Université Nice Sophia Antipolis

Faculté de Médecine

THESE D'EXERCICE DE MEDECINE

Pour le

DIPLÔME DU DOCTORAT EN MEDECINE

ETUDE D'IMPACT D'UN PROTOCOLE D'ANTIBIOTHERAPIE DANS LES INFECTIONS CUTANEES COMMUNAUTAIRES

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Par

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Résumé synthétique du travail :

En dehors des zones de prévalence du Staphylocoque doré résistant à la méthicilline dans la communauté, il n'y a à notre connaissance aucun travail ayant étudié le lien entre le traitement antibiotique des érysipèles ou des cellulites, et l'évolution clinique des patients. L'objectif de cette étude était donc de mesurer l'impact d'un protocole interne d'antibiothérapie sur la morbi-mortalité.

Cette étude était basée sur le tableau de bord du service des maladies infectieuses du CHU de Nice. Il s'agit d'une base de données enregistrant 28 paramètres pour tous les patients hospitalisés dans le service. Nous avons inclus les patients admis pour érysipèle ou cellulite d'origine communautaire ; les critères d'exclusion étaient les infections nécrotiques ou abcédées d'emblée ; les cellulites à porte d'entrée ORL ou dentaire ; les infections consécutives aux morsures animales ; les pyomyosites ; et les durées de séjour inférieures ou égales à deux jours (considérant qu'il s'agissait d'une erreur d'orientation ou d'une hospitalisation injustifiée). Le respect du protocole, basé sur les recommandations nationales, a été défini par l'utilisation de l'amoxicilline, de l'amoxicilline-acide clavulanique, de la clindamycine, ou de la pristinamycine, en monothérapie ou en association ou successivement. Une évolution défavorable était définie par la nécessité de recours à la chirurgie (par exemple : drainage d'abcès, amputation, excision de nécrose) de transfert en réanimation ou la mortalité, survenant après cinq jours ou plus d'antibiothérapie.

De juillet 2005 à juin 2017, 630 cas d'érysipèle ou de cellulite ont été inclus. Les hémocultures effectuées chez 567 patients (90 %) étaient positives dans 39 cas (6,9 %), dont 33 à Streptocoques. Le taux d'antibiothérapies adhérentes au protocole était de 65 % (410 cas). Une évolution défavorable a été enregistrée chez 54 patients (8,5 %), moins fréquemment en cas de conformité au protocole : 26/410 (6,3%) vs 28/220 (12,7%), p = 0,007. En analyse multivariée, deux facteurs de risque étaient associés à une évolution défavorable : l'artériopathie oblitérante des membres inférieurs, AOR 4,80 (2,20-10,49) et la bactériémie, AOR 5,21 (2,31-11,76), tandis que le respect du protocole était le seul facteur protecteur modifiable, OR 0,48 (0,26-0,89).

En conclusion, dans les érysipèles et cellulites communautaires non abcédées et non nécrosantes, le respect du protocole était associé à un risque plus faible d'évolution défavorable. L'utilisation de l'amoxicilline-acide clavulanique semble être un choix sûr dans ces infections en cas d'incertitude sur l'étiologie streptococcique.

Adherence to antibiotic guidelines for erysipelas or cellulitis is associated with a favourable outcome

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Abstract

Purpose

Outside areas of *S. aureus* strains resistant to methicillin (MRSA) in the community, no studies showed a relationship between the treatment for erysipelas or cellulitis and the outcome. We aimed to measure the impact of an internal therapeutic protocol, based on national guidelines on patients' outcome.

Methods

This study was based on the dashboard of the infectious diseases department, which prospectively includes 28 parameters for all admitted patients. We included community acquired erysipelas and cellulitis; exclusion criteria were abscesses at admission, ear nose throat or dental cellulitis, pyomyositis and length of stay ≤ 2 days. Adherence to guidelines was defined by the use of amoxicillin, amoxicillin/clavulanic acid, clindamycin or pristinamycin, alone or in combination or successively. A poor outcome was defined by surgical procedure or intensive care requirement or death occurring after 5 days or more of antibiotic therapy.

Results

From July 2005 to June 2017, 630 cases of erysipelas or cellulitis were included. Blood cultures performed in 567 patients (90%) were positive in 39 cases (6.9%). Adherence rate to guidelines was 65% (410 cases). A poor outcome was recorded in 54 (8.5%) patients, less frequently in case of adherence to guidelines: 26/410 (6.3%) *vs* 28/220 (12.7%), p = 0.007. In logistic regression analysis, 2 risk factors were associated with a poor outcome: peripheral arterial disease: AOR 4.80 [2.20 – 10.49] and bacteraemia: AOR 5.21 [2.31 - 11.76], while guideline adherence was the only modifiable protective factor: OR 0.48 [0.26 - 0.89].

Conclusion

In erysipelas and cellulitis, adherence to guidelines was associated with a favourable outcome.

Keywords: erysipelas; cellulitis; SSTI; antibiotic therapy; guidelines; outcome

Erysipelas and cellulitis are frequent cutaneous skin and soft tissue infections (SSTI) that lead to hospitalizations due to the disease and/or patients' comorbid conditions [1,2]. Thus, several guidelines have been published worldwide to help the clinicians with antibiotic prescription. The French guidelines published in 2000 [1] focusing on erysipelas and necrotizing fasciitis highlighted the main role of *Streptococcus pyogenes* and indicated a short selection of antibiotic treatments to be used in these infections. Amoxicillin is recommended for erysipelas, plus clindamycin or rifampicin in case of necrotizing fasciitis, amoxicillin + clavulanic acid in case of IV drug use and finally pristinamycin in case of penicillin allergy. These recommendations are based on microbial and clinical data.

Since 2000, there was no significant change in microbial epidemiology in erysipelas and cellulitis in France, which differs from the United States of America [2,3,4]. More particularly, we do not observe the emergence of *S. aureus* strains resistant to methicillin (MRSA) in the community in France, in contrast with its high prevalence in US.

More than fifteen years after the French guideline publication, few studies have reported the antibiotic use in erysipelas and cellulitis [2,5-9]. Moreover, as far as we know, there is no study assessing the impact of this guidelines on morbidity and mortality of patients presenting with erysipelas or cellulitis. The aim was to study the relationship between physicians' adherence to an hospital-based antibiotic protocol, according to the French guideline for erysipelas and cellulitis, and patients' outcome.

Methods

Patient selection and data collection

We conducted a cohort study at the University Hospital of Nice, France, a tertiary care centre with a single infectious diseases department. This study was based on data collected through the department's medical dashboard put into practice since July 2005 [10]. This dashboard works as a large database for observational studies. It is declared to the French Data Protection Authority, number 1430722.

It prospectively records 28 parameters for all hospitalized patients, including initial and final diagnosis, comorbid conditions, microbiological data, antibiotic therapy, adverse effects and outcome. Comorbid conditions were defined by their specific treatment at admission or newly diagnosed during hospital stay.

We selected all cases of community-acquired erysipelas or cellulitis from the 1st of July 2005 to the 30th of June 2017, healthcare-associated infections being defined a diagnosis established ≥ 48 h after hospital admission or when observed less than one month after surgery and less than one year in case of surgical device implantation.

For this study we have specifically verified in the patient's chart the accuracy of the blood culture's results and community-acquired characteristics of the infection when the bacteria were reputed for its nosocomial features such as antimicrobial-resistant *Enterobacteriaceae* or *Pseudomonas aeruginosa*.

We excluded patients with abscess or necrosis or pyomyositis requiring a surgical approach at admission or in the first 5 days in hospital, considering that those complications requiring surgical procedure were already present at admission. Also, infections following animal bite, ear nose throat (ENT) or dental origin were excluded. Lastly, patients with length of stay ≤ 2 days were excluded considering that hospitalization in the infectious diseases department was unnecessary or inappropriate.

Protocol adherence

In the infectious diseases department, the internal protocol for erysipelas and cellulitis was defined in April 2009. It was based on the French national guidelines published in year 2000. Those official guidelines have not been changed or revised since then. We proposed to use amoxicillin alone in case of non-necrotizing infections. In case of penicillin allergy, we proposed to use pristinamycin alone. This choice was based on microbial data highlighting the main prevalence of *S. pyogenes* in those infections. In case of IV drug use or traumatic wound, we proposed to use amoxicillin + clavulanic acid in aim to cover Methicillin-Sensible

Staphylococcus aureus (MSSA). Lastly, in case of severe case or suspicion of necrotizing form of infections, clindamycin was recommended in combination with other molecules. This choice was based on data suggesting the benefit of clindamycin to inhibit the harmful effect of bacterial toxins [11].

Protocol adherence was defined by the use of amoxicillin, amoxicillin/clavulanic acid, clindamycin or pristinamycin, alone or in a combination or successively.

Poor outcome was a composite criterion, defined by the need of surgical procedure and/or transfer to intensive care unit (ICU) and/or death at least after 5 days of antibiotic treatment. This outcome was recorded at any moment of the hospitalization until discharge.

Statistical analysis

The data were analysed with Statview® software version 5.0 and statistical significance was established at $\alpha = 0.05$. We used Mann–Whitney non-parametric test, and the $\chi 2$ or Fisher's exact test, when appropriate. Logistic regression was used for multivariate analysis of the impact of guideline adherence on all causes of unfavourable outcome, and results are presented as adjusted odds ratios (AORs) with their 95% confidence intervals (CIs).

Variables were selected as candidates in multivariate analysis on the basis of the level of significance of the univariate association with unfavourable outcome ($p \leq 0.1$).

Results

Epidemiology of erysipelas and cellulitis

From July 2005 to June 2017, 514 cases of erysipelas and 116 cases of cellulitis were included in the study according to successive selection criteria (see Figure 1-A). The most frequent comorbid conditions were diabetes (95 cases, 15%), liver diseases (72 cases, 11%) and venous insufficiency (72 cases, 11%). The patients with erysipelas were older ($p < 0.001$) and presented more frequently with venous insufficiency ($p = 0.043$) compared to patients with cellulitis. The clinical presentation was also different, erysipelas being more often localized on inferior limbs than cellulitis, 86% *vs* 57%, $p < 0.001$.

Microbiological data

Blood cultures were performed in 567 patients (90%), and 39 were positive (7%), including 33 cases of streptococci (85%), 3 cases of *Enterobacteriaceae* (8%), 2 cases of *Pseudomonas* (5%), and only one *Staphylococcus aureus* (3%). There was no significant difference between both groups. No other germs were isolated in bacteraemic patients. The only case of *S. aureus* was susceptible to methicillin. Both cases of *P. aeruginosa* were susceptible to Cefepime and Meropenem, one was susceptible to Tazocillin and the other was intermediate. Concerning the 3 recorded cases of *Enterobacteriaceae*, there was no case of ESBL production or cephalosporinase hyper production.

Therapeutic means

The two most used antibiotics were amoxicillin alone (271 cases, 43%) and amoxicillin/clavulanic acid (71 cases, 11%). Protocol adherence was recorded in 410 (65%) cases, being higher in erysipelas compared to cellulitis: 73% *vs* 29%, p <0.001. Antibiotic therapies differing from the protocol (n = 220, 35%) were assessed through the patient's chart analysis and were explained in 66/220 cases (30%). Microbial data were the main source of deviation from the protocol: 27/66 cases (41%), especially in case of cellulitis.

Outcome and impact of adherence to antibiotic protocol

Unfavourable outcome was less frequently observed in erysipelas compared to cellulitis: 37 (7%), *vs* 17 (15%), p = 0.01. Surgery procedure requirement was significantly more frequent in case of non-adherent treatment: 12/410 (3%) *vs* 19/220 (9%); p = 0.002. Surgical procedures included drainage (n = 12), necrosis excisions (n = 8), amputation (n = 5), angioplasty (n = 3), skin graft (n = 2) or arthroscopic lavage (n = 1).

We also observed a trend towards more ICU requirements and ultimately deaths in case of non-adherent treatment (see Table 1). Thus, according to the study's definition, an unfavourable outcome was observed in 54 (8.5%) patients, more frequently in case of non-adherent treatment: 28/220 (13%) *vs* 26/410 (6%), p = 0.007.

In multivariate analysis (see Table 2), the 2 risk factors associated with unfavourable outcome were peripheral arterial disease (AOR 4.80 [2.20 – 10.49]) and bacteraemia (AOR 5.21 [2.31 - 11.76]). Protocol adherence was protective of unfavourable outcome: OR 0.48 [0.26 - 0.89], p = 0.007.

Discussion

This cohort study over 12 years shows a better outcome for adult patients admitted for erysipelas or cellulitis when adherence to antibiotic protocol was observed. The risk of poor outcome was almost doubled in case of non-adherent treatment. This composite criterion seems to be appropriate as it reflects severe complications in erysipelas and cellulitis. The univariate analysis indicated that surgical requirement was the main element of poor outcome. Besides, other results indicated that peripheral arterial disease as well as bacteraemia were associated with a poorer outcome.

This study has several limitations. The main one is that we were unable investigate the exact reasons for non-adherent prescriptions. Extensive analysis of the patient's chart revealed that only one third of non-adherent prescriptions 66/220 (30%) were explained by physician. Moreover, the dashboard does not assess the initial severity of the infection, which may explain the discrepancies between guidelines and senior physicians' prescriptions. However, the data suggest that, except the microbiological reassessment of the empirical antimicrobial treatment, there is no benefit to deviate from guidelines. Also, the database did not record antibiotic therapies received prior hospital admission. However, in France most of erysipelas and cellulitis receive the first course of antibiotic in hospital [2]. Another limit is the inclusion of both erysipelas and cellulitis, those are two clinical entities have several differences in pathophysiology, and causal bacteria. However, this study and others indicated no significant difference in term of causal bacteria [12]. Also, current classification includes these 2 entities under the same terminology "non-necrotizing acute bacterial skin and structure infections" [13].

In the infectious diseases department, the global adherence to the protocol was 65%, being higher in erysipelas (73%). Pulido-Cejudo *et al* underlined on the heterogeneity in skin and soft tissue infection management as well as the high frequency of inappropriate antibiotic therapy, > 20% of the cases [13]. Thus, the high incidence of erysipelas and cellulitis suggests that a better use of antibiotics in skin and soft tissue infections may have a favourable ecological impact.

Very few studies aimed to assess the relationship between recommended antibiotic therapy and outcome. Inappropriate antibiotic therapy for skin and soft tissue infections has been associated at least with prolonged duration of hospitalisation stay and more surgical requirement [13,14]. Yet, Figtree *et al* reported a retrospective analysis of 395 episodes of cellulitis and erysipelas with a mortality rate of 2.5%, in which bacteraemia was also associated with a fatal outcome [15]. However, the authors did not study the impact of the antibiotic treatment on the outcome, even if infectious disease physician input was associated with more frequent use of a first-generation cephalosporin empirically and less frequently the combination of penicillin and flucloxacillin. Also, in that study, a surgical procedure was required in 87 cases (22%), which is far more than what we observed: the difference might be due to the exclusion criteria, considering surgical procedure requirement before 5 days of antibiotic therapy as the reflect of undetected abscess, collection or necrosis at admission. These exclusion criteria may appear in contradiction with recent positions suggesting that the antibiotic efficiency should be evaluated 48-72 h after initiation of therapy [3,16]. But the way to optimize the management of clinical failure is not acutely determined.

In multivariate analysis, peripheral arterial disease was associated with a poor outcome as previously reported [15,13]. As an explanation, peripheral arterial disease leads to poor antibiotic delivery in infected tissue and/or necrosis [17].

Bacteraemia, searched in 90% of the patients, was observed in 7% in this study. Its relationship with poor outcome was observed in several situations such as respiratory or bone

infections [18, 19]. These data argue for systematic microbial investigations including blood cultures. Bacterial results, at least from blood cultures, demonstrate the major implication of streptococci, validating the appropriateness of the current French antibiotic guideline, and extensively of the internal protocol. Of note, in this study no MRSA was detected, indicating the need for national bacteriological survey to establish recommendations. Accordingly, current antibiotic guideline is adequate in community-acquired erysipelas and cellulitis in which *Streptococcus spp* are still predominant. At least in France, amoxicillin + clavulanic acid seems to be a safe choice in case of doubts between these 2 clinical entities.

Compliance with ethical standards

Funding: none

Conflict of Interest: All of the authors declare that they have no conflicts of interest. Ethics approval: Observational studies don't require ethical approval in France. Antimicrobial stewardship is promoted by the French National Health Agency. Internal dashboard is declared to French Data Protection Authority, number 1430722. Informed consent: patients or their relatives provided their written consent for digitization of their personal data for hospitalization purposes.

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Figure 1-A: Flow chart

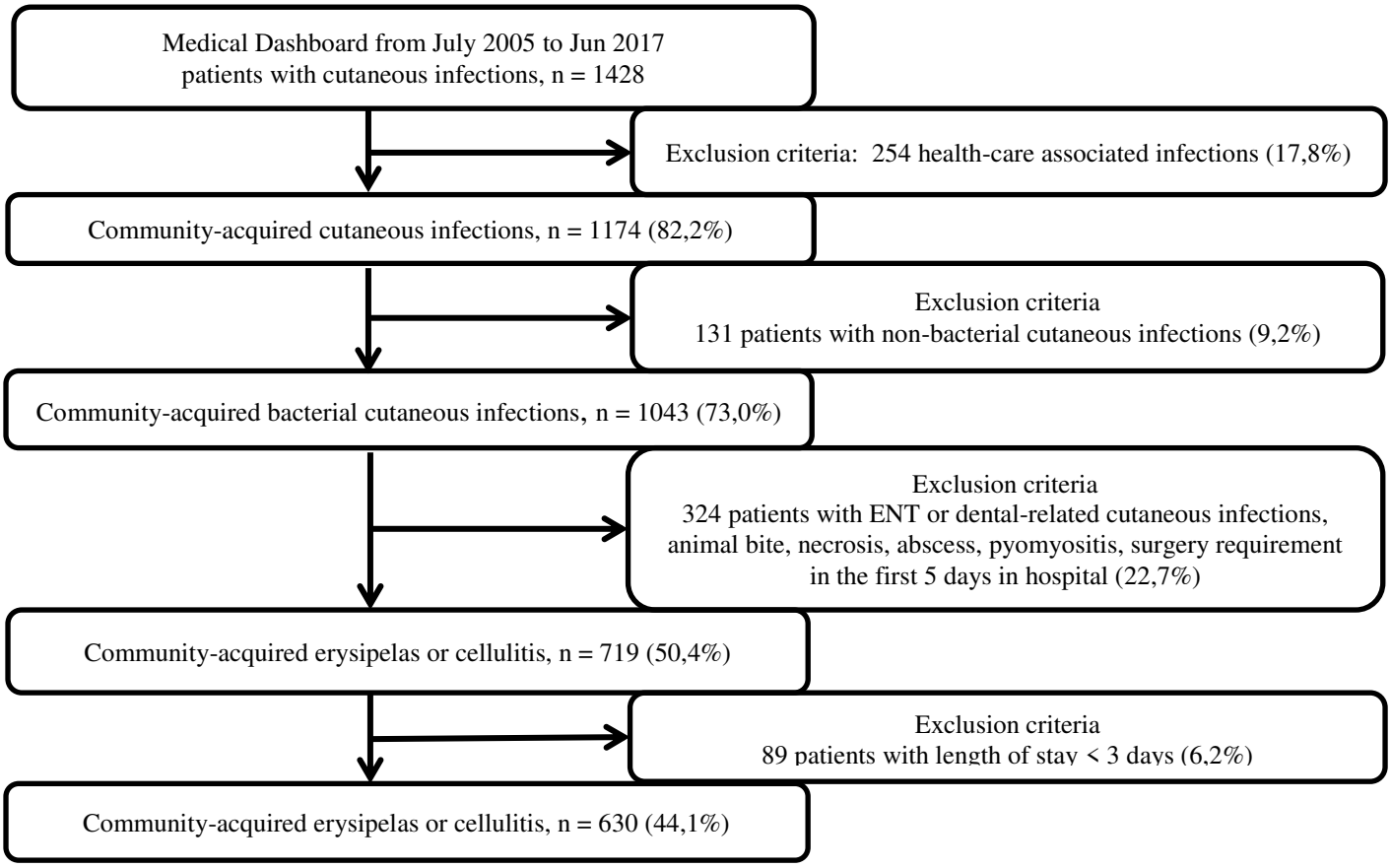


Figure 1-B: Patients with poor outcome

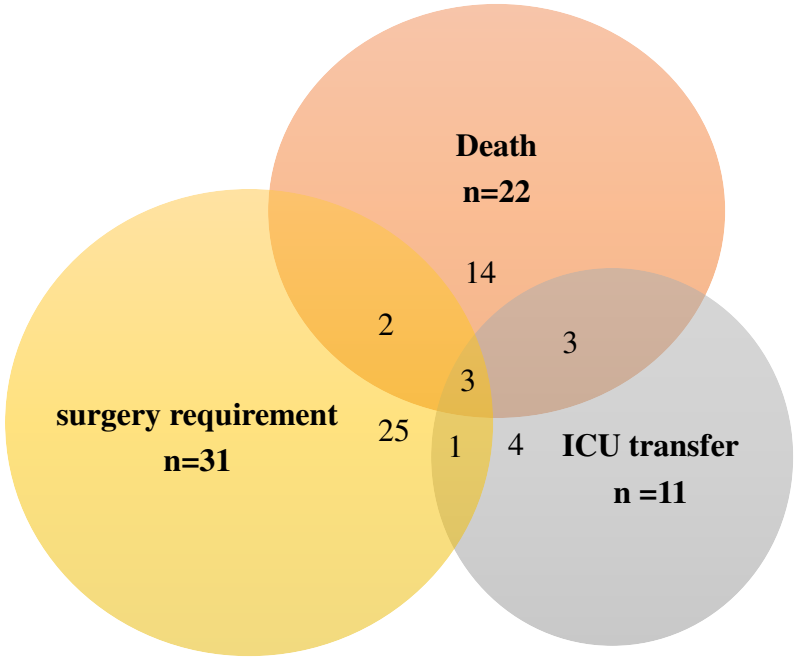


Table 1: Main characteristics of the patients according to the guideline's adherence.

	Adherence n = 410 (65%)	**Non-adherence n = 220 (35%)**	**p**
Age (years ± standard deviation)	66±18	58±20	<0.001
Sex-ratio (M/F)	1.39	2.16	0.013
Final diagnosis			
Erysipelas	375 (92)	139 (63)	<0.001
Cellulitis	34 (8)	82 (37)	<0.001
Comorbidities			
Liver disease	40 (10)	32 (14)	0.077
Alcoholism	40 (10)	27 (12)	0.344
Diabetes	61 (15)	34 (15)	0.875
Venous insufficiency	46 (11)	26 (12)	0.845
Active cancer	34 (8)	18 (8)	0.942
Peripheral arterial disease	25 (6)	20 (9)	0.172
IV drug use	18 (4)	27 (12)	<0.001
Penicillin Allergy	8 (2)	11 (5)	0.034
Infection site			
Lower limb	348 (85)	159 (72)	<0.001
Upper limb	41 (10)	30 (14)	0.179
head	13 (3)	21 (10)	<0.001
others	7 (2)	11 (5)	0.019
Microbiological data			
Blood cultures performed	367 (89)	200 (91)	0.577
Bacteremia, n= 39 (6.2%)	27 (6.5)	12 (6)	0.541
Streptococci, n = 33	27 (6.5)	6 (3)	<0.001
Staphylococcus aureus, n = 1	0	1	
Others, n = 5	0	5	
Antibiotic prescription			
amoxicillin alone	271 (66)	0	<0.001
amoxicillin + clindamycin	18 (4)	3 (1)	0.072
clindamycin alone	6 (1)	7 (3)	0.152
pristinamycin alone	24 (6)	0	<0.001
amoxicillin + clavulanic acid	55 (13)	15 (7)	0.011
other first line antibiotics	59 (14)	205 (93)	<0.001
≥ 2 successive antibiotics	33 (8)	131 (59)	<0.001
Reasons for non-adherent treatment			
- microbial data	na*	27 (41)	
- comorbidities/medical file	na	14 (21)	
- associated diagnosis	na	17 (26)	
- treatment failure	na	8 (12)	
Length of stay (days ± std dev)	**7.4±5.4**	**10±6.2**	**<0.001**
Poor outcome	**26 (6)**	**28 (13)**	**0.007**
Death	12 (3)	10 (5)	0.299
Transfer to ICU	5 (1)	6 (3)	0.296
Surgery requirement	12 (3)	19 (9)	0.002

*na = none applicable

Table 2: Risk factors for a poor outcome. The latter was defined as surgery requirement (n = 31) and/or transfer to intensive care unit (n = 11) and/or death (n = 22).

	Favourable outcome n = 576 (91.4%)	**Poor outcome n = 54 (8.6%)**	**p**	**AOR**
Age (years ± standard deviation)	63±19	69±17	0.017	
Sex-ratio (M/F)	1.62	1.57	0.920	
Final diagnosis				
Erysipelas	477 (83)	37 (69)	0.010	
Cellulitis	99 (17)	17 (31)	"	
Comorbidities				
Liver disease	64 (11)	8 (15)	0.413	
Alcoholism	59 (10)	8 (15)	0.297	
Diabetes	82 (14)	13 (24)	0.053	
Venous insufficiency	65 (11)	7 (13)	0.711	
Active cancer	46 (8)	6 (11)	0.425	
Peripheral arterial disease	32 (6)	13 (24)	< 0.001	4.80 [2.20-10.49]
IV drug use	41 (7)	4 (7)	> 0.999	
Penicillin Allergy	18 (3)	1 (2)	0.915	
Infection site				
Lower limb	462 (80)	45 (83)	0.580	
Upper limb	67 (12)	4 (7)	0.475	
head	32 (5)	2 (4)	0.794	
others	15 (3)	3 (6)	0.414	
Microbial data				
Blood culture performed, n = 567 (90%)	518 (90)	49 (91)	0.849	
Bacteremia, n = 39	28 (5)	11 (22)	< 0.001	5.21 [2.31-11.76]
Streptococci, n = 33	27 (4.5)	6 (11)	0.005	
Staphylococcus aureus, n = 1	0	1		
Others, n = 5	1	4		
Adherence to protocol, n = 410 (65%)	384 (66)	26 (48)	0.007	0.48 [0.26-0.89]