RESEARCH ARTICLE

Gram-negative bacteria as emerging pathogens affecting mortality in skin and soft tissue infections

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Abstract

Introduction: Skin and soft tissue infections (SSTIs) are commonly encountered in clinical practice and mainly caused by gram-positive cocci such as *S.aureus* and β-hemolytic streptococci. Complicated SSTIs involving deeper tissues often necessitate surgical intervention and occur in patients with significant comorbidities such as diabetes or immunocompromising conditions.

Methods: In this study, we retrospectively reviewed the epidemiology, clinical characteristics, microbiology, and treatment of patients admitted with SSTI during a five-year period in the Internal Medicine Department of a tertiary hospital.

Results: During the study period, 317 patients were recorded, with a mean age of 72.1 years. The most common underlying medical conditions were diabetes mellitus, chronic kidney disease, and heart failure. Cultures were positive in 23.3 % of cases, 62.2 % of which were polymicrobial. The most frequently isolated microorganisms were *Enterococci*, *Escherichia coli*, and *Pseudomonas aeruginosa*. Significant antimicrobial resistance rates were noted, in particular for gram-negative microorganisms. Mortality was higher than described in the literature and associated with age, comorbidities, and infection by gram-negative microorganisms.

Conclusion: This study denotes the role of gram-negative bacteria in SSTI epidemiology. Therapeutic protocols regarding the empiric treatment of SSTIs should necessarily take into account the local epidemiology of isolated pathogens and antimicrobial resistance. HIPPOKRATIA 2018, 22(1): 23-28.

Keywords: Skin infection, soft tissue infection, cellulitis, antimicrobial resistance

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Introduction

Skin and soft tissue infections (SSTI) are an increasingly identified cause of Emergency department visits and hospitalizations with a significant impact on healthcare costs[1-7]. They consist of a heterogeneous group of infections that range from superficial uncomplicated infections to complicated SSTIs[8]. Complicated SSTIs (cSSTIs) are infections that extend deep into the subcutaneous tissues, the fascia or the muscles, require surgical intervention, or involve patients with significant comorbidities such as diabetes mellitus, vascular deficiency or immune insufficiency[9], which undermine response to treatment.

The most commonly reported microorganisms causing SSTIs are *Staphylococcus aureus* and β-hemolytic streptococci; however other streptococci, enterococci, and gram-negative bacteria can also cause SSTIs[2,3,8,10-13]. Importantly, cSSTIs have different microbiology with a higher prevalence of polymicrobial infections and gram-negative microorganisms, such as in patients with diabetes, in neutropenic patients, and patients with malignancy[14-18]. Furthermore, successful treatment of these infections depends on the local patterns of microbiology and antimicrobial resistance[5,10,14].

The increasing frequency of SSTIs and the varying treatment options underline the necessity to study their clinical characteristics and microbiology further. This study aimed to report the clinical, epidemiological, and microbiological characteristics of patients admitted with SSTI in a tertiary-care referral centre in Greece, which is a country with a very high incidence of antibiotic resistance[19].

Materials and Methods

This is a retrospective cohort study that enrolled adult-only patients admitted in the Internal Medicine Department of the University Hospital of Crete from January 2011 to December 2015 with a diagnosis of SSTI. The discharge notes and the Internal Medicine Department electronic database were screened to identify eligible patients that were hospitalized with SSTI. Then, the hard copies of the patients' files and the electronic

database were reviewed for data extraction regarding demographics (age, gender), medical history including comorbidities, previous episodes of SSTI, and antibiotic use or hospitalizations in the preceding three months before the recorded admission. We also collect data regarding the clinical presentation of SSTI and complications suffered, microbiological data and antimicrobial susceptibility, treatment administered for the SSTI, and outcomes including length of hospitalization, infection outcome, and readmissions due to SSTI within the subsequent three months. If a patient had more than one admission, the first admission was only included for analysis. Ethical committee approval was waived as the study was retrospective, started many months after the last patients had been discharged, personal data were protected, and patients had received standards of care according to institutional protocols at the time of treatment.

Infection was evaluated by use of the Systemic Inflammatory Response Syndrome (SIRS) criteria, whereby sepsis was defined as the presence of two out of four SIRS criteria[20]. Comorbid conditions were recorded in accordance with the Charlson weighted comorbidity index[21]. Blood cultures and tissue cultures in the case of surgical debridement were obtained from the SSTIs and the vast majority was collected within 48 hours after admission. Species identification and antibiotic susceptibility testing were performed using a VITEK®2 system (bioMérieux SA, Marcy- l'Étoile, France) in accordance to the Clinical and Laboratory Standards Institute (CLSI) standards[22] for all antibiotics except for tigecycline. As far as tigecycline is concerned, susceptibility was determined by Etest (AB BIODISK, Solna, Sweden).

Categorical data were analyzed with Fisher's exact test or the Pearson's chi-square test, as appropriate. Continuous variables were compared using Student's t-test for normally distributed variables and the Mann-Whitney U-test for non-normally distributed variables, after performing a D'Agostino-Pearson omnibus normality test. All tests were two-tailed and p-values <0.05 were considered to be significant. Data are presented as number (%) for categorical variables and median [interquartile range (IQR)] for continuous variables. All statistics were calculated with GraphPad Prism 5.0 (GraphPad Software, Inc., San Diego, CA).

Results

During the five-year study period, 317 patients hospitalized for an SSTI were recorded. Figure 1 shows the flowchart of patient inclusion. The patient characteristics are shown in Table 1. The mean age of the patients was 72.1 years, and 137 (43.2 %) were male. The most common underlying medical conditions were diabetes mellitus (41 %), chronic kidney disease (defined as an estimated creatinine clearance of < 60 ml/min)[23] (32.2 %), heart failure (30 %), ischemic heart disease (23.7 %), dementia (20.8 %), chronic respiratory disease (19.9 %), cerebrovascular disease (13.2 %), and peripheral artery disease (10.4 %). The median Charlson score was six (IQR: four to eight). A local skin lesion (most commonly due to diabetic foot) or recent trauma (in the preceding four weeks before SSTI) were present in 24.3 % and 13.6 % of the patients, respectively. Immunosuppressive treatment had been administered to 7.3 % of patients, most commonly long-term glucocorticoid and methotrexate (39.1 % and 30.4 % of patients that received immunosuppression, respectively). Recent antibiotic use was noted in 30.3 % of the patients, most commonly used were beta-lactams (71.6 %), fluoroquinolones (27.1 %), and clindamycin (25.1 %). Previous SSTI (within the preceding three months) was documented in 17.7 % of the patients, 82.1 % of which was located in the same anatomical site.

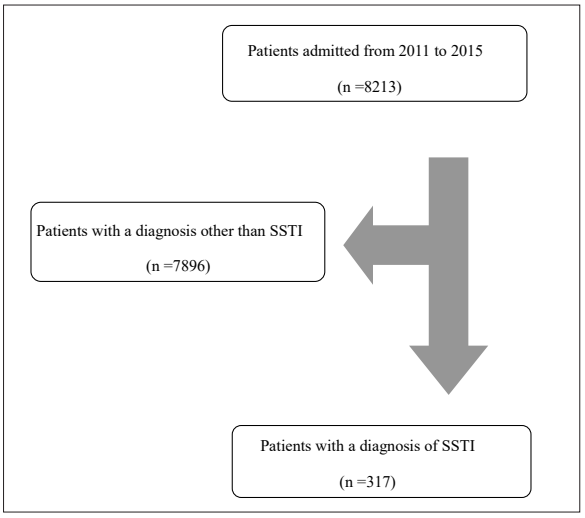

Figure 1: Flowchart of the patient inclusion in the retrospective cohort study conducted in the Internal Medicine Department during a five-year period.

Pus and tissue cultures were positive in 23.3 % of cases (74 cases), and 62.2 % of positive cultures were polymicrobial, yielding a total of 172 microorganisms, while no blood culture came back positive. Isolated microorganisms were gram-negatives in 54.6 %, gram-positives in 37.8 %, and fungi in 7.6 %. The most frequently isolated microorganisms were *Enterococci* (in 35.1 % of cases), *E.coli* (in 28.4 % of cases), *Pseudomonas aeruginosa* (in 24.3 % of cases), and *S.aureus* (in 21.6 % of cases). Among *Enterococci* and *Staphylococci*, 38.5 % and 43.8 % were resistant to penicillin and methicillin, respectively. The extended spectrum beta-lactamase (ESBL) phenotype was detected in 51.4 % of *Enterobacteriaceae* (Table 2).

For the treatment of SSTIs, fluoroquinolones combined with clindamycin was the most common regimen (40.3 %), followed by piperacillin in combination with tazobactam (25.2 %), vancomycin (24 %), aminopenicillins (17.4 %), daptomycin (10.7 %), and carbapenems (9.8 %).

The median total length of stay was seven days (IQR: 5-12 days). The overall hospital mortality rate was 6 % (19 out of 317 patients). The readmission rate within three months following discharge was 17.1 % (51 out of 298

Table 1: Characteristics of the 317 patients hospitalized for skin and soft tissue infection in the Internal Medicine Department during a five-year period.

Patient characteristics	
Mean age (years, SD)	72.1 (15.7)
Male (n, %)	137 (43.2)
Past medical history	
Diabetes Mellitus (n, %)	130 (41)
Chronic Kidney Disease (n, %)	102 (32.2)
Heart failure (n, %)	95 (30)
Ischemic heart disease (n, %)	75 (23.7)
Dementia (n, %)	66 (20.8)
Chronic respiratory disease (n, %)	63 (19.9)
Cerebrovascular disease (n, %)	42 (13.2)
Peripheral artery disease (n, %)	33 (10.4)
Median Charlson Index (IQR)	6 (4-8)
Skin lesion predisposing to an SSTI (n, %)	77 (24.3)
Diabetic foot (n, %)	30 (9.5)
Trauma predisposing to an SSTI (n, %)	43 (13.6)
Immunosuppression (n, %)	23 (7.3)
Recent antibiotic use (n, %)	96 (30.3)
Previous SSTI (within the last 3 months) (n, %)	56 (17.7)
Same anatomical site (n, %)	46/56 (82.1)
Positive Culture [n, % of all cases (n =317)]	74 (23.3)
Gram-negative (n, % of all pathogens)	94 (54.65)
Gram-positive (n, % of all pathogens)	65 (37.79)
Fungi (n, % of all pathogens)	13 (7.56)
Polymicrobial culture (% of culture-positive SSTI)	46 (62.2)
Median length of hospitalization (days, IQR)	7 (5-12)
Overall mortality (n, %)	19 (6)
Readmission at three months (n, %)	51 (17.1)

n: Number, SD: standard deviation, IQR: interquartile range.

patients). Among the readmitted patients, 18 were admitted with a diagnosis of SSTI, and three patients died.

In terms of mortality, factors including age, Charlson index and underlying skin condition predisposing of SSTI, were found to be significantly correlated with death in univariate analysis (Table 3).

Discussion

The present study re-evaluates important data on the clinical characteristics, epidemiology, microbiology, and outcomes of patients hospitalized with SSTI during a five-year period.

In our study, patients with SSTI were older compared to other studies[24-27]. This is consistent with the fact that increased age is a risk factor for SSTI[26] and could reflect the higher general population median age in Greece, compared to the countries where the abovementioned studies were conducted (namely USA, South Korea, and China)[28].

Interestingly, the most common pathogens identified in our study were *Enterococci* and gram-negative microorganisms, while *S.aureus* was the fourth most frequent pathogen. These data significantly differ from the literature, where *S.aureus* is the main causative agent of SSTIs[14,17,24,29-31]. This difference could be attributed to the older age of our cohort, the higher comorbidity rate and

Table 2: Microbiology of the positive pus and tissue cultures in 74 patients with skin and soft tissue infections (172 microorganisms in 74 cultures).

Pathogen & Resistance patterns	n	%
Enterococcus	26	35.1
Enterococci PenR	10/26	(38.5)
VRE	2/26	(7.7)
Escherichia coli	21	28.4
E.coli ESBL	8/22	(33.3)
E.coli CarR	2/22	(9.5)
Pseudomonas aeruginosa	18	24.3
P.aeruginosa resistant to piperacillin	7/18	(38.9)
P.aeruginosa MDR	4/18	(22.2)
P.aeruginosa CarR	3/18	(16.7)
S.aureus	16	21.6
MRSA	7/16	(43.8)
Proteus spp	15	20.3
Proteus ESBL	4/15	(26.7)
Klebsiella pneumoniae	13	17.6
Klebsiella ESBL	10/13	(76.9)
Klebsiella CarR	8/13	(61.5)
Coagulase-negative *Staphylococci*	11	14.9
Coagulase-negative *Staphylococci* MethR	9/12	(72.7)
Candida spp	10	13.5
Streptococcus spp	9	12.2
Morganella morganii	8	10.8
Acinetobacter baumanii	4	5.4
Acinetobacter CarR	3/4	(75)
Bacteroides spp	4	5.4
Citrobacter spp	2	2.7
Citrobacter ESBL	1/2	(50)
Corynebacterium	2	2.7
Serratia marcescens	2	2.7
Myroides spp	2	2.7
Stenotrophomonas maltophila	2	2.7
Providencia stuartii	1	1.4
Enterobacter aerogenes	1	1.4
Alcaligenes faecalis	1	1.4
Vagococcus fluvialis	1	1.4
Fusarium spp	1	1.4
Sporothrix	1	1.4
Stephnoascus ciferri	1	1.4

n: Number of microorganisms, PenR: Penicillin resistant, VRE: Vancomycin resistant *Enterococci*, MRSA: Methicillin resistant *Staphylococcus aureus*, ESBL: Extended Spectrum Beta Lactamase, CarR: Carbapenem resistant; MDR: Multi-drug resistant.

the notable rates of recent previous hospitalization and antibiotic exposure, which are all associated with a higher risk of infection by gram-negative microorganisms[32-34]. In accordance with the current study, in a previous study performed in our institution that involved oncologic patients from 2002 to 2006, *Enterococci, Escherichia*, and *Pseudomonas* were the commonest pathogens[16]. As a result, despite the different patient populations in these studies, it is reasonable to support that local epidemiology holds an important role in SSTI microbiology.

Recent studies with resistance rates in SSTIs are limited[17,19,26,30,35]. In this study, resistance rates of *Enterococci* to vancomycin were similar to other European countries (7.7 %), higher than Latin America (2.9 %), but lower than North America (14.8 %)[30]. The alarming resistance rates in gram-negative pathogens found in our study are in line with the observation that resistance rates in Greece are among the highest reported[19]. In particular, 33.3 % of *E.coli* and 76.9 % of *K.pneumoniae w*ere ESBL producers, which are much higher compared to SSTIs in North America, South America, and Europe[30]. Similarly, high resistance rates were noted among *Pseudomonas* strains, which are much higher compared to the SENTRY program from North America and Europe but similar to those in Latin America. Methicillin-resistant *S.aureus* (MRSA) rates in our study (43.8 %) were higher or similar compared to Latin America, Europe, China (38.3 %, 22.4 %, and 2.6 %, respectively), and North America (32-51 %)[17,26,27,30,36,37].

The longer hospitalization found in our study compared to previous studies (median: seven vs four to five days)[29,38,39] probably reflects the more complex medical history of our patient population[14,24]. It may also be attributed to the higher rates of gram-negative microorganisms and their high resistance rates that necessitated prolonged use of intravenous antibiotics[14]. Mortality in our study was higher compared to other studies[24,29,38,39], and the non-survivors were older, with a higher comorbidity rate, more severe infection upon presentation, and higher frequency of a skin lesion predisposing to an SSTI. Importantly, SSTIs in non-survivors implicated more gram-negative bacteria, with a notable rate of antimicrobial resistance. These findings are supported by other studies in the literature that also show a worse prognosis of SSTIs due to gram-negative bacteria, especially in the presence of antimicrobial resistance[16,40]. To that direction, implementation of a local protocol concerning antibiotic administration based on local antimicrobial resistance rates can reduce the consequences of inappropriate antibiotic use, such as antimicrobial resistance, thus reducing the possibility of selecting inappropriate empiric therapy in patients with SSTIs or other infections[16].

Our study has several limitations that we acknowledge. Firstly, its retrospective design may have led to an underestimation of the precise number of SSTIs. Furthermore, despite the fact that our institution is a referral center for South Greece, post-discharge visits to other healthcare institutions may have been missed, and there-

Table 3: Comparison of characteristics between patients who survived and patients who died during hospitalization for skin and soft tissue infections.

Patient Characteristics	Survivors (n =298)	Non-survivors (n =19)	p
Mean age (years, SD)	76 (15.7)	86 (9.9)	0.0027
Male (n, %)	132 (44.3)	5 (26.3)	0.16
Median Charlson Index (IQR)	6 (4-8)	7 (6-9)	0.04
Non-traumatic skin lesion* predisposing to an SSTI adjacent to the infection site (n, %)	68 (22.8)	9 (47.4)	0.025
Diabetic foot (n, %)	23 (7.7)	7 (36.8)	<0.001
Trauma (within 4 weeks) predisposing to an SSTI (n, %)	43 (14.4)	0 (0.0)	0.09
Previous SSTI (within the last 3 months) (n, %)	53 (17.8)	3 (15.8)	1.00
Systemic symptoms (≥ 2 SIRS criteria) (n, %)	219 (73.5)	19 (100)	0.0052
Positive Culture [n, % of all cases (n =317)]	68 (22.8)	6 (31.6)	0.40
Gram-negative (n, % of all pathogens)	83/158 (52.5)	11/14 (78.6)	0.09
Gram-positive (n, % of all pathogens)	63/158 (39.9)	2/14 (14.3)	0.08
Fungi (n, % of all pathogens)	12/158 (7.6)	1/14 (7.1)	1.00
Polymicrobial culture (n, %)	35 (51.5)	4 (66.7)	0.68
Median length of hospitalization (days, IQR)	7 (5-12)	8 (5-13)	0.23

n: Number, SD: standard deviation, IQR: interquartile range, *: Non-traumatic skin lesion implies a skin lesion unrelated to recent trauma, such as skin ulceration, burn and animal bite, SIRS: systemic inflammatory response syndrome, SSTI: Skin and soft tissue infection.

fore the readmission rate may have been underestimated. As far as the microbiology of SSTIs, the limited number of isolated pathogens does not allow for accurate comparisons between survivors and non-survivors. Additionally, our patient population mainly consists of elderly individuals with a high comorbidity rate and rates of previous hospitalization and antibiotic exposure. This could have contributed to the different microbiology of the SSTIs, thus, making the extrapolation of our results for the general population difficult. Finally, even though we only included patients with a clinical diagnosis of SSTI, some isolates may have been colonizers and not true pathogens. Nevertheless, compatibility with a clinical syndrome and the fact that the vast majority were gram-negative bacteria, which are not common skin colonizers, significantly eliminates this possibility.

In conclusion, the present study provides a comprehensive description of patients admitted with SSTI and denotes the importance of gram-negative bacteria as emerging causative agents affecting mortality. In addition, the observed high resistance rates support that SSTI treatment should be based on antimicrobial treatment protocols, derived from local epidemiology. Future studies should focus on risk factors and outcomes of SSTIs by gram-negative bacteria.

Conflict of interest

Authors declare no conflict of interest.

Acknowledgement

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