diagnosis (6).

We describe a case of a male patient presenting simultaneously one hepatic and two intra-abdominal hydatid cysts (one of them in the mesentery), who was treated surgically in our department.

CASE REPORT

A 39-year-old male patient was referred to our department with mild abdominal distention and pain that was located especially in the right upper abdomen. His symptoms were present during last year, with gradual deterioration. He did not present any fever and occurrence of symptoms was not related to food intake. In his clinical history, he did not mention any previous operations or other medical conditions, whereas he did mention owning two dogs in a rural area.

Laboratory blood examination showed results within normal ranges (white blood cells 10.90 K/μL with 57.7% neutrophils, SGOT 20 U/L, SGPT 22 U/L, γ-GT 19 U/L, ALP 111 U/L, and negative quantitative C.R.P. test). Level of eosinophils cells was normal (0.7%), while eosinophilia is present only in 25–40% of all patients. An *Echinococcus* rapid test based on ELISA IgG antibodies detection was positive (quantitative method). Upper abdominal ultrasound revealed a hepatic lesion with vague characteristics. An abdominal CT revealed a large hepatic lesion (9.5 cm × 6.2 cm × 6.8 cm) with a hyperdense wall and multiple internal calcifications (**Figure 1**). A similar, well circumscribed mass in relation to an ileal loop, that caused external pressure (**Figure 2A**) to the urinary bladder (5.3 cm × 3.6 cm × 9 cm) and a second, smaller, completely calcified, lesion (2.3 cm × 2 cm × 2.5 cm) near the right side of the urinary bladder (**Figure 2B**) were also present. Further control for fecal presence of parasites was negative, but blood control for echinococcal antibodies (considering the patient's history of having dogs in his surroundings and the rather endemic presence of the disease in his area) was positive. All lesions classified according WHO-IWGE (Informal Working Group on Echinococcosis) classification system. After the establishment of the diagnosis, surgical intervention was considered necessary in order to avoid any further abdominal translocation of the parasite. Under general anesthesia, the patient underwent an exploratory laparotomy through midline incision. The hepatic hydatid cyst (CE3a WHO-IWGE) was opened and evacuated from daughter cysts using suction. Washout with hypertonic saline 15% was immediately performed, and a drainage tube was fixed on its location (**Figures 3A,B**). The other two intra-abdominal lesions, the one found in the mesentery (**Figure 4**) (CE4 WHO-IWGE) and the smaller near the urinary bladder (CE5 WGO-IWGE), were simply excised (**Figure 5**). Total length of operation was 125 min. Histopathological findings of mesenteric cyst was possible for primary hydatid cyst, while revealed a lamellated ectocyst and germinal layer with a thick outer, non-cellular membrane in the wall of the cyst. The post-operative period was uneventful and the patient was discharged on the ninth day after the surgery. The patient received albendazole (ABZ) 4 days before surgery (10–15 mg/kg/day) twice a day and was advised

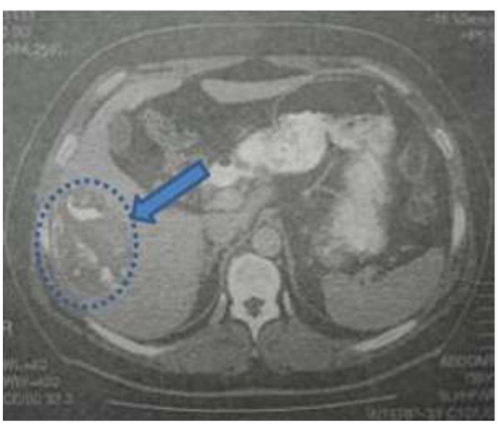

FIGURE 1 | Abdominal computed tomography indicating a hepatic lesion with hyperdense walls, diffuse calcification, and foci of fat in the interior.

A

B

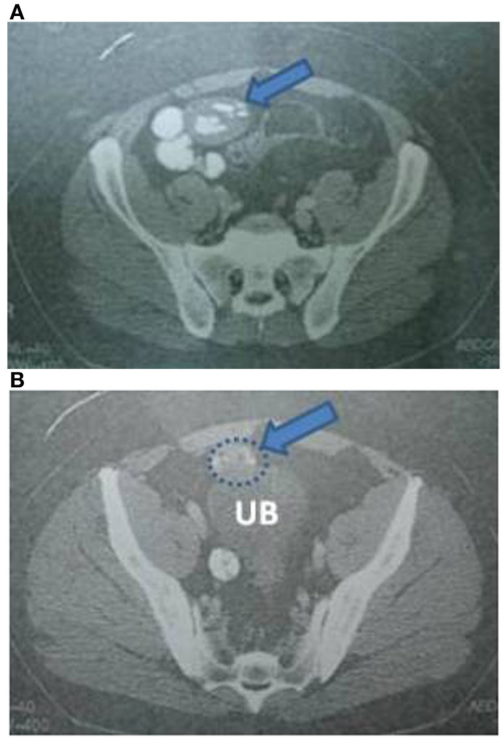

FIGURE 2 | **(A)** Abdominal CT indicating an intra-abdominal cystic lesion, located near an ileal loop. **(B)** Abdominal CT indicating the aforementioned cystic lesion causing external pressure to the urinary bladder, and a smaller cyst at the right side of the wall of the urinary bladder.

A

B

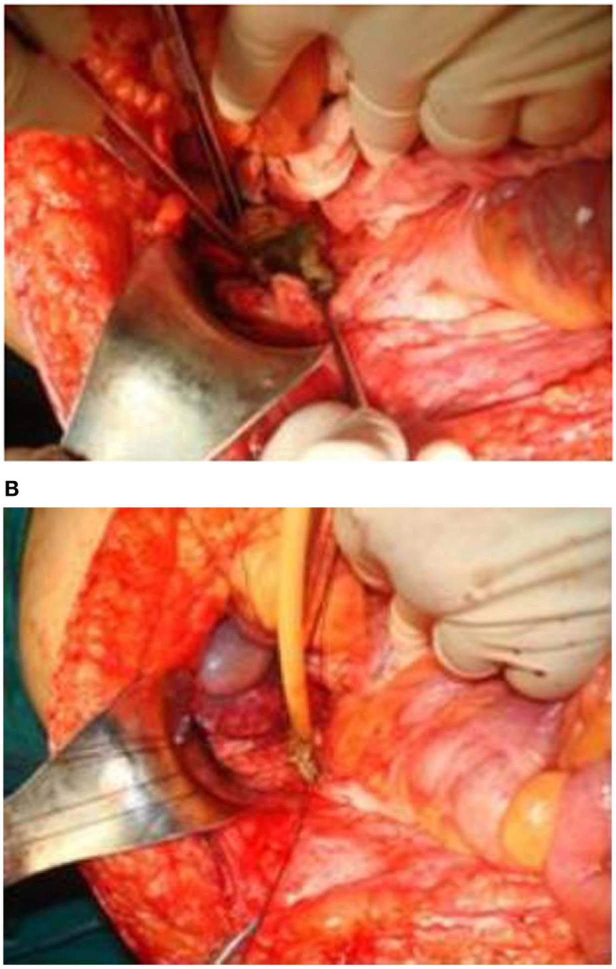

FIGURE 3 | **(A,B)** The hepatic hydatid cyst was opened and drained. A drainage tube was placed in the area.

FIGURE 4 | Presence of one hydatid cyst in the mesentery.

FIGURE 5 | Post-operative specimens. Numerous daughter cysts included in the hepatic cyst near the urinary bladder.

to continue treatment with ABZ for 3 months after surgery by 14 days intervals. Pre- and post-operative treatment reduces the risk of recurrence. Three months after surgery, a new chest and abdominal CT was realized, without any signs of recurrence. Patient should be also monitored every 2 weeks with CBC and liver enzyme evaluation for the first 3 months and then every 4 weeks. An *Echinococcus* rapid test based on ELISA sandwich IgG antibodies detection was negative (quantitative method) after 3 months which post-operative treatment with albendazole completed. Follow-up was recommended every 6 months for the first 2 years and then once a year.

DISCUSSION

Most common sites of hydatid disease are the liver (approximately 70%) and the lungs (15–47%). Kidney (2–4%), bones, and brain are less likely to be involved. Incidence of the disease in other sites, such as the heart, spleen, pancreas, and muscles, is extremely rare. In all cases, involvement of two organs occurs in about 5–13% of the cases (7, 8).

Humans are usually asymptomatic for long period of time while the cysts are growing slowly. In most cases, there is only one cyst, whereas in some cases, multiple cysts may be present (20–40%). Symptoms depend on the size and the number of cysts and possible compression of surrounding structures (9). As in our case, signs of mesenteric hydatid disease may include a non-specific abdominal mass, pain due to traction on the mesentery and pressure effects on adjacent organs.

The signs and symptoms of liver hydatid disease, when present, include hepatomegaly, right upper abdominal or epigastric pain, nausea, and vomiting. Cyst leakage or rupture may lead to systemic immunological responses. Rupture in the peritoneal cavity may also cause secondary disease. In case of involvement with portal vein or biliary tract, cysts may be responsible for segmental or lobar liver atrophy (9). In the case of our patient, the mesenteric hydatid disease was caused possibly by rupture of small daughter cyst from the exterior of the main liver cyst to the peritoneum (10, 11). Although patient had not exhibited signs of anaphylaxis in the past, he had not undergone any other abdominal procedure or suffered from abdominal trauma. Retrograde spread from the liver *via* the hepatic portal vein into the peritoneal cavity was also referred (12).

In the modern era, and with the advent of more sophisticated imaging techniques, such as contrast CT, MRI, and MRCP, there has been a great improvement in the diagnostic accuracy which, in turn, aids even more the clinician to differentiate between other space occupying lesions and to form a treatment plan for the individual patient (13). In addition to imaging, antibody assays are useful to confirm a presumptive radiologic diagnosis (2, 13).

The aim of treatment in hydatid disease is complete elimination of the parasite. Prevention of recurrence and minimization of mortality is essential. Mebendazole (MBZ) and ABZ are the benzimidazole compounds (BMZs) used for the treatment of hydatid disease (2). BMZs may be used alone for the treatment of small (<5 cm) cysts or for inoperable patients. ABZ is considered the drug of choice, because it is more active *in vitro* and it has a better gastrointestinal absorption and bioavailability. The usual dose of orally administered ABZ is 10–15 mg/kg per day in two divided doses; if MBZ is administered, the daily dose is 40–50 mg/kg in three divided doses. The WHO recommends the post-operative administration of ABZ for at least 1 month or MBZ for 3 months but the risk of peritoneal recurrences determines the continuation of the treatment; the longest period reported in the literature was 1 year (5, 14). A perioperative administration of a BMZ agent is also recommended, to reduce the risk of anaphylactoid reactions and prevent recurrence.

Target of surgical procedures is the inactivation of infectious scolices and germinative membranes. Prevention of intra-operative contamination to peritoneal cavity is important while ruptured cysts can lead to systematic anaphylaxis. Recognition and management of complicated cysts requires specialized hepatobiliary surgical team (15). Surgical options may be divided into radical (pericystectomy and organ resection) and conservative approaches (unroofing or capitonnage) (16). In our patient due to the size of the major lesion (liver) and synchronous omentum lesions, we decided to perform abdominal exploration. The liver cyst was opened, sterilized with hypertonic saline washout, and drained with tube placement. The other two intra-abdominal lesions were simply excised. Some randomized trials suggest omentoplasy after cyst removal. In our case, due to involvement of the omentum with peritoneal spread of the disease, we avoided this option (17).

Minimally invasive surgical approaches, utilizing laparoscopic techniques, have been also employed for patients with hydatid disease. There are promising results with laparoscopic treatment but further experience is required (18). Imaging-guided percutaneous puncture, aspiration of the liquid contents, and injection of a protoscolicidal agent (e.g., 95% ethanol or hypertonic saline) for at least 15 min are alternative techniques (2, 19).

Surgery is the treatment of choice of the rupture prone hydatid cysts, all complicated and the most complex cases of liver hydatid disease. Objectives of surgery are (a) inactivating infectious material, (b) preventing contamination, (c) eliminating all viable elements (endocyst), and (d) managing the residual cavity. Surgery is indicated for the treatment of large liver cysts with multiple daughter cysts. As in our case we have a large hepatic cyst and two others in mesentery we choose the open procedure.

Due to the rarity of mesenteric hydatid disease, all the abdominal cystic lesions including mesenteric, pancreatic, gastrointestinal duplication, ovarian cysts, and lymphangiomas must be considered in the differential diagnosis (20).

CONCLUSION

Simultaneous presence of cysts on different locations presents a low incidence in hydatid disease, while their presence in the mesentery is rarely reported. In endemic areas, this entity should be included in the differential diagnosis of cysts within the peritoneal cavity. Thorough imaging examination and surgical excision play a key role in the patient's overall treatment.

ETHICS STATEMENT

Our patient provide his consent for this study with a written informed consent, approved by AHEPA University Hospital of Thessaloniki/Greece Scientific Council.

AUTHOR CONTRIBUTIONS

DP, KK, AK, and PB were responsible for the diagnosis and treatment of the patient and assisted in the preparation of the manuscript. VP, SA, and AM provided useful insights.

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Incidence and Risk Factors for Organ/Space Infection after Radiofrequency-Assisted Hepatectomy or Ablation of Liver Tumors in a Single Center: More than Meets the Eye

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Introduction: Surgical site infections (SSIs) and especially organ/space infection (O/SI) after resection or ablation of liver tumors are associated with increased morbidity and mortality. A secondary blood stream infection (BSI) is considered an O/SI but the exact prevalence is unknown. We aimed to investigate the incidence of O/SI and BSIs in a cohort of consecutive patients after liver resection or ablation, to seek for a possible connection between them and to search for potential risk factors.

Materials and methods: We reviewed all patients who underwent hepatic resection or intraoperative liver ablation between January 2012 and December 2016 in our department. We focused on age, gender, Child–Pugh score, preoperative biliary drainage, indication for surgery, type of resection, resection or ablation of tumor, need for bilioenteric reconstruction, additional procedure to hepatectomy, blood transfusion, operative time, postoperative admission to ICU, and antibiotic chemoprophylaxis. All positive cultures from intra-abdominal fluids and blood were recorded. O/SI and BSIs were diagnosed by the criteria set by Centers for Disease Control. All variables were compared between the group with O/SI and the group without infection. BSIs were associated with these infections also.

Results: Eighty-one consecutive patients with a mean age of 64 years were enrolled. Fifteen patients presented a positive culture postoperatively: intra-abdominal fluid in eight, blood cultures in six, and both blood and intra-abdominal fluid in one patient. The directly estimated incidence of O/SI amounted to 11.1%. Four blood cultures were secondary to O/SI, and the remaining two secondary to central line catheter. O/SI was diagnosed indirectly, through the BSI in an additional 4.9% of the patients, raising the incidence of SSI to 16%. Among the factors studied, only admission to the ICU was found to be statistically significant as a risk factor for the development of O/SI ($p = 0.026$).

Abbreviations: SSI, surgical site infection; O/SI, organ/space infection; BSI, blood stream infection; CLABSI, central line-associated blood stream infection; CDC, Centers for Disease Control.

Conclusion: O/SI should be actively seeked for after liver surgery including blood cultures. Patients with affected physical status, comorbidities are in greater risk of developing O/SI.

Keywords: organ/space infection, radiofrequency, hepatectomy, bloodstream infections, surgical site infections, ablation, bacteremia

INTRODUCTION

Postoperative infection is a common complication after liver resection or ablation of liver tumors. It is associated with increased length of stay, morbidity, and mortality (1). Despite the recent improvements in surgical techniques and devices, hepatectomy-related surgical site infections (SSIs) account for about 1/3 of the nosocomial infections (2, 3). SSIs are classified into incisional (superficial and deep) and organ/space infection (O/SI), an important distinction due to the difference in their pathogenesis (4). O/SI occasionally leads to bacteremia and secondary blood stream infection (BSI) which in this case is also considered as SSI (4). We investigated the incidence of O/SI and BSI in a cohort of consecutive patients who underwent resection or ablation of liver tumors. We also seeked for a possible connection between them and searched for potential risk factors.

MATERIALS AND METHODS

We reviewed the medical records of all patients who underwent either radiofrequency-assisted liver resection or intraoperative radiofrequency liver ablation in our department from 2012 till 2016. Patients' age and gender, preoperative liver function, existence of preoperative biliary stent, operative data, and postoperative need for ICU were specifically addressed. With the exception of a laparoscopic excisional biopsy, all other operations were open. All resections were RF-assisted according to the method initially described by Habib (5), and all ablations were conducted through radiofrequencies. The Cool-tip™ RF Ablation System (Medtronic Co) was employed in all operations. Drainage tube was placed in all patients. Enteral feeding was started quickly as tolerated by the patients. Antibiotic chemoprophylaxis was administered to all patients 1 h prior to the skin incision. Chemoprophylaxis scheme consisted of metronidazole combined with either cefoxitin or, in case of allergy to β-lactamic antibiotics, with ciprofloxacin. Patients with cholangitis prior to surgery were treated with piperacillin/tazobactam, and the operation was performed when all evidence of infection was eliminated and blood cultures became repeatedly negative. Patients with severe comorbidities and not ready to be extubated immediately postoperatively were transferred to ICU for a timely extubation, in compliance with the anesthesiologists' instructions. A central venous line was inserted to all patients immediately preoperatively and removed the first postoperative day or the first post-extubation day.

Primary end-points of the study were the detection of O/SI after liver resection or ablation and the detection of BSI secondary to OSI. According to the Centers for Disease Control (CDC) definition, diagnosis of *organ/space SSI must meet the following criteria: the infection occurs within 30 days after the operative procedure if no implant is left in place or within one year if implant is in place and the infection appears to be related to the operative procedure and the infection involves any part of the anatomy (e.g., organs or spaces), other than the incision, opened or manipulated during the operative procedure. In addition, it must meet at least one of the following: purulent drainage from a drain that is placed through a stab wound into the organ/space; organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space; an abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination; or diagnosis of an organ/space SSI by a surgeon or attending physician* (6).

We discriminated primary BSI from secondary-to-SSI ones based on the CDC definition: *for a bloodstream infection to be determined secondary to another site of infection the following requirements must be met: a site-specific definition must be met; either one of the CDC/NHSN Surveillance Definitions for Specific Types of Infections, or UTI, PNEU or SSI definition AND one of the following scenarios must be met: Scenario 1: At least one organism from the blood specimen matches an organism identified from the site-specific infection that is used as an element to meet the NHSN site-specific infection criterion AND the blood specimen is collected during the secondary BSI attribution period (infection window period + repeat infection timeframe) OR Scenario 2: An organism identified in the blood specimen is an element that is used to meet the NHSN site-specific infection criterion, and therefore, is collected during the site-specific infection window period* (7).

Central line-associated blood stream infections (CLABSIs) were defined as *laboratory-confirmed bloodstream infection (LCBI) where central line (CL) was in place for >2 calendar days on the date of event, with day of device placement being Day 1, AND the line was also in place on the date of event or the day before. If a CL was in place for >2 calendar days and then removed, the date of event of the LCBI must be the day of discontinuation or the next day to be a CLABSI* (7).

Consequently, O/SIs were recorded by positive cultures from intra-abdominal fluids (abscess, fluids from drainage tube, etc.). Positive blood cultures with evidence or proof of O/SI were also recorded as O/SI according to the previously mentioned scenario 2 (7). We investigated a possible correlation between these infectious complications and the preoperative or perioperative parameters.

All continuous data were expressed as the mean ± SD. Chi-square test was used for statistical comparisons employing SPSS® v 22 Software.

RESULTS

From January 2012 till December 2016, a total of 81 patients (48 males, 33 females) underwent either hepatic resection or intraoperative liver ablation in our department. As it can be seen in **Table 1**, the mean patient age was 64.07 ± 12.3 years old, no difference between the two sexes. Indications for liver surgery are listed in **Table 2**. Seventy-two patients (88.9%) underwent surgery for malignancy and 9 (11.1%) for benign tumors. Nine patients had liver ablation, 25 patients an anatomical hepatectomy, and 47 patients underwent metastasectomies or non-anatomical liver resection (**Table 3**). Metastasectomy was the most frequent operation (41 patients, 50.6% overall), and hepatic adenoma was the most common benign tumor (2.4% overall, 22.2% of benign tumors). No patient had a bilioenteric anastomosis prior to surgery; however, 12 patients had a biliary stent inserted preoperatively due to refractory jaundice. In these 12 patients and 7 additional ones, i.e., in 19 patients in total, bilioenteric continuity was maintained with the creation of a hepaticojejunostomy (**Table 4**). An additional concomitant operation, mostly a colectomy, was performed in 17 patients (**Table 5**). Seventy-six patients had a Child–Pugh score A, 5 patients a score B, and none a score C. No patient developed post-hepatectomy liver failure. Perioperative characteristics by occurrence of SSI are depicted in **Table 6**. Fifty-two patients needed blood transfusion with a mean blood transfusion of 2.1 units of packed red blood cells (range: 0–11, median: 1). With the exception of one patient suffering from lymphoma, all packed red blood cells used were not leukocyte depleted. Mean operative time for all patients was 417 ± 113 min. Sixty-seven patients received the typical chemoprophylaxis scheme. Fourteen patients were treated with piperacillin/tazobactam preoperatively. All patients had a central venous line (mostly jugular) inserted immediately preoperatively. This was removed either the first postoperative or the first post-extubation day. Nineteen patients were admitted in the ICU immediately postoperatively for a "timely extubation" due to preexisting comorbidities. ICU mean length of stay was 3.37 days (ranging 1–15 days).

Fifteen patients (11 males, 4 females) with signs of infection presented evidence of postoperative blood or organ/space SSI. Only intra-abdominal fluid cultures were positive in eight patients while blood only cultures were positive in six patients. One patient had both intra-abdominal fluid and blood cultures positive. **Table 7** shows the bacteriological data of all positive cultures. *Enterococcus* sp. was isolated in seven cultures, *Kebsiella* sp. in three, *E. coli* in two, *Pseudomonas* sp. in one, and *Serratia* sp. in one. In one blood culture, both *E. coli* and *Enterococcus* were isolated. Two bloodstream infections could not be associated to SSI, one with *Candida albicans* and the other with *Staphylococcus*

TABLE 1 | Preoperative variables by occurrence of surgical site infection.

	All patients ($n = 81$)	No postoperative infection ($n = 66$)	Postoperative infection ($n = 15$)	*p* Value
Mean age (years)	64	64	64.2	
Gender (M/F)	48/33	37/29	11/4	0.175
Child–Pugh Score (A/B)	76/5	61/5	15/0	0.651
Biliary stent (yes/no)	12/69	8/58	4/11	0.151
Malignant/benign	72/9	58/6	14/1	0.472

TABLE 2 | Indication for surgery and occurrence of positive cultures.

Diagnosis	No.	(+)ve culture
Liver metastasis	*n*	
Colorectal adenocarcinoma	33	4
Small bowel NET	1	
Colonic NET	1	
Adrenocortical carcinoma	1	1
Malignant insulinoma	1	1[a]
Sarcoma	1	
Fallopian tube carcinoma	1	
Clear cell renal cancer	1	
Breast cancer	1	
Cholangiocarcinoma	13	5
Gallbladder cancer	4	1
Hepatocellular carcinoma	14	2
Hepatic lymphoma	1	1[a]
Liver adenoma	2	
Focal nodular hyperplasia	1	
Liver hemangioma	1	
Cholangitis	1	
Hydatidosis	1	
Liver cirrhosis	1	
Trauma	1	
Total	81	15

[a]*Central line-associated blood stream infection—blood stream infection but not surgical site infection.*

TABLE 3 | Type of liver intervention and infection occurrence.

Type of intervention		No.	Inf
Ablation		9	2[b]
Anatomic resections		35	7
Bisegmentectomies	6		
Left lateral	7		1
Left hepatectomy	6		1
Right hepatectomy	7		2
Central hepatectomy	5		1
Extended right hepatectomy	4		2
Metastasectomies/non-anatomic resections		37[a]	7
Total		81	

[a]*1 laparoscopic excisional biopsy included.*
[b]*Central line-associated blood stream infection—blood stream infection but not surgical site infection (Candida, Staphylococcus).*

TABLE 4 | Type and indication of intervention leading to bilioenteric anastomosis, occurrence of surgical site infection.

Operation	No.	Inf	Diagnosis	No.	Inf
Extended right hepatectomy	4	2	HCC	5	1
Right hepatectomy	4	2	Cholangiocarcinoma	10	2
Central hepatectomy	5	2	Gall bladder cancer	4	4
Left hepatectomy	4				
Non-anatomic resections	2	1			
Total	19	7		19	7

TABLE 5 | Hepatic surgery combined with other operations and occurence of organ/space infections (O/SI).

Type of operation	No.	Diagnosis	O/SI
Right colectomy + metastasectomies	6	5 Colonic cancer + 1 colonic NET	
Left colectomy + metastasectomies	2	Colonic cancer	
Sigmoidectomy + left lateral hepatectomy	1	Colonic cancer	
Sigmoidectomy + kidney resection + metastasectomies	1	Colonic cancer + renal clear cell carcinoma	
Kidney resection + right hepatectomy	1	Renal clear cell carcinoma	
Left adrenalectomy + metastasectomies	1	Adrenocortical carcinoma	1
Small bowel resection + metastasectomies	1	Small bowel NET	
Low anterior resection + metastasectomies	3	Rectal cancer	
Low anterior resection + ablation	1	Rectal cancer	
Total	17		

coagulase (−) ve. In fact, these infections fulfilled the criteria for being characterized CLABSI and were considered as such. The remaining four BSIs were considered secondary to O/SI both by clinical and laboratory data. In conclusion, we recorded 9 patients with O/SI and 4 patients with BSI secondary to O/SI, i.e., 13 patients (16%) with SSI in total. Twelve patients had an O/SI classified as Dindo II treated only with medications. The patient with both blood culture and intra-abdominal fluid culture positive was classified as Dindo IIIA because he underwent radiological guided drainage.

No significant difference was observed among the patients who developed organ/space or bloodstream infection regarding age, gender, Child–Pugh score, existence of preoperative biliary stent, or indication for surgery. Also, there was no significant difference in any of the perioperative parameters between the patients who developed a SSI and those who did not. In contrast, the incidence of postoperative O/SI was significantly higher in the patients needing ICU when compared to those hospitalized exclusively in the ward (36.1 vs 12.9%, $p = 0.026$).

DISCUSSION

Postoperative infections continue to play a significant role in morbidity and mortality of surgical patients. Especially, in major procedures like hepatectomies, infections have a high impact on length of stay, total cost and can result in postoperative death (2).

We investigated the incidence of bloodstream infection and organ/space SSI after liver surgery and searched for associated risk factors. We detected an O/SI after liver resection or ablation in 11.1% of our patients following the definition (6). This complies with the 6–10% commonly reported by others (8–10). An additional 4.9% of our patients were detected through a secondary BSI to suffer from to O/SI. In these patients, blood culture has been the sole microbiological data. In fact, two of three of our positive blood cultures had an isolated microbe matching O/SI. Consequently, the total true incidence of organ/space SSI in our cohort should increase to 16% with a difference of approximately 50%.

This difference can be easily missed for many reasons. First of all, early aggressive treatment of any infection either organ/space or bloodstream with antibiotics may cover microbiological data and obscure further the diagnosis. Second, a correlation between bloodstream infection and O/SI might not have been attempted in every case. Finally, blood microbiological data are not needed for the diagnosis of O/SI, consequently blood cultures may not be taken routinely and data may be missing. O/SIs are not always verified with microbiological data and may be diagnosed after clinical suspicion, or signs of infection followed by radiological evidence only. If these are lacking the patient may be, temporarily, discharged from the hospital, only to be readmitted later on. This is supported by the findings of Spolverato et al. where after 338 hepatectomies 14.2% of the patients were readmitted within 30 days, and 22.9% of the readmissions were due to intra-abdominal abscess (11). Along the same vein, intra-abdominal infections leading to readmission, and thus diagnosed late, represented 75% of all the intra-abdominal infections of a cohort of 712 hepatectomies (12). In both series, intra-abdominal abscess was the most common reason for readmission.

The incidence of BSI secondary to an O/SI is not clear. About 11% of 403 patients developed a post-hepatectomy BSI (13). This was considered secondary in 46% of the cases, and the source of infection was an intra-abdominal abscess in 28%. Furthermore, in 46% of the bacteremias, the onset of the infection was more than 2 weeks after hepatectomy. Clearly, in a number of patients O/SI will be diagnosed late due to the late appearance of either the primary infection or the secondary BSI.

Many risk factors and predictors have been implicated in the development of OSI. Use of silk sutures (14), postoperative bile leakage (3, 9, 15, 16), failure of the remnant liver (9), portal vein resection (1), preexisting bilioenteric anastomosis (17), and, interestingly, perioperative peritoneal lavage (18) have all been associated with increased rates of OSIs. In contrast, use of broad spectrum antibiotics in chemoprophylaxis (17) as cefuroxime alone confers no protection (19), employment of minimally invasive techniques (20), and avoidance of postoperative bile leak through the air leak test (21) seem to confer a prophylactic effect. Preexisting chronic liver disease and cirrhosis (22) and ERCP and stenting of the common bile duct (17) seem to have no effect on either SSI or OSI.

Perioperative blood loss, transfusion of blood or blood products have been reported also to have no effect on the development of SSI (23, 24) although others disagree (15). Our data indicate that blood transfusion has no effect on the development of SSI in liver surgery. However, we cannot draw any conclusion on the effect of the type of transfused blood, as described in colorectal surgery (25), and suggested by Okabayashi et al. (15) because only one of our patients received leukocyte-depleted blood.

A similar debate seems to exist regarding concomitant bowel surgery: it has been reported that it has no effect on the incidence rates of OSI (1, 24, 26) while according to others it leads to increased infection rates (27). Operating on the right colon presents a different infective morbidity compared to colectomies of the hindgut (28) but evidence regarding the combination of liver and colorectal surgery is missing. Our results imply that

TABLE 6 | Intraoperative characteristics and admission to ICU by surgical site infection occurrence.

	All patients ($n = 81$)	No postoperative infection ($n = 66$)	Postoperative infection ($n = 15$)	*p* Value
Type of antibiotic (simple/advanced)	67/14	57/9	10/5	0.080
Resection/ablation	72/9	59/7	13/2	0.528
[a]Type of resection (anatomic/non-anatomic)	35/37	28/31	7/6	0.455
Constructed bilioenteric anastomosis (yes/no)	19/62	13/53	6/9	0.094
Additional procedure (yes/no)	17/64	16/50	1/14	0.119
Blood transfusion (yes/no)	52/29	41/25	11/4	0.307
Operative time (min)	417	411	444	0.320
ICU (yes/no)	19/62	12/54	7/8	0.026

[a]*Number of patients (n) = 72. Ablated patients were excluded.*

TABLE 7 | Association between type of positive culture and bacteria.

Culture type/bacteria	Blood	Intra-abdominal fluid	Blood and intra-abdominal fluid	Total
E. coli		1		1
Enterococcus	2	3	1	6
Pseudomonas	1			1
Klebsiella		3		3
Candida	1[a]			1
Staphylococcus	1[a]			1
Serratia		1		1
Mix culture: *Enterococcus* and *E. coli*	1			1
Total	6	8	1	15

[a]*Positive blood cultures not associated with surgical site infection but associated with central line.*

the addition of another procedure to hepatectomy has no effect on O/SI. In our cohort, neither midgut nor hindgut resections were followed by an infective complication. The only significant risk factor we were able to point out was postoperative admission to the ICU. This association may be well explained by the overall status of the patients. As most of the operative data were similar for those developing SSI and those who did not, postoperative need for ICU reflects the comorbidities and the bad performance status. Conducting a major operation to these fragile patients rendered them susceptible to infection, increasing morbidity.

Our study has the disadvantage of being a small retrospective study comprising of only 81 consecutive cases of hepatectomy or intraoperative liver ablation. Perhaps, a greater number of patients would allow us to exhibit the significance of additional risk factors as reported in the literature. However, these are well described and probably we would not add anything new to the existing knowledge. What we aimed at was a focused investigation in O/SIs after hepatectomy, with emphasis in secondary bloodstream infections. We believe that true O/SIs are more frequent than reported because many cases are not identified or are identified late and not included in the published reports. Alternatively, they may be classified as infections of other type. Of course, larger studies are needed to confirm our observation and perhaps to identify additional risk factors. In this manner, we will be able to provide special care to the vulnerable patients being at higher risk.

ETHICS STATEMENT

This study was specifically reviewed and approved by the ethics committee of our institutional review board with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

IK, SO, and AA designed the study. SO, AA, AM, and DS collected and analyzed the patients' data. SO and IK wrote the paper. JG critically revised the draft. EP supervised the manuscript.

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Early Diagnosis and Surgical Treatment for Necrotizing Fasciitis: A Multicenter Study

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Background: Necrotizing fasciitis (NF) is a group of relatively rare infections, usually caused by two or more pathogens. It affects the skin and subcutaneous tissues of lower and upper limbs, perineal area (Fournier's gangrene), and the abdominal wall. Early diagnosis and aggressive surgical management are of high significance for the management of this potentially lethal disease.

Methods: We conducted a retrospective study in patients who presented, during the last decade, at four University Surgical Departments in the area of Athens, Greece, with an admission diagnosis of NF. Demographic, clinical, and laboratory data were gathered, and the preoperative and surgical treatment, as well as the postoperative treatment was analyzed for these patients.

Results: A total of 62 patients were included in the study. The mean age of patients was 63.7 (47 male patients). Advanced age (over 65 years) ($P < 0.01$) and female sex ($P = 0.04$) correlated significantly with mortality. Perineum was the mostly infected site (46.8%), followed by the lower limbs (35.5%), the upper limbs, and the axillary region (8.1%). Diabetes mellitus was the most common coexisting disease (40.3%), followed by hypertension (25.8%) and obesity (17.7%). The most common symptom was local pain and tenderness (90.3%). Septic shock occurred in eight patients (12.9%) and strongly correlated with mortality ($P < 0.01$). Laboratory data were used to calculate the LRINEC score of every patient retrospectively; 26 patients (41.9%) had LRINEC score under 6, 20 patients (32.3%) had LRINEC score 6–8, and 16 patients (25.8%) had LRINEC score >9. Surgical debridement was performed in all patients (mean number of repeated debridement 4.8), and in 16 cases (25.8%) the infected limb was amputated. The mean length of hospital stay was 19.7 days, and the overall mortality rate of our series was 17.7%.

Conclusion: Diagnosis of NF requires high suspect among clinicians, as its clinical image is non-specific. Laboratory tests can depict the severity of the disease; therefore, they must be carefully evaluated. Urgent surgical debridement is the mainstay of treatment in all patients; the need of repetitive surgical debridement is undisputed.

Keywords: necrotizing fasciitis, LRINEC score, debridement, VAC therapy, Fournier's gangrene

INTRODUCTION

Necrotizing fasciitis (NF) is actually a group of relatively uncommon, but life-threatening infections, which have the same clinical course and require urgent treatment. It usually affects the skin, soft tissues, and muscles, and may progress rapidly through the fascia planes, resulting in gradual destruction of the fascia. Its brisk clinical development can be explained by the pathogens that are usually involved, as in the majority of cases, a synergy of two or more pathogens are detected (1). NF is commonly located in the lower extremities, the perineum and genital area (Fournier's gangrene), the abdominal wall, and in upper extremities (2). NF is sometimes falsely called as "gas gangrene" due to free gas accumulating in the soft tissue spaces, giving the characteristic image of gas gangrene on plain X-rays and computed tomography (CT) scans (3); however, this term describes only the third type of NF, where the infection is caused mainly by *Clostridium* species.

Necrotizing fasciitis clinical onset and outcome has been correlated with numerous comorbidities. The most frequent comorbidity is diabetes mellitus, which can be found in 40–60% of patients with any NF type (4). Currently, it is under consideration whether diabetes mellitus is correlated with worse outcome or not (5, 6). Obesity and preexisting hypertension are also present in patients with NF, with no correlation with higher mortality rates (7). Although advanced age is widely accepted as a prognostic factor for NF, it is currently uncertain whether sex may influence NF clinical course and outcome. Nevertheless, patients who are critically ill on admission may suffer from the fulminant form of NF.

Given its rapid progression, it is understandable that any delay in the diagnosis of NF could prove fatal. Although it is not easy, an early diagnosis must be obtained within 4 h after admission. During this limited time, surgeons must evaluate mainly laboratory results, which can be very helpful not only for establishing the diagnosis but also for estimating the severity of the infection (8). When NF is suspected, patients should be managed with aggressive fluid resuscitation, antibiotic treatment, and emergency surgical debridement. The extent, the number of consecutive surgical debridements, and other operations that may be needed are decisive factors for better outcome (9).

In this retrospective study, we analyzed the profile of patients with NF and evaluated the diagnostic modalities that we used to set an early diagnosis. Furthermore, we present our therapeutic strategy that had a clear effect in the clinical outcome.

PATIENTS AND METHODS

This is a retrospective study, including all patients admitted at our Departments (1st Propedeutic Department of Surgery, Hippokration General Hospital; 2nd Propedeutic Department of Surgery, Laikon General Hospital; 3rd Department of Surgery, Attikon University Hospital; and 4th Department of Surgery, Attikon University Hospital) between 2005 and 2015 with a diagnosis of NF. The initial diagnosis was established mainly at the Emergency Surgical Department, based on patient's clinical data and laboratory results. In equivocal cases, the diagnosis was ascertained with imaging studies, mainly CT scan and/or plain radiography. The medical records of these patients were thoroughly analyzed. Specifically, we gathered the demographic data, the presenting symptoms (systematic and local changes of the infected skin), the site of infection, the possible comorbidities, and the results of the laboratory and imaging studies. Utilizing laboratory data, we retrospectively calculated the LRINEC score of every patient. The Laboratory Risk Indicator for NF was proposed by Wong et al., which consisted of six laboratory results (C-reactive protein, white-blood-cell count, hemoglobin, sodium, creatinine, and glucose) and stands for an early diagnosis and classification of patients into risk categories. In addition, LRINEC score can provide information about the severity of infection, which is helpful in comparing the results of the treatment. The cultures along with antibacterial sensibilities from the wound samples could not be safely recorded and therefore were not included in our study. We analyzed the preoperative management, the surgical procedure, and the postoperative treatment. Moreover, we evaluated the length of hospital stay among patients with different postoperative management and the overall mortality rate. Statistical analysis was made using SPSS v23.0 software. All values are presented as mean and/or median followed by the range. A standard Chi squared analysis was used for statistical correlations, and the level of statistical significance was set at $P = 0.05$. We also ran a univariate analysis for determining prognostic factors for mortality using a Cox regression model. The study has been approved by the local Ethics Committee.

RESULTS

From 2005 to 2015, 62 patients were admitted to the 4 centers collaborating in the study with a diagnosis of νF. The mean age of the patients was 63.7 (median: 56 years old, range 37–87 years) with a male-to-female ratio of 3:1. Fournier's gangrene was the predominant type of NF, as the perineum was infected in 29 patients (46.8%) (**Figure 1**). Twenty-two patients had infection of the lower limbs (35.5%). The upper limbs' axillary region was infected in only five patients (8.1%) and the infection was spread in the abdominal wall in nine patients (14.5%). Diabetes mellitus was the most common comorbidity, as 25 patients had deregulated diabetes mellitus (40.3%). Hypertension was also a relatively

FIGURE 1 | **A 65-year-old woman with extensive gas gangrene at the perineal area was managed with extensive debridement of necrotic skin and subcutaneous tissue**.

TABLE 1 | Patients' characteristics.

	Number of patients	Percentage	Correlation with mortality (*P* value)
Demographics			
Age, mean	63.7		<0.01
Female gender	15	24.2	0.04
Site of infection			
Perineum	29	46.8	
Lower limbs	22	35.5	
Upper limbs	5	8.1	
Comorbidities			
Diabetes mellitus	25	40.3	0.10
Hypertension	16	25.8	0.14
Obesity	11	17.7	0.33
Liver cirrhosis	3	4.8	0.09
Renal impairment	2	3.2	0.08
Chronic heart failure	2	3.2	0.08

TABLE 2 | Patients' symptomatology.

	Number of patients	Percentage
Local symptoms		
Tenderness	56	90.3
Pain	48	77.4
Swelling	46	74.2
Erythema	43	69.4
Necrotic skin	29	46.8
Hemorrhagic bullas	14	22.6
Crepitus	6	9.7
Systemic symptoms		
Tachycardia (<10 bpm)	21	33.9
Fever (38°C)	19	30.7
Hypotension (SAP <100 mmHg)	9	14.5
Septic shock (at least 2 criteria)	8	12.9

common comorbidity (25.8%), as well as obesity (17.74%). Other comorbidities recorded were liver cirrhosis, renal impairment, and chronic heart failure (**Table 1**).

The univariate analysis demonstrated that advanced age (over 65 years), with *P* value <0.01, as well as female sex ($P = 0.04$), was statistically significantly correlated with mortality. Univariate analysis of patients' comorbidities showed no statistically significant correlation with mortality. Although not statistically significant, our results are indicative for a correlation between renal impairment and chronic heart failure and mortality ($P = 0.08$).

Nearly all patients were admitted in a serious condition, with both systemic and local symptoms. The vast majority had tenderness (90.3%) and pain (77.4%) on the infected site, which in some cases was inexorable. In 46 patients, the site of infection was edematous (74.2%), and in 43 patients, the infected skin was erythematous (69.4%). However, the simultaneous presence of these 3 symptoms, pain, tenderness, and erythema, which are characterized in the literature as "the classic triad of NF," was recorded in only 16 patients (25.8%). In addition, the infected skin was found necrotic in 29 patients (46.8%), and in 14 patients hemorrhagic bullas had developed (22.6%). Crepitus was present in six patients (9.7%), manifesting gas gangrene. As far as the systematic symptoms are concerned, tachycardia was found in 21 patients (33.9%) and 19 patients were febrile (30.7%). Nine patients (14.5%) had developed hypotension (systolic blood pressure <100 mmHg) and 8 of them finally developed septic shock (12.9%), which was strongly correlated with mortality ($P < 0.01$) (**Table 2**).

The retrospective evaluation of laboratory tests provided interesting results. The mean white-blood-cell count was 16,008/mm^3 (median 15,476, 8,450–32,520), and in 45 patients WBC was over 15,000/mm^3 (72.6%). C-reactive protein was elevated in 39 patients (62.9%), and its mean value was 195 mg/L (median 193, range 112–282). Anemia (hemoglobin <13.5 d/dL) was found in 47 patients (75.8%), but hemoglobin levels under 11 mg/dL were found only in 12 patients (19.4%). Mean serum sodium levels were calculated at 132.65 mmol/L (median 131, range 125–135) and mean creatinine levels at 153 mmol/L (median 150, range 90–210). Mean blood glucose value was 202.35 (11.242 mmol/L), with a median value 196 g/dL. Using the results of the above laboratory values in every patient, we retrospectively calculated the LRINEC score. Interestingly, 26 patients had LRINEC score under 6, which is regarded as the cutoff value in terms of NF severity (41.9%). Twenty patients had LRINEC score 6–8 (32.6%), and 16 patients had LRINEC score over 9 (25.8%). In terms of imaging studies, an X-ray was done in the vast majority of patients (50 patients; 80.6%), mainly for excluding other possible diseases. CT of the infected site was performed in 19 cases, in which the diagnosis was not yet ascertained (30.7%). CT findings were mainly fascial swelling, inflammation, and gas formation; furthermore, CT was helpful in showing the extent of tissue infection.

The majority of patients were initially treated with aggressive fluid resuscitation and empirical antibiotic treatment consisted of ampicillin–sulbactam and metronidazole. In 11 cases (17.7%), a carbapenem, mainly meropenem was used instead, with no significant difference regarding the patient's clinical condition. The results of culture's sample were not available for all patients; therefore, the pathogens were not recorded. Antibiotic treatment was started in almost all patients intraoperatively, and it was continued proportionally to infection parameters. The mean duration of antibiotic treatment was 18.2 days (median 13; range 1–41 days). The average time from admission to operation was 12.8 h (median 8.7 h, range 5.3–27.2 h), and only in three cases the surgery was delayed more than 24 h (4.8%). We performed aggressive surgical debridement in all patients, and we performed repeated debridement in almost all of them. The median number of repetitive debridement needed for every patient was 5 (1–9). In eight cases with infection of the abdominal wall, the underlying peritoneum was infected, and part of the underlying large intestine was not viable; therefore, a colectomy was required (12.9%). Moreover, in five patients with Fournier's gangrene, an orchiectomy was also performed (8.1%). Furthermore, in 16 cases (25.8%) with NF of the upper and lower limbs, we proceeded to the amputation of the infected limb (5 upper limb amputations–11 lower limb amputations). Thirty-two patients were transferred immediately after operation to the intensive care unit (ICU) (51.6%). The mean length of ICU hospitalization was 2.45 days; however, the median length of ICU hospitalization was 12 days (0.75–35). In four patients, we used a vacuum-assisted device to accelerate wound healing. This technique had excellent results in terms of wound healing and tissue viability but did not reduce significantly the hospitalization period ($P = 0.20$). The mean length of hospital stay was 19.7 days with a median length of stay of 14 (10–43), and the overall mortality rate of our series was 17. 7% (**Table 3**).

DISCUSSION

Necrotizing fasciitis is a rare clinical entity, with an annual incidence of 1,000 cases annually, and global prevalence of 0.040 cases per 1,000 person-years (10). Numerous studies have shown that there is a preference for men, with a male-to-female ratio of 3:1; this ratio results most possibly from the increased incidence of Fournier's gangrene in men (11). There is no age predilection for NF; however, middle-aged and elderly patients (over 50 years of age) are more likely to be infected (2). Indeed, the median age of our patients is comparable to other clinical series (12). The advanced age of patients with NF seems to be a crucial risk factor for higher mortality. We noted a statistically significant correlation between advanced age and mortality, and this is in accordance with large clinical studies that have shown that advanced age is a strong, independent predictor of mortality (13). However, other studies have maintained that although advanced age is a risk factor for mortality, it must be accompanied by a more aggressive clinical course as well (14). Unlike age, sex as a risk factor for mortality is still a topic of debate. In our series, there was a correlation between female sex and mortality, with a considerable level of significance. Moreover, in a study from Czymek et al., the mortality was significantly higher among females (50% F vs. 7.7% M) (15), but in larger clinical studies, female sex did not seem to affect mortality (16). As far as the site of infection is concerned, in a large clinical study from Anaya et al., lower extremities were mostly infected (57, 8%), followed by the abdomen and the perineum (17), unlike our series in which Fournier's gangrene was the predominant form. Nevertheless, it is widely agreed that NF of the upper limbs is significantly rare compared to that of the lower limbs (18).

TABLE 3 | Surgical treatment and outcome.

	Number of patients	Percentage
Surgical treatment		
Median no of debridements	4.8	
Limb amputation	16	25.8
Colectomy	8	12.9
Orchiectomy	5	8.1
ICU admission	32	51.6
Mortality	11	17.7

Patients with NF, mainly due to their advanced age, usually have at least one comorbidity. The most frequent comorbidity is diabetes mellitus. Goh et al. calculated the prevalence of diabetes mellitus in patients with NF at 44.5%, which is quite close to our series (12); it is doubtful whether diabetes mellitus affects mortality (5, 18). In our series, there was no statistically significant correlation between diabetes and mortality. Chronic renal failure is also a frequent comorbidity in patients with NF, which seems to be a decisive risk factor for mortality. Elevated serum creatinine, along with elevated blood urea, is strongly associated with high mortality rates (19). Other common comorbidities include preexisting hypertension, obesity, liver cirrhosis, chronic heart failure, alcohol abuse, immunodeficiency, systemic lupus erythematosus, Addison's disease, and peripheral vascular disease (6, 7).

The clinical onset of patients with NF is not always evident, leading usually to misdiagnosis. The most common symptoms are local pain, swelling, and erythema; however, the simultaneous presence of these three symptoms is not a common phenomenon (20). Local skin changes consist of tenderness, crepitus, skin necrosis, and hemorrhagic bullas. The presence of crepitus suggests infection from anaerobic bacteria, which is useful for treatment strategy. Regularly, these symptoms combine with tachycardia (>100 beats/min) and fever, followed by hypotension (SAP <100 mmHg) and tachypnea (>20/min). According to the ACCP/SCCM Consensus Conference Committee, the presence of two or more from the above (or 1 and WBC $>12 \times 10^3/\text{mm}^3$ or WBC $<4 \times 10^3/\text{mm}^3$) indicates development of systemic inflammatory response syndrome (21). Taking into account that NF is caused by bacteria/fungi infection, we assume that patients who meet the SIRS criteria can develop sepsis, and when hypotension is resistive to fluid resuscitation patients may develop septic shock, which is indisputably a risk factor for mortality. In our series, all patients who developed septic shock did not manage to survive ($P < 0.01$). This strong correlation between septic shock and mortality has been repeatedly reported in the literature (22–24).

As the clinical presentation of patients with NF is not characteristic, the laboratory tests can provide not only useful information regarding the diagnosis of NF but may also indicate its severity. Elevated white-blood-cell count is a common feature in patients with NF (25) and white-blood-cell count in excess of 20,000/L is usually present in this disease. Blood urea nitrogen >18 mg/dL and serum creatinine >1.2 mg/dL may also be present, implying ongoing renal failure, which is often present in these patients. It is also suggested that C-reactive protein >16 mg/dL or creatine kinase >600 IU/L generally precludes group A b-hemolytic streptococcal infection (26). Apart from these observations, the severity of NF can be generally estimated utilizing the Laboratory Risk Indicator for NF (LRINEC) (27). After numerous studies for validation of LRINEC, it has been proposed that the cutoff value for diagnosis of NF is 6 and the severity of the infection can be estimated as follows: low (score <6), moderate (<8), and severe (≥9). In our series, 46 patients had LRINEC score under 8 (26 of them under 6), which indicates that the two-thirds of study population had a moderate form of NF. This can indirectly explain many of the results of our treatment, like relatively low hospital rate, and foremost our low mortality rate. However, in most of our cases, the diagnosis was equivocal; therefore, we used CT more frequently than in other series to set the diagnosis (16). Apart from CT and plain radiography, which we widely used, magnetic resonance imaging (MRI) or ultrasonography can also be used. Plain radiography is useful only in cases of gas gangrene, where gas formation is present. Despite its low sensitivity, it is generally widely used due to its low cost (28). A CT scan can demonstrate the extent of tissue infection, fascial swelling, inflammation, and gas formation. An MRI scan may provide additional information but is rarely used. Ultrasonography is also a feasible option, mainly in cases of gas gangrene. Bedside tests such as finger test and frozen section biopsy are occasionally used for confirmation of diagnosis, and when the diagnosis remains unclear, surgical exploration can set the diagnosis (29). Common findings in these bedside tests is the characteristic "dishwater pus," along with the lack of bleeding and lack of tissue resistance to blunt finger dissection (20). Actually, the combination of surgical exploration and microbiological and histopathological analysis of 1 cm^3 of soft tissue is considered the gold standard for confirming diagnosis, when the latter is ambivalent; however, because of the acute nature of the disease this combination is rarely used by the clinicians.

Undoubtedly, the time from admission to surgery is the most decisive factor for survival. Emergency surgical debridement should be performed in all patients within 12–15 h after admission, since a delay in treatment beyond 12 h especially in the fulminant forms of NF can prove fatal (30). At any case a delay over 24 h is unacceptable, as the mortality rate can be nine times greater when primary surgery is performed 24 h after the onset of symptoms (4). We managed to maintain a mean time of 12.8 h from admission to surgery, which eventually contributed to higher survival rates. Nonetheless, before surgery and during diagnostic procedures, patients should be resuscitated with crystalloids, and broad-spectrum antibiotics should be given. Although blood culture results are not always available in an emergency basis, the empirical usage of antibiotics is based on the suspected microbiological type of NF. Medical history and imaging tests can also be indicative for the microbiological type. When a polymicrobial infection is suspected, ampicillin or ampicillin–sulbactam combined with metronidazole or clindamycin are used (31). Alternatively, carbapenems can be administered. In cases of previously hospitalized patients, piperacillin–tazobactam, ticarcillin–clavulanate acid, third- or fourth-generation cephalosporins, or carbapenems are used, but at a higher dosage. Monomicrobial infection by beta-hemolytic streptococcus A is treated with first- or second-generation cephalosporins, except of cases with suspected MRSA coinfection, in which vancomycin, or daptomycin and linezolid are used (31). Gas gangrene is usually a result of *Clostridium* species infection and is treated with clindamycin and penicillin. Finally, NF caused by fungi can be treated with amphotericin B or fluoconazole, with disappointing results (20).

Aggressive surgical debridement, necrosectomy, and fasciotomy are the main points of surgical treatment. Barely one surgical debridement is enough for proper treatment. Usually, debridement is repeated during the next 24 h or later, depending on the clinical course and patient's general condition. Special consideration is required for the extent of the first debridement. Generally, debridement should be extended until healthy tissue is found (32) (**Figure 2**). In a study from Mok et al. the relative risk of death was 7.5 times greater when a restricted primary debridement was performed (32). When the surgical wound after the first debridement is considered as complicated, a "second-look operation" with radical surgical debridement is usually required (33). In addition, it has been reported that a complicated surgical wound may require up to 40 additional operations (10). Our mean number of debridement repetitions was 4.8, which are relatively high compared to other series (12), but we strongly believe that this contributed a lot to our low mortality rate. In NF of the limbs, there is always a dilemma on amputation of the infected limb. Tang et al. have proposed specific criteria for amputation, and the most significant is extensive soft tissue necrosis with involvement of the underlying muscles and rapidly progressing infection with a large area of tissue necrosis (34). Amputation is associated with less blood loss than a radical debridement; therefore, patients with fulminant form of NF who have already developed septic shock are clearly benefited (20). Notwithstanding, limb amputations overall do not affect significantly the mortality rate (5).

Postoperative treatment is also crucial for survival. Any evidence of hemodynamic instability demands immediate resuscitation, transfer to an ICU, nutritional support, and enteral feeding.

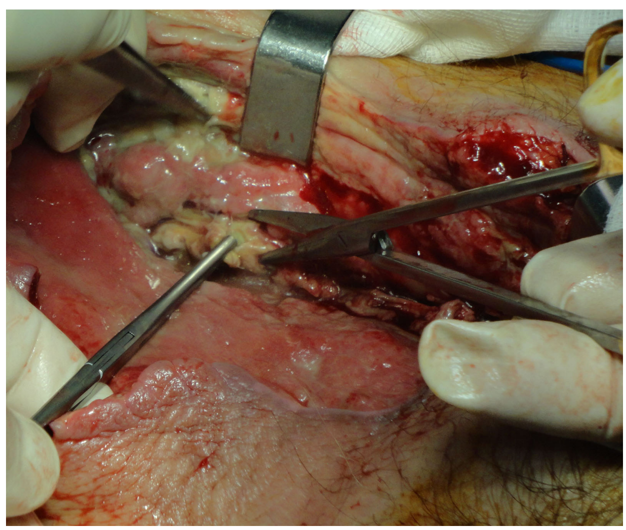

FIGURE 2 | **A 75-year-old woman with gas gangrene at the proximal right thigh**. Aggressive surgical debridement with excision of all necrotic tissues was performed.

The majority of our patients were transferred to ICU, although the mean length of stay in ICU was relatively short. As far as the wound healing is concerned, we observed a significant reduction of wound surface area in cases where VAC devices were used. However, there was no statistical significant difference in terms of the hospitalization period ($P = 0.20$), and combining the higher cost of VAC therapy compared to conventional gauze therapy, we suggest VAC be used only in wounds with large surface and/or in patients with several comorbidities.

The mortality rate of our series was 17.7%, which is considerably low compared to other series (12). Overall, the mortality rate of patients with NF is a controversial issue. Goh et al. concluded that a median mortality ratio was 21.5% (12), but mortality rates from 8.7 to 76% have been reported (35). Nonetheless, without treatment, the mortality rate of this disease reaches 100% (20). Therefore, early diagnosis and early surgical treatment are the key points in managing this disease. More frequently, using imaging studies, we managed to maintain a low time period from admission to surgery, which indisputably played a positive role in terms of survival. The mean LRINEC score of patients showed that the severity of the majority of our cases was moderate, which can explain our low mortality rate. Apart from that, we need to point that repeated extensive surgical debridement undoubtedly leads to better outcomes regarding mortality. Moreover, the repetitive use of surgical debridement compared to other studies played a significant role in better survival compared to other studies. Finally, hospitalization of the patients in ICU for a more intensive postoperative treatment was also compelling.

ETHICS STATEMENT

This study been accomplished after it had taken approval by the Bioethics Committee of Attikon University Hospital numbered EBD 1578/2-6-2016 at the 16th meeting of 6-7-2016.

AUTHOR CONTRIBUTIONS

EM: study design, study supervision, and discussion section. GB: data collection, methodology, and results section. IP: clinical advisor, results section, and study supervision. ND: data collection, methodology, and results section. PP: clinical section and results section. NM: data collection, methodology, and results section. TK: data collection, results section, and discussion section. NArkadopoulos: study design and discussion section. KT: data collection, methodology, and results section. NAlexakis: data collection, methodology, and results section. MK: study supervision and discussion section. GZ: clinical section, results section, and discussion section. VS: clinical section and discussion section. GK: study design, data interpretation, and discussion section. AM: clinical section, results section, and discussion section.

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