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ORIGINAL RESEARCH

Necrotizing Fasciitis: A Retrospective Review of the Microbiological Aspects and Factors Associated with Multi-Drug Resistance from a Saudi Tertiary Care Hospital

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Background: Necrotizing fasciitis (NF) is a potentially lethal soft tissue infection, with a high rate of morbidity and mortality. Data on the microbiological aspects of NF from Saudi Arabia are extremely lacking. Thereby, we endeavored in this study to highlight the microbial causes of NF and their antimicrobial resistance profiles, as well as the risk factors and independent predictors for development of multi-drug resistant (MDR) strains.

Methods: Over a period of three years, we retrospectively reviewed the medical, intraoperative, and laboratory electronic records of adult patients diagnosed with NF in our institution. We analyzed the risk factors for acquisition of MDR-NF using univariate analysis, whereas a multivariate regression model was generated to identify the independent predictors for MDR-NF.

Results: Out of 38 adult patients diagnosed with NF, 27 (71.1%) were males and the mean age was 60.11 ±13.57 years. The lower extremities were the most common site for NF (36.8%). Overall, monomicrobial NF (58%) was more frequent than the polymicrobial type (42%). A relatively high rate of MDR organisms was identified amongst the Gram-negative isolates (33.3%). Risk factors for MDR-NF included increased hospital length of stay, intensive care unit (ICU) admission, old age, coexisting malignancy, and increased Laboratory Risk Indicator for Necrotizing Fasciitis score. The multivariate analysis identified lengthy hospital stays and ICU admission as the independent predictors for MDR infections.

Conclusion: Our study showed that MDR-NF is a growing challenge in clinical practice that poses negative impacts on the patient outcomes as well as health care resources. On that premise, it is crucial to enforce antimicrobial stewardship guidelines, and to improve our infection control policies to mitigate the escalating surge of MDR organisms. Furthermore, thorough active surveillance studies and enhanced collaboration amongst healthcare professionals are pivotal for early recognition and intervention.

Keywords: antibiotics, mortality, multi-drug-resistant, necrotizing fasciitis, pathogen, risk factors

Introduction

The term necrotizing fasciitis (NF) describes a subset of relatively rare and fulminant necrotizing skin and soft-tissue infections (NSSTIs) that are characterized by progressively spreading necrosis in the subcutaneous tissues, including the superficial and deep fascia and subcutaneous fat.[1] Although the estimated annual incidence of this disease ranges from 0.3 to 15 cases per 100,000 population, the mortality rate may reach up to 100% in delayed diagnosis and treatment.[2] NF may occur anywhere in the body; however, it occurs more frequently in the extremities, genitalia, and perineum, and less commonly in the trunk and cervical region.[3]

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The risk factors for developing NF are poorly understood; however, recent surgical procedures, immunosuppression, malignancy, diabetes mellitus (DM), kidney disease, and obesity are among the previously reported reasons.[4] The pathophysiology of NF involves microbial inoculation into the subcutaneous tissue either via external trauma or direct invasion from a perforated viscus or urogenital tract. The uncontrolled bacterial multiplication within the superficial fascia associated with release of different enzymes and toxins promote the perpetuation of tissue infection, ischemia, and eventually necrosis.[5]

At the initial stages of presentation, many infected patients may be asymptomatic or experience localized signs and symptoms, such as superficial erythema, edema, tenderness, or excruciating pain disproportionate to the clinical examination. Besides, some patients may have systemic symptoms, including fever, nausea, vomiting, and generalized malaise.[6] With subsequent progression of the infection to the deeper tissues, more specific signs and symptoms may develop such as bluish dark discoloration of skin and induration, formation of blisters with foul smelling fluid, hemorrhagic bullae, and ultimately skin necrosis.[7]

Microbiologically, many of the cases of NF are polymicrobial (type I), involving a combination of anaerobic bacteria, facultative anaerobic streptococci, and members of the family Enterobacteriaceae. These infections account for 70–80% of the cases, and often occur in immunocompromised individuals with underlying morbidities.[8] On the other hand, monomicrobial (type II) NF can develop in otherwise healthy individuals, and is caused primarily by group A β-haemolytic streptococci, either alone or in association with *Staphylococcus aureus*. In addition, type III NF can occur secondary to infection with marine-related Gram-negative bacteria such as *Vibrio* species, while type IV is known as fungal NF and usually involves immunosuppressed individuals.[9]

The heterogeneity of the causative organisms of NF is substantial, and understanding their antibiotic resistance trends is imperative for effective treatment strategies. Cumulatively, bacterial resistance to antimicrobials is dramatically rising in all parts of the world. According to the late Global Research on Antimicrobial Resistance (GRAM) analysis, the yearly deaths ascribed to antimicrobial resistance are predicted to increase from 1.14 million in 2021 to about 1.91 million in 2050.[10] Given the shortage of literature from Saudi Arabia regarding the microbiological characteristics of NF, we deemed to conduct this study to gain valuable insights into the spectrum of the causative organisms of NF in our institution and their antimicrobial resistance profiles, in addition to delineate the risk factors and independent predictors for the emergence of multi-drug resistant (MDR) strains.

Patients and Methods

Ethics Approval and Informed Consent

The current study followed the tenets of the Declaration of Helsinki. The study design was certified approval by the Institutional Review Board (IRB) of DSFH under the reference number 334/IRB/2022. Patient consent was waived due to the retrospective nature of the study, and all data were anonymized before analysis.

Study Design, Eligibility, and Setting

This three-year, hospital-based, retrospective, cohort study included all adult patients (≥ 18 years) confirmed to have NF by surgical exploration, between January 2019 and December 2021, in Dr. Soliman Fakeeh Hospital (DSFH), Jeddah, Saudi Arabia. This hospital is a 500-bedded private, tertiary-care facility, that provides inpatient and outpatient services for the residents of the Kingdom.

The patients were suspected to have NF if presented with signs of local inflammation (fever, crescendo pain out of proportion with tissue injury, and rapidly progressive erythema and swelling), and systemic toxicity. After patients' admission, surgical explorations were done and NF was identified by the following criteria upon surgical intervention: presence of greyish necrotic soft tissue, lack of resistance of normally adherent fascia to gentle digital dissection, and presence of foul-smelling discharge having dishwater appearance.[11]

Exclusion Criteria

(1) Pediatric patients, (2) negative cultures from the collected specimens, (3) pre-existing chronic wound, (4) re-occurring NF, (5) concomitant infectious diseases, and (6) missing clinical data.

Microbiological Work-Up

During the period of interest, intraoperative tissue specimens were collected for subsequent microbiological investigations (aerobic, anaerobic, fungal, and mycobacterial cultures). The collected specimens were transported immediately to the Microbiology Laboratory of DSFH where culture and sensitivity testing were performed according to the standard protocols of the hospital laboratory, including quality control procedures, adherence to biosafety guidelines, and maintenance of thorough documentation. The VITEK TWO (BioMérieux, Brazil) automated system was used for the identification and antibiotic susceptibility testing of the recovered isolates. The following antibiotic disks were included in the testing panels: amoxicillin/clavulanate (AMC), piperacillin/tazobactam (TZP), cefuroxime (CXM), ceftazidime (CAZ), ceftriaxone (CRO), cefepime (FEP), imipenem (IPM), meropenem (MEM), gentamicin (GM), amikacin (AK), ciprofloxacin (CIP), levofloxacin (LEV), trimethoprim/ sulfamethoxazole (SXT), tigecycline (TGC), and colistin (COL). Interpretation of the susceptibility testing results was done according to the updated guidelines of the Clinical and Laboratory Standards Institute (CLSI). The breakpoints set by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) were used to interpret tigecycline susceptibility results.[12] Multi-drug resistant (MDR) strains were identified as bacteria resistant to at least one agent in three or more classes of antimicrobials, as previously described.[13] Quality control testing was performed using the CLSI- recommended quality control strains *Escherichia coli* ATCC 25922, *Klebsiella pneumoniae* ATCC 700603, *Pseudomonas aeruginosa* ATCC 27853, *Staphylococcus aureus* ATCC 29213, and *Enterococcus faecalis* ATCC 29212.

Data Extraction of the Study Participants

We conducted a retrospective analysis of DSFH medical, intraoperative, and laboratory electronic patients' database. Patients diagnosed with NF were identified by reviewing the diagnosis code of the 10th revision of the International Classification of Diseases (ICD 10; M72.6). Patients' medical record numbers (MRN) were used to extract the relevant data to the study cohort including patients' demographics, clinical presentation of NF, duration of symptoms, referral from other hospitals, body mass index (BMI), site of infection, comorbidities, predisposing factors for NF, surgical procedures (number of surgical debridement, amputation, and skin graft), administered antibiotics, length of stay (LOS), complications (septic shock, intensive care unit admission), and in-hospital mortality.

Results of hematological and biochemical investigations at the time of admission were also recorded including; WBC count (10^3/µL), absolute neutrophil count (10^3/µL), hemoglobin concentration (gm/dL), random blood glucose (mg/dL), glycosylated hemoglobin (HbA1c; %), creatinine (mg/dL), albumin (gm/dL), sodium (mmol/L), lactate (mmol/L), bicarbonate (mmol/L), C-reactive protein (CRP; mg/L), procalcitonin (ng/mL), troponin (ng/mL), and international normalized ratio (INR). For each patient, we additionally calculated the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score.[14] Microbiological data including the causative microorganisms and their antibiotic susceptibility testing results were also retrieved.

Statistical Analysis

The data were analyzed using IBM®SPSS® Statistics program version 26.0 for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables were described as means ± standard deviation (SD). The independent samples *t*-tests were used to analyze the means of two independent groups. Categorical variables were described as numbers and percentages with Pearson's Chi-Squared ($\chi 2$) test was employed to analyze the association between each of the independent factors and the outcomes of interest. Odds ratios (ORs) and 95% confidence intervals (CIs) were determined to evaluate the magnitude of any correlations. A univariate analysis was performed to identify the risk factors for acquisition of MDR-NF. A multivariate logistic regression model was generated to determine the independent predictors for development of MDR-NF. Statistical significance was set at p-values ≤ 0.05 (2-tailed).

Results

Study Population and Baseline Characteristics

After exclusion, a total of 38 adult patients with NF were eligible to the present study, as depicted in Figure 1. Of which, 27 were males (71.1%), with an average age of 60.11 ± 13.57 years (32–83 years). Amongst our cohort, Saudi nationals

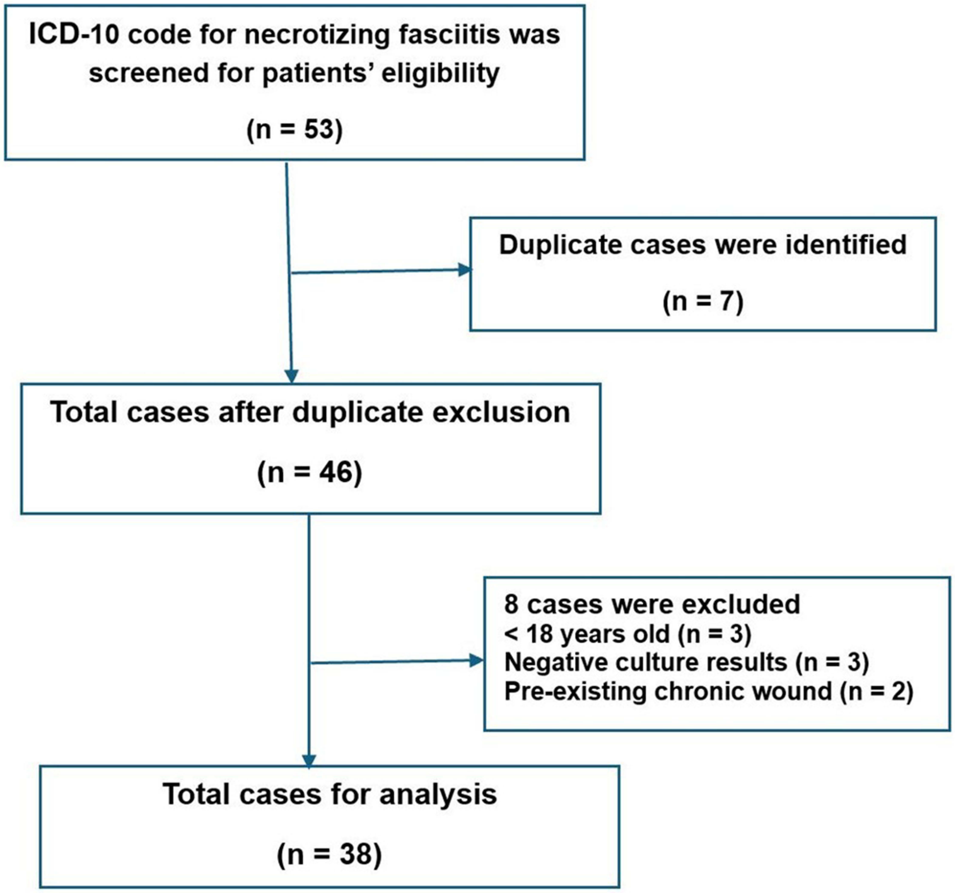

Figure 1 Flowchart showing the study inclusion and exclusion criteria. ICD-10: International Classification of Diseases, Tenth revision. Out of 53 initially identified patients, 38 met our inclusion criteria after applying exclusion protocols: pediatric cases (n=3), negative cultures (n=3), pre-existing chronic wounds (n=2).

were the most preponderant (n = 28; 73.8%). Almost half of the enrolled patients were obese (n = 20; 52.6%). DM was the most dominant comorbidity (n = 31; 81.6%), followed by hypertension (n = 21; 55.3%) Baseline characteristics of the study cohort are displayed in Table 1.

Clinical Characteristics of the Study Cohort

Amongst the study cohort, the lower extremities were the most frequent site for NF (n = 14; 36.8%). On the other hand, 13 patients (34.2%) developed NF at multiple body sites, including pelvic region and thigh (n = 5; 13.2%), pelvic region,

Table 1 Demographics and Baseline Characteristics of the Study Cohort

Variables	Patients with Necrotizing Fasciitis (n = 38)	Percentage (%)
Age (years)		
< 60	18	47.4
≥ 60	20	52.6
Gender		
Male	27	71.1
Female	11	28.9

(*Continued*)

Table 1 (Continued).

Variables	Patients with Necrotizing Fasciitis (n = 38)	Percentage (%)
Nationality		
Saudi	28	73.8
Non-Saudi	10	26.2
Body mass index (kg/m2)		
< 18.5	3	7.9
18.5–24.9	5	13.2
25–29.9	10	26.3
≥ 30	20	52.6
Underlying comorbidities		
Diabetes mellitus	31	81.6
Hypertension	21	55.3
Chronic kidney disease	11	28.9
Malignancy	11	28.9

thigh and leg (n = 3; 7.9%), abdominal wall and pelvic region (n = 2; 5.3%), abdominal wall, pelvic region, thigh and leg (n = 1; 2.6%), shoulder, back, pelvic region, thigh and leg (n = 1; 2.6%), and abdominal wall, ankle and foot (n = 1; 2.6%). The anatomic distribution of NF in the study group is shown in Figure 2.

Half of our patients (n = 19) presented mainly with pain and swelling of the infected organ. Data related to the physical signs upon clinical examination were extremely lacking. The mean duration of symptoms was 40.68 ± 29.82 days (range: 3–120), while the mean duration of hospital stay was 30.95 ± 32.03 days (range: 4–161). Around 58% of the enrolled patients (n = 22) required ICU admission during their hospital stay, whereas 28.9% (n = 11) underwent amputation of the infected organ. Approximately, 29% of our patients (n = 11) passed away during their hospitalization (7 males and 4 females) due to septic shock. Different clinical features of the study cohort are listed in Table 2.

Microbiological Profile of the Study Population

During the study interval, 54 isolates were recovered from body tissue specimens received from the recruited patients. Monomicrobial NF was more common than polymicrobial NF, accounting for 58% (22/38) versus 42% (16/38), respectively. The polymicrobial infections included two pathogens collected from 16 patients. Overall, infections with Gram-negative bacteria were more predominant (77.8%; n = 42 isolates), as compared to Gram-positive bacteria (20.4%; n = 11), with one fungal isolate (*Candida dubliniensis*; 1.8%) was recovered. No anaerobic bacteria or *Mycobacteria* species were identified during the study span. Distribution of the collected isolates is shown in Table 3.

Antimicrobial Resistance Patterns of the Recovered Isolates

Amongst our Gram-positive cocci (n = 11), no resistance was detected for vancomycin, teicoplanin, linezolid, and tigecycline. All of the obtained *Staphylococcus aureus* (n = 4) and *Staphylococcus epidermidis* (n = 2) isolates were resistant to cefoxitin and oxacillin (methicillin-resistant *Staphylococcus aureus* "MRSA" and methicillin-resistant *Staphylococcus* epidermidis "MRSA", respectively). Relatively, low resistance rates were demonstrated to fluoroquinolones, by which 27.3% (n = 3) and 18.2% (n = 2) of the total Gram-positive isolates were resistant to levofloxacin and moxifloxacin, respectively (Figure 3).

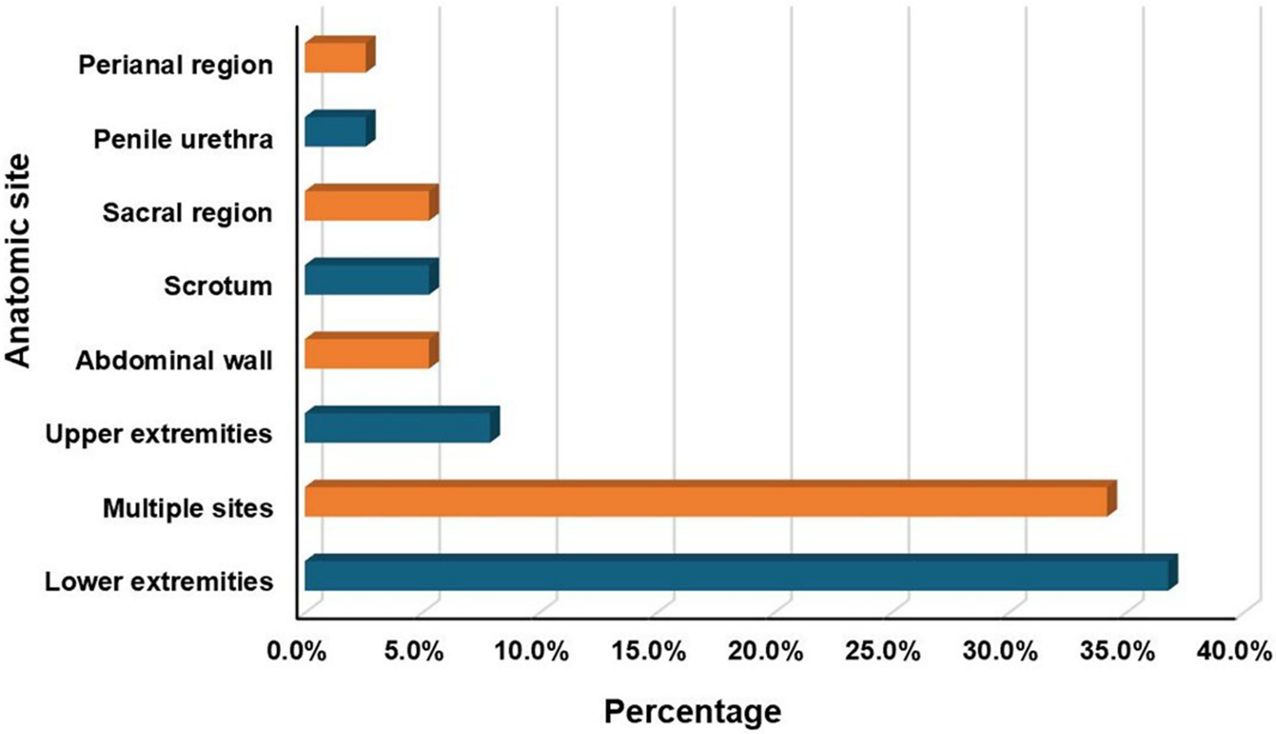

Figure 2 Anatomic distribution of necrotizing fasciitis amongst 38 adult patients. Amongst the study cohort, the lower extremities predominated (n = 14; 36.8%), while 13 (34.2%) and 3 (7.9%) of the patients developed NF at multiple body sites and the upper extremities, respectively.

Regarding trimethoprim/sulfamethoxazole, gentamicin, ciprofloxacin, and rifampin, they were tested only against *Staphylococcal* species (n = 6), whereby four isolates (66.7%), three isolates (50%), two isolates (33.3%) and one isolate (16.7%) displayed resistance, respectively. For clindamycin, no resistance was identified amongst the test isolates. On the other side, increased resistance rates were seen to tetracycline (72.7%), penicillin (54.5%), and erythromycin (45.5%). None of the identified Gram-positive bacteria showed MDR pattern. For the identified *Candida dubliniensis* strain, it was sensitive to flucytosine, amphotericin B, and voriconazole.

Amongst the 42 recovered Gram-negative isolates, low resistance rates were recorded to amikacin (19%; n = 8), followed by meropenem (21.4%; n = 9), and imipenem (28.6%; n = 12). On the opposite side, high resistance rates were observed to cefepime (52.4%; n = 22), ciprofloxacin (57.1%; n = 24), and ceftazidime (59.5%; n = 25). Out of 26 tested isolates against amoxicillin/clavulanate, 77% were resistant (n = 20), while 60.5% of the investigated isolates against ceftriaxone showed resistance (23/38). More importantly, 33.3% of our Gram-negative strains were found to be MDR (n = 14). Details of the antimicrobial resistance trends of different Gram-negative bacteria are illustrated in Table 4.

Table 2 Clinical Characteristics of Patients Diagnosed with Necrotizing Fasciitis

Variables	Patients with Necrotizing Fasciitis (n = 38)	Percentage (%)
Chief presentation		
Pain and swelling	19	50
Abdominal pain and vomiting	10	26.3
Crescendo pain	6	15.8
Sinus discharge	3	7.9

(*Continued*)

Table 2 (Continued).

Variables	Patients with Necrotizing Fasciitis (n = 38)	Percentage (%)
Duration of illness (days)		
< 30	13	34.2
≥ 30	25	65.8
Predisposing factors		
Pre-existing ulcer	4	10.5
Fracture	2	5.3
Road traffic accident	1	2.6
Fish bite	1	2.6
Referral from another hospital	4	10.5
Length of stay (days)		
< 14	17	44.7
≥ 14	21	55.3
Surgical interventions		
Skin graft	29	76.3
Debridement frequency		
≤ 3	23	60.5
> 3	15	39.5
Amputation	11	28.9
Complications		
Intensive care unit admission	22	57.9
Septic shock	11	28.9
In-hospital mortality	11	28.9
Prior antibiotic therapy	29	76.3

Table 3 Distribution of the Recovered Isolates from Patients Diagnosed with Necrotizing Fasciitis

Pathogens	Number (n = 54)	Percentage (%)
Gram-negative bacteria		
Escherichia coli	13	24.1
Klebsiella pneumoniae	10	18.4
Enterobacter species	5	9.3
Citrobacter species	4	7.4

(*Continued*)

Table 3 (Continued).

Pathogens	Number (n = 54)	Percentage (%)
Pseudomonas aeruginosa	4	7.4
Proteus mirabilis	3	5.6
Morganella morganii	3	5.6
Gram-positive bacteria		
Staphylococcus aureus	4	7.4
Enterococcus faecalis	3	5.6
Staphylococcus epidermidis	2	3.7
Streptococcus agalactiae	2	3.7
Fungi		
Candida dubliniensis	1	1.8

Risk Factors for Multi-Drug-Resistant-Necrotizing Fasciitis and Outcome of Infection

Different likely demographic, clinical, and laboratory risk factors for infection with MDR organisms were analyzed using univariate analysis as demonstrated in Tables 5 and 6. Statistically significant variables were being older than 60 years ($p = 0.01$), concomitant malignancy ($p = 0.02$), hospital stay beyond 14 days ($p = 0.0001$), and being admitted to the ICU ($p = 0.003$). Amongst the laboratory findings, a high LRINEC score was identified as the only risk factor for MDR-NF ($p = 0.004$). No mortality was recorded between non-MDR-NF group, as compared to 78.6% in patients with MDR-NF ($p = 0.0001$).

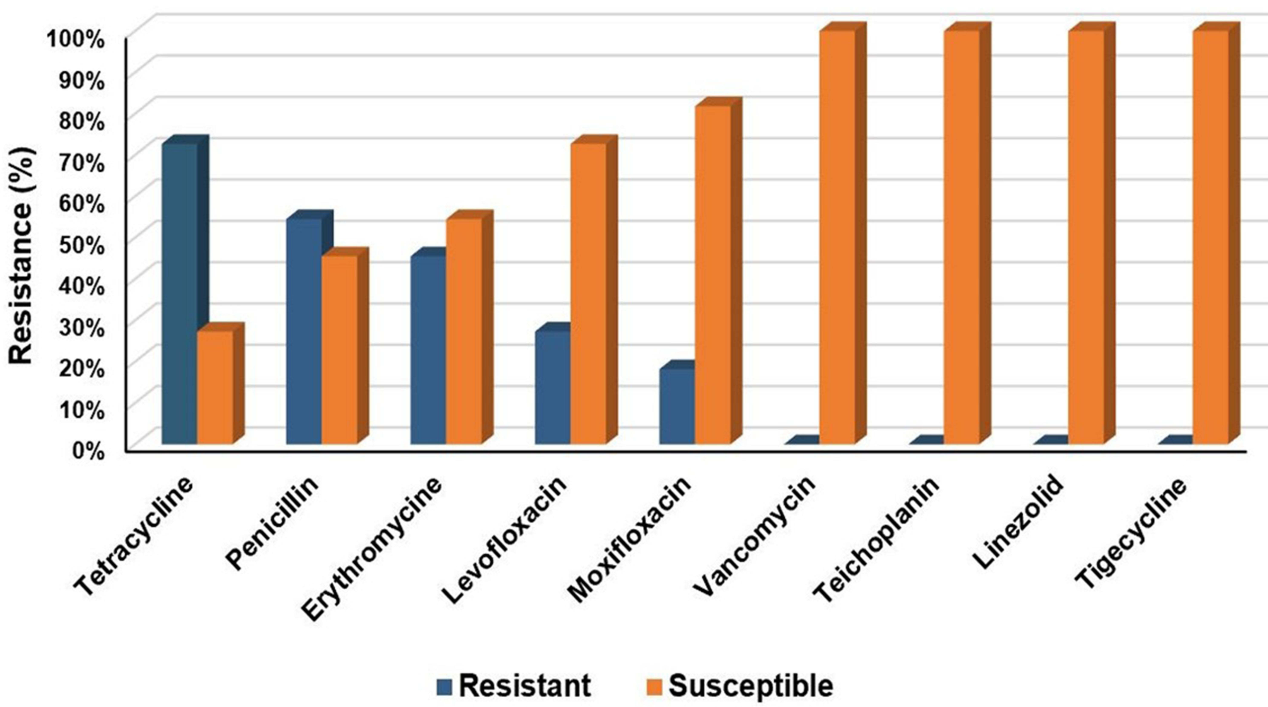

Figure 3 Antibiotic resistance profile of the test Gram-positive bacteria. High resistance rates were demonstrated to tetracycline (72.7%), penicillin (54.5%), and erythromycin (45.5%). About 27% and 18% of the total Gram-positive isolates were resistant to levofloxacin and moxifloxacin, respectively. No resistance was detected for vancomycin, teicoplanin, linezolid, and tigecycline.

Table 4 Antimicrobial Resistance Profiles of Gram-Negative Isolates Collected from Patients with Necrotizing Fasciitis

Antibiotics	*E. coli* (n = 13)	*K. pneumoniae* (n = 10)	*Enterobacter* species (n = 5)	*Citrobacter* species (n = 4)	*P. aeruginosa* (n = 4)	*P. mirabilis* (n = 3)	*M. morganii* (n = 3)
AMC	10 (77%)	8 (80%)	NT	NT	NT	2 (66.7%)	NT
TZP	5 (38.5%)	6 (60%)	2 (40%)	1 (25%)	2 (50%)	0 (0.0)	0 (0.0)
CXM	11 (84.6%)	8 (80%)	NT	NT	NT	2 (66.7%)	NT
CAZ	11 (84.6%)	8 (80%)	3 (60%)	1 (25%)	2 (50%)	0 (0.0)	0 (0.0)
CRO	11 (84.6%)	8 (80%)	3 (60%)	1 (25%)	NT	0 (0.0)	0 (0.0)
FEP	10 (77%)	7 (70%)	2 (40%)	1 (25%)	2 (50%)	0 (0.0)	0 (0.0)
IPM	3 (23%)	5 (50%)	1 (20%)	0 (0.0)	1 (25%)	1 (33.3%)	1 (33.3%)
MEM	2 (15.4%)	5 (50%)	1 (20%)	0 (0.0)	1 (25%)	0 (0.0)	0 (0.0)
AK	3 (23%)	5 (50%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
GM	9 (69.2%)	6 (60%)	0 (0.0)	0 (0.0)	2 (50%)	1 (33.3%)	2 (66.7%)
CIP	10 (77%)	6 (60%)	1 (20%)	1 (25%)	3 (75%)	0 (0.0)	3 (100%)
LEV	NT	NT	NT	NT	3 (75%)	NT	NT
SXT	9 (69.2%)	6 (60%)	3 (60%)	2 (50%)	NT	3 (100%)	3 (100%)
TGC	0 (0.0)	0 (0.0)	1 (20%)	1 (25%)	NT	NT	3 (100%)
COL	NT	NT	NT	NT	0 (0.0)	NT	NT
ESBL-producers	8 (61.5%)	6 (60%)	NT	NT	NT	NT	NT
MDR isolates	4 (30.8%)	4 (40%)	1 (20%)	0 (0.0%)	2 (50%)	1 (33.3%)	2 (66.7%)

Note: Results of antimicrobial resistance are expressed as numbers and percentages.
Abbreviations: *E. coli, Escherichia coli; K. pneumoniae, Klebsiella pneumoniae; P. aeruginosa, Pseudomonas aeruginosa; P. mirabilis, Proteus mirabilis; M. morganii, Morganella morganii*; NT, not tested; AMC, amoxicillin/clavulanate; TZP, piperacillin/tazobactam; CXM, cefuroxime; CAZ, ceftazidime; CRO, ceftriaxone; FEP, cefepime; IPM, imipenem; MEM, meropenem; AK, amikacin; GM, gentamicin; CIP, ciprofloxacin; LEV, levofloxacin; SXT, trimethoprim/sulfamethoxazole; TGC, tigecycline; COL, colistin; ESBL, extended-spectrum β-lactamase; MDR, multi-drug resistant.

Table 5 Univariate Analysis of Potential Demographic and Clinical Risk Factors for Multi-Drug-Resistant-Necrotizing Fasciitis and Outcome of Infection

Variables	Non-MDR-NF (n = 24)	MDR-NF (n = 14)	OR (95% CI)	*p*-value
Age (years)				
< 60	15 (62.5%)	3 (21.4%)	6.11 (1.34–27.96)	0.01 *
≥ 60	9 (37.5%)	11 (78.6%)		
Gender				
Male	17 (70.8%)	10 (71.4%)	1.02 (0.24–4.41)	0.96
Female	7 (29.2%)	4 (28.6%)		

(*Continued*)

Table 5 (Continued).

Variables	Non-MDR-NF (n = 24)	MDR-NF (n = 14)	OR (95% CI)	*p*-value
Nationality				
Saudi	19 (79.2%)	9 (64.3%)	0.47 (0.11–2.06)	0.32
Non-Saudi	5 (20.8%)	5 (35.7%)		
BMI (kg/m2)				
< 18.5	1 (4.2%)	2 (14.3%)	0.55–0.58	0.48
18.5–24.9	3 (12.5%)	2 (14.3%)		
25–29.9	8 (33.3%)	2 (14.3%)		
≥ 30	12 (50%)	8 (57.1%)		
Comorbidities				
Diabetes mellitus	19 (79.2%)	12 (85.7%)	1.58 (0.26–9.48)	0.62
Hypertension	15 (62.5%)	6 (42.9%)	0.45 (0.12–1.72)	0.24
Chronic kidney disease	5 (20.8%)	6 (42.9%)	2.85 (0.67–12.10)	0.15
Malignancy	4 (16.7%)	7 (50%)	5.0 (1.12–22.81)	0.02 *
Involved site				
Lower extremities	11 (45.8%)	3 (21.4%)	0.08–0.09	0.08
Multiple	5 (20.8%)	8 (57.1%)		
Upper extremities	3 (12.5%)	0 (0.0)		
Others	5 (20.8%)	3 (21.4%)		
LOS (days)				
< 14	16 (66.7%)	1 (7.1%)	26.0 (2.87–235.57)	0.0001 *
≥ 14	8 (33.3%)	13 (92.9%)		
ICU admission	9 (37.5%)	13 (92.9%)	21.66 (2.41–194.6)	0.003 *
Prior antibiotics	19 (79.2%)	10 (71.4%)	0.65 (0.14–3.01)	0.58
In-hospital mortality	0 (0.0)	11 (78.6%)	0.11 (0.04–0.32	0.0001 *

Notes: For all variables, significance was tested using Pearson's chi-squared test ($\chi 2$). * Significant difference ($p \leq 0.05$).
Abbreviations: MDR-NF, multi-drug-resistant-necrotizing fasciitis; OR, odds ratio; CI, confidence interval; BMI, body mass index; LOS, length of stay; ICU, intensive care unit.

Independent Predictors for Development of Multi-Drug-Resistant Strains in the Study Cohort

As illustrated in Table 7, the independent predictors for acquisition of MDR-NF were prolonged hospital stay (OR; 0.05, 95% CI; 0.00–0.65, p = 0.02), and ICU admission (OR; 0.07, 95% CI; 0.01–0.98, p = 0.04).

Discussion

Despite being a lethal condition, statistics designating the microbiological landscape of NF from the Eastern Mediterranean region, including Saudi Arabia, remain largely unexplored. Besides, the escalating incidence of anti-microbial resistance amongst the microbial causes of NF underscores the urgent demand for incessant research to update

Table 6 Univariate Analysis of the Likely Laboratory Risk Factors for Multi-Drug-Resistant-Necrotizing Fasciitis

Variables	Non-MDR-NF (n = 24)	MDR-NF (n = 14)	OR (95% CI)	*p*-value
WBC count (× 103/μL)				
< 15	11 (45.8%)	4 (28.6%)	0.06–0.08	0.06
15–25	13 (54.2%)	7 (50%)		
> 25	0 (0.0%)	3 (21.4%)		
Neutrophilia	10 (41.7%)	10 (71.4%)	3.5 (0.85–14.41)	0.07
Hemoglobin (gm/dL)				
< 11	18 (75%)	12 (85.7%)	2.0 (0.34–11.61)	0.43
11–13.5	6 (25%)	2 (14.3%)		
CRP (mg/L)				
≤ 150	7 (29.2%)	6 (42.9%)	0.55 (0.13–2.17)	0.39
> 150	17 (70.8%)	8 (57.1%)		
HbA1c (%)				
Good control (≤ 7)	11 (45.8%)	8 (57.1%)	0.63 (0.16–2.39)	0.74
Poor control (> 7)	13 (54.2%)	6 (42.9%)		
RBG (mg/dL)				
≤ 180	6 (25.0%)	1 (7.1%)	4.33 (0.46–40.5)	0.17
> 180	18 (75.0%)	13 (92.9%)		
Albumin (gm/dL)	2.60 ± 0.56	2.58 ± 0.45	–	0.93
Creatinine (mg/dL)				
≤ 1.6	20 (83.3%)	10 (71.4%)	2.0 (0.41–9.71)	0.38
> 1.6	4 (16.7%)	4 (28.6%)		
Sodium (mmol/L)				
≥ 135	7 (29.2%)	7 (50%)	0.41 (0.10–1.61)	0.19
< 135	17 (70.8%)	7 (50%)		
Lactate (mmol/L)	3.32 ± 2.72	2.99 ± 1.68	–	0.68
Bicarbonate (mmol/L)	22.12 ± 4.14	22.44 ± 5.66	–	0.84
Procalcitonin (ng/mL)	11.26 ± 28.04	8.37 ± 15.73	–	0.72
Troponin (ng/mL)	61.39 ± 45.95	83.47 ± 45.75	–	0.16
INR	1.32 ± 0.51	1.32 ± 0.33	–	0.96
LRINEC score				
Low (≤ 5)	6 (25.0%)	2 (14.3%)	–	0.004 *
Medium (6–7)	12 (50.0%)	1 (7.1%)		
High (≥ 8)	6 (25.0%)	11 (78.6%)		

(*Continued*)

Table 6 (Continued).

Variables	Non-MDR-NF (n = 24)	MDR-NF (n = 14)	OR (95% CI)	*p*-value
Polymicrobial NF	8 (33.3%)	8 (57.1%)	2.66 (0.68–10.4)	0.15
ESBL-producing strains	6 (25.0%)	8 (57.1%)	2.77 (0.60–12.9)	0.18

Notes: Categorical variables are presented as numbers and percentages and were tested using the Pearson's chi-squared test ($\chi 2$). For continuous variables, they are presented as means ± standard deviation (SD) and were tested using the independent samples *t*-test. * Significant difference ($p \leq 0.05$).
Abbreviations: MDR-NF, multi-drug resistant-necrotizing fasciitis; OR, odds ratio; CI, confidence interval; WBCs, white blood cells; CRP, C-reactive protein; HbA1c, glycosylated hemoglobin; RBG, random blood glucose; INR, international normalized ratio; LRINEC score, the Laboratory Risk Indicator for Necrotizing Fasciitis score; ESBL, extended-spectrum β-lactamase.

Table 7 Multivariate Analysis for Independent Predictors of Multi-Drug-Resistant-Necrotizing Fasciitis

Variables	Non-MDR-NF (n = 24)	MDR-NF (n = 14)	Multivariate	
			OR (95% CI)	*p*-value
Age (years)				
< 60	15 (62.5%)	3 (21.4%)	1.4 (0.04–43.1)	0.86
≥ 60	9 (37.5%)	11 (78.6%)		
Malignancy	4 (16.7%)	7 (50%)	0.35 (0.02–6.5)	0.48
LOS (days)				
< 14	16 (66.7%)	1 (7.1%)	0.05 (0.00–0.65)	0.02 *
≥ 14	8 (33.3%)	13 (92.9%)		
ICU admission	9 (37.5%)	13 (92.9%)	0.07 (0.01–0.98)	0.04 *
LRINEC score				
Low (≤ 5)	6 (25.0%)	2 (14.3%)	0.91 (0.59–1.41)	0.68
Medium (6–7)	12 (50.0%)	1 (7.1%)		
High (≥ 8)	6 (25.0%)	11 (78.6%)		

Note: *Significant difference ($p \leq 0.05$).
Abbreviations: MDR-NF, multi-drug-resistant necrotizing fasciitis; OR, odds ratio; CI, confidence interval; LOS, Length of stay; ICU, intensive care unit; LRINEC score, the Laboratory Risk Indicator for Necrotizing Fasciitis score.

the available treatment strategies. In this context, we sought to outline the microbiological aspects of NF in a cohort of 38 adult patients recruited from a tertiary care hospital in Saudi Arabia, as well as to address the risk factors and independent predictors for acquisition of infection with MDR strains. Demographics, baseline, and clinical characteristics of the study cohort are summarized in Tables 1 and 2.

Our results brought out that the causative organisms of NF are diverse and unpredictable (Table 3). Overall, monomicrobial NF was relatively the dominant type (58%), in agreement with Molewa et al from South Africa;[15] however, conflicting the findings of Tam et al from South Australia.[2] Additionally, Gram-negative rods caused the majority of infections (77.8%), of which *E. coli* was the leading pathogen. Contradictory to our observations, other studies disclosed that Gram-positive bacteria were more commonly associated with NF, particularly *Staphylococcus aureus* and *Streptococcus* species.[16,17] According to a recent retrospective review of 99 NF patients from Eastern Thailand, monomicrobial NF was the most frequent (52.7%), which supports our result; however, *Streptococcus pyogene* was the most commonly identified organism (28.6%).[18] This inconsistency could be traced to differences in the anatomical distribution of NF and proximity to the bowel microbiota, as 34.2% of our patients had NF at multiple body sites, including the abdomen and pelvic region, along with eight cases (21.1%) had NF at sites other than the extremities, including the anogenital region. Our finding shed light on the importance of enhancing hand hygiene and environmental disinfection practices to interrupt the chain of transmission of infection in our center. In their work, Tsai et al deduced that patients with Gram-negative NF had a fulminant course with a more liability to develop bloodstream infections and poor outcomes.[19] Nonetheless, we did not verify this hypothesis in our study, due to limited sample size.

With the purpose of formulating evidence-based empiric antibiotic guidelines for NF patients in our setting, we retrospectively reviewed the antimicrobial susceptibility profiles of the recovered isolates. In our study, we found that all of the identified *Staphylococcus aureus* isolates (n = 4) were methicillin-resistant, contributing to 7.4% of the total isolates (4/54), in keeping with an earlier study from our region.[20] On the flip side, a higher prevalence of MRSA amongst NF patients was documented from Europe.[21] This discrepancy most probably stems from distinct genetic backgrounds as well as epidemiologic traits of the enrolled populations. It should be noted that 50% of the identified MRSA isolates in this study had been acquired on admission to our institution, which highlights the significance of strict adherence to infection control measures, along with periodic screening and decolonization of the carriers. On the counter side, development of 50% of MRSA infections amongst our cohort regardless of patients' hospitalization suggests that these superbugs can emerge in the community with a growing risk of pooling into the hospital milieu, in alignment with a previous study.[22]

Among the collected MRSA isolates, no resistance was recorded to clindamycin, which has long been considered the most potent toxin-suppressing antibiotic in NF.[23] Our observation underscores the worth of this antibiotic as an adjuvant drug in the initial therapy of the infected cases in our hospital, compatible with the recent antibiotic policies.[24] In a contemporary study from Canada, Li et al found that out of 140 *Streptococcus pyogenes* clinical isolates, 7.1% were resistant to clindamycin.[25] In the present study, the collected Gram-positive cocci demonstrated high resistance rates to tetracycline (72.7%), penicillin (54.5%), and erythromycin (45.5%). The increased resistance patterns could be explicated by the frequent prescription of these antibiotics as empiric therapy in our health-care facility. In contrast to our results, lower resistance patterns to tetracycline (12%) and erythromycin (8.7%) were reported amongst *Streptococcus pyogenes* isolates in another study from Spain,[26] mostly due to differences in the geographical region and demographics of the study cohort.

A significant finding of our study is the presence of tetracycline and erythromycin co-resistance in 36.4% of the investigated Gram-positive isolates (n = 4). In an earlier study by Rubio-López et al, co-resistance was noticed in 2.1% of the isolates.[27] According to previous investigators, tetracycline-erythromycin co-resistance is linked to promiscuous transposons that carry resistance determinants to both drugs.[28] This phenomenon is awesome, as these transposons can transfer resistance genes between bacterial species, resulting into widespread treatment failure. Future research should take place to elucidate the underlying molecular mechanisms for development of co-resistance in our setting. In the current study, none of the test isolates exhibited resistance to vancomycin, teicoplanin, linezolid, and tigecycline, which corresponds to another study from Kuwait.[29]

Amongst our Gram-negative isolates, the antimicrobial susceptibility testing revealed striking patterns of resistance to the generally available antibiotics and a worrisome rise in bacterial resistance to the majority of empiric antibiotics (Table 4). Discordant with a previous publication,[15] 77% of our Gram-negative isolates demonstrated resistance to amoxicillin/clavulanate. Increased resistance rates were also seen to other β-lactam antibiotics, including ceftazidime (59.5%), cefepime (52.4%), and ceftriaxone (60.5%; n = 23/38). It is important to note that the vast majority of *E. coli* (85%) and *K. pneumoniae* isolates (80%) showed resistance to third-generation cephalosporins, in favor of a recent study from Yemen.[30] Contrariwise, Chen et al found that most of the identified Gram-negative bacteria were ceftriaxone-susceptible, including the aforementioned bacteria.[31] Employment of different laboratory techniques in the antimicrobial susceptibility testing is a plausible etiology for such disagreement. Besides, increased use of ceftriaxone in our hospital for surgical prophylaxis may act as a selection pressure for resistant strains.

Though piperacillin/tazobactam is believed to be a potential carbapenem-sparing antibiotic, we observed a moderately high resistance rate (38%), with *K. pneumoniae* (60%) and *Pseudomonas aeruginosa* isolates (50%) being the most resistant (Table 4). On the other hand, Yaacoub et al found that 64.7% of the test isolates were piperacillin/tazobactam-resistant.[32] This incongruity could be justified by different demographics of the study cohort, as they included only war-wounded patients from a traumatology center with more complex nature of the disease. In our work, Gram-negative isolates showed a relatively low resistance rate to amikacin (19%), in harmony with a recent study from Pakistan.[33] The decreased amikacin resistance in the current study may be allied to the infrequent use in our hospital due to its serious adverse effects, as well as injection administration route. In contrast to our previous research,[34] all of the identified *Morganella morganii* isolates herein (n = 3) were resistant to tigecycline. This divergence might be related to different collected specimens, as the present study included only tissue specimens from NF patients, compared to different biologic specimens examined in our preceding analysis.

Bacterial production of ESBLs poses a growing public health threat. In the existing study, we found that 61.5% of *E. coli* and 60% of *K. pneumoniae* isolates were ESBL-producers (Table 4). The irrational use of β-lactam antibiotics in our institute, including penicillins as well as third- and fourth- generation cephalosporins, is a possible reason for such high burden. Close to our findings, a prospective cohort study from Sierra Leone proved that up to 59.2% of the collected Gram-negative bacterial strains were ESBL producers.[35] A retrospective study from a tertiary orthopedic care center in Iraq demonstrated even a higher rate of ESBLs amongst *E. coli* (93.3%) and *Proteus mirabilis* (100%) isolates.[36] On the other side, ESBL-producing Gram-negative bacteria accounted for 47.3% in a late study from Tanzania.[37] This apparent disagreement mostly arises from different study settings and criteria of the recruited patients. The increasing proportion of ESBL-producing bacteria amongst NF patients signals an urgent need to develop newer antibiotics as well as regular antimicrobial resistance surveillance to improve the outcome of those vulnerable patients.

Carbapenems are acknowledged as the antibiotics of choice to treat infections caused by ESBL-producing strains.[38] The cumulative resistance rates of our Gram-negative isolates to carbapenems were 21.4% to meropenem and 28.6% to imipenem, with half of *K. pneumoniae* and one-fourth of *Pseudomonas aeruginosa* isolates being resistant to both drugs (Table 4). These results are concerning, especially with increased resistance rates to the majority of the investigated antibiotics in our assay. In a retrospective Ugandan study, carbapenem-resistant bacteria were responsible for 27% of the infections, corroborating our results.[39] By contrast, the overall prevalence of carbapenem-resistant Enterobacteriaceae (CRE) in another Colombian study was 13.3%.[40] This inconsonance could be attributed to different screening techniques for carbapenem-resistant organisms. A meta-analysis evaluating the magnitude of antimicrobial resistance in skin and soft-tissue infections from Africa explored that around 20% of *Pseudomonas aeruginosa* isolates were resistant to imipenem or meropenem, agreeing with our result; however, the pooled resistance rates of *E. coli* (6–19%) and *K. pneumoniae* (8–24%) to carbapenems were lower than our estimates.[41] No doubt that the unsupervised use of carbapenems is a core element for the development of resistant strains, which dictates the importance of adopting carbapenem-sparing policies in our facility.

The increasing incidence of MDR bacteria, particularly in the context of NF, warrants epidemiological studies in our locality to elucidate the burden of this huge challenge. As opposed to Gram-positive bacteria (0.0%), up to one-third of our Gram-negative bacteria were MDR (33.3%), as shown in Table 4, accounting for 26% of the total cultured bacteria (14/54). This finding is parallel to Thy et al from France,[42] but quite dissimilar from the conclusions of Castelli et al from Spain.[17] Our result highlights the pressing need to effective implementation of antimicrobial stewardship program to curb further propagation of resistant bacteria in our institution and reserve the last-line antibiotics. In the Tanzanian study, the overall MDR rate was reported to be 40.9%; with 39.8% of the Gram-negative isolates were MDR as compared to 10.9% of the Gram-positive bacteria.[37]

Interestingly, an alarming prevalence of MDR strains (100%) was described from another observational study from Ethiopia.[43] The substantial heterogeneity most probably comes from dissimilarities in the compliance with hospital infection control policies between different health-care settings. Incompatible with our results, a systematic review by Chelkeba et al concluded that the pooled estimates of MDR among *E. coli* and *K. pneumoniae* isolates were 76% and 84%, respectively.[44] In the present study, we noticed an outstanding susceptibility of MDR *Pseudomonas aeruginosa* isolates to colistin (100%); however, none of our patients received this drug during the study period. The detrimental side effects and complex pharmacokinetics of colistin are likely justifications for discouraging the use of this antibiotic in our institution.[45]

To the best of our knowledge, little is known about the risk factors for acquisition of MDR bacteria in NF patients, peculiarly in Saudi population. The potential clinical and laboratory risk factors alongside the independent predictors are wrapped-up in Tables 5–7, respectively. A closer inspection of these variables denotes that prolonged hospital stay was a significant risk factor ($p = 0.0001$) and independent predictor ($p = 0.02$) for MDR infections, whereby patients admitted to the hospital beyond two weeks were 26 times more likely to develop MDR-NF. This correlation has been, also, ascertained elsewhere.[46] Prolonged hospitalization will increase the possibility of patients' exposure to healthcare-associated risks, including invasive procedures and empiric antimicrobials. This implies that physicians should minimize the hospital LOS as much as possible, and boost the nutritional status of the infected patients to curtail MDR infections.

Amongst our series, ICU admission turned out to be another risk factor ($p = 0.003$) and independent predictor ($p = 0.04$) that increased the probability of MDR infections around 22 times. The same conclusion was also drawn by Althaqafi et al.[47] According to Alsehemi et al, patients admitted to the ICU had about eight times increased risk to develop MDR-NF (OR; 8.71, 95% CI; 3.04–24.99, $p < 0.001$).[48] In comparison to the other hospital sections, the frequency of antibiotic prescription in the ICUs is generally much higher, which endorses the selection and circulation of resistant strains.[49] Our finding points out to the importance of careful use of antibiotics in ICU admitted patients, along with the appropriate de-escalation based on the microbiological results and the clinical response.

In the present study, the majority of MDR-NF patients had unfavorable prognoses, whereby 78.6% died during the study period due to septic shock. On the other side, no mortality was recorded amongst patients with non-MDR-NF ($p = 0.0001$), as shown in Table 5. These findings provide critical insights into the clinical impact of MDR-NF. Likewise, in a recent retrospective study of 35 patients with Fournier's gangrene, MDR bacteria were identified in 66.7% of the non-survivors, as compared to 13.8% of the survivors ($p = 0.005$).[50]

Parallel to another publication from China,[51] old age was additional risk factor for MDR-NF ($p = 0.01$), with patients older than 60 years had about six times more odds of developing MDR infection (CI; 1.34–27.96). Jeopardized immune system as well as the presence of multiple comorbidities are leading causes for frequent hospital admissions and long-term antibiotic therapy among elderly people, thus amplifying the risk of being infected with MDR strains. Clinicians should stratify the patient population at the greatest potential of acquiring MDR infections upon institutionalization, in order to optimize the antibiotic regimen.

In this study, patients with underlying malignancy had a 5-fold greater risk to acquire MDR-NF (CI; 1.12–22.81, $p = 0.02$), concordant with Enokida et al.[52] The role of cancer in MDR infections is multifactorial, including chemotherapy-induced neutropenia, repeated hospitalizations and insertion of indwelling catheters,[53] and dysbiosis of the microbiota due to frequent courses of antibiotics.[54] It is worthy mentioning that prior antibiotic exposure was not identified as a risk factor for MDR infection in our patients, discrepant to what was previously validated from other studies.[47,55] A reasonable interpretation is that the majority of our patients received empiric therapy prior to culture-guided antibiotics, causing the difference between both MDR-NF and non-MDR-NF groups to be negligible.

The LRINEC score has been proposed by Wong et al, in 2004, as a diagnostic system to differentiate NF from other severe soft tissue infections. It depends upon six laboratory parameters (C-reactive protein, total white blood cell count, hemoglobin level, sodium, creatinine, and glucose concentrations), and sorts out patients into low (≤ 5), medium (6–7), or high (≥ 8) risk of NF.[7] Several studies have surveyed the clinical relevance of LRINEC score; however, both the predictive ability and diagnostic accuracy showed contradictory results.[56] A new finding of our study is that increased LRINEC score (≥ 8) was more commonly associated with MDR-NF (78.6%), as compared to non-MDR-NF (25%), as shown in Table 6. We also noticed that most of the individual laboratory parameters of the LRINEC score showed higher values among the MDR-NF cohort, but without statistically significant differences. These data suggest that a high LRINEC score could be a risk factor for MDR-NF; however, our observations need to be indorsed by further prospective analyses.

Whilst our study provides new data about the microbiology of NF as well as the antimicrobial resistance trends of the culprit organisms, it has some limitations that need to be addressed. One of these limitations is the number of patients and health care centers involved in this study, as we included only patients from a single tertiary care hospital. Studies in the future should collaborate multiple health care facilities to consolidate our results. In addition, the retrospective nature of our study makes it liable to selection bias of the study cohort, which calls for ancillary prospective studies. Furthermore, though eleven patients died during the study period, we did not map out the underlying risk factors for mortality, because of small sample size. Finally, we did not decrypt the molecular mechanisms beyond the emergence of MDR bacteria, and this gap should be bridged in subsequent studies.

Conclusions

This study underscores the escalating challenge of MDR-NF in our cohort, necessitating a multifaceted approach to curb transmission of resistant pathogens and improve the clinical outcome of NF patients. Early debridement, optimized wound care, and expedited discharge protocols should be promoted to minimize the hospital LOS. In addition, culture-guided de-escalation, implementation of carbapenem-sparing regimens, strict hand hygiene, environmental disinfection, MRSA screening/decolonization for high-risk patients (eg, elderly, malignancy), particularly in ICU setting, are essential to curtail MDR risk. Prospective surveillance, molecular characterization of resistance mechanisms, and multi-center collaborations are recommended in future studies to mitigate MDR risk, reduce mortality, and alleviate healthcare burdens.

Abbreviations

NF, Necrotizing fasciitis; MDR, Multidrug-resistant; NSSTIs, Necrotizing skin and soft-tissue infections; DSFH, Dr. Soliman Fakeeh Hospital; LOS, Length of stay; MRSA, Methicillin-resistant *Staphylococcus aureus*; LRINEC, Laboratory Risk Indicator for Necrotizing Fasciitis.

Data Sharing Statement

All data are available from the corresponding author on reasonable request.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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The authors declare no conflicts of interest in this work.

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