European Journal of Clinical Microbiology & Infectious Diseases (2019) 38:703–709
https://doi.org/10.1007/s10096-019-03490-6

ORIGINAL ARTICLE

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

Camille Klotz[1] · Johan Courjon[1,2] · Céline Michelangeli[1] · Elisa Demonchy[1] · Raymond Ruimy[2,3] · Pierre-Marie Roger[1,2,4]

Received: 9 November 2018 / Accepted: 16 January 2019 / Published online: 26 January 2019

Abstract

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. 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. 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, two risk factors were associated with a poor outcome: peripheral arterial disease, AOR 4.80 (2.20–10.49); and bacteremia, AOR 5.21 (2.31–11.76), while guideline adherence was the only modifiable protective factor, OR 0.48 (0.26–0.89). In erysipelas and cellulitis, adherence to guidelines was associated with a favorable 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 USA [2–4]. 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 the USA.

More than 15 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 these guidelines on morbidity and mortality of patients presenting with erysipelas or cellulitis. The aim was to study the relationship between physicians' adherence to a hospital-based antibiotic protocol, according to

✉ Camille Klotz
klotzcamille@yahoo.fr

[1] Infectiologie, Hôpital de l'Archet, Centre Hospitalier Universitaire de Nice, Nice, France

[2] Faculté de Médecine, Université de Nice Sophia-Antipolis, Nice, France

[3] Bactériologie, Hôpital de l'Archet, Centre Hospitalier Universitaire de Nice, Nice, France

[4] Groupe Elsan, Rue de la Boétie, 75008 Paris, France

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 center 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 1 month after surgery and less than 1 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, and 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 the 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 analyzed with Statview® software version 5.0 and statistical significance was established at $\alpha = 0.05$. We used Mann–Whitney non-parametric test, and the χ^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 unfavorable 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 unfavorable 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 Fig. 1a). 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*

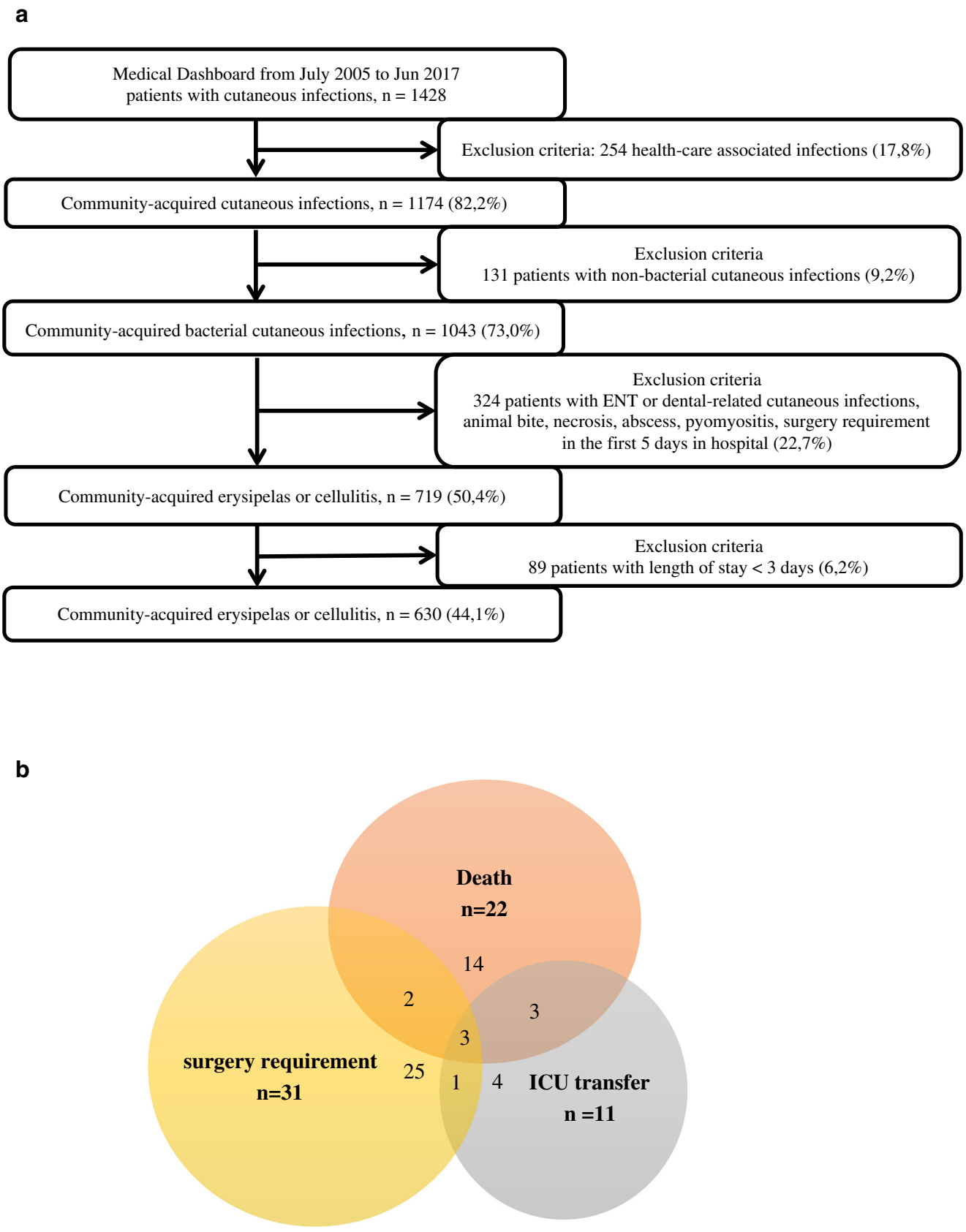

Fig. 1 **a** Flow chart. **b** Patients with poor outcome

(5%), and only one *Staphylococcus aureus* (3%). There was no significant difference between both groups. No other germs were isolated in bacteremic 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

Unfavorable 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 unfavorable 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 two risk factors associated with unfavorable outcome were peripheral arterial disease (AOR 4.80 [2.20–10.49]) and bacteremia (AOR 5.21 [2.31–11.76]). Protocol adherence was protective of unfavorable 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 and bacteremia 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 two 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 favorable 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 hospitalization 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 bacteremia 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

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

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

Table 2 Risk factors for a poor outcome

	Favorable 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]

The latter was defined as surgery requirement ($n = 31$) and/or transfer to intensive care unit ($n = 11$) and/or death ($n = 22$)

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 [13, 15]. As an explanation, peripheral arterial disease leads to poor antibiotic delivery in infected tissue and/or necrosis [17].

Bacteremia, 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 two clinical entities.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval Observational studies do not 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.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Erysipèle et fasciite nécrosante. Prise en charge. Conférence de consensus (2000) Med Mal Inf 30(Suppl 4):252–72
2. Bernard P, Christmann D, Morel M (2005) Management of erysipelas in French hospitals: a post-consensus conference study. Ann Dermatol Venereol 132:213–217
3. Food and Drug Administration (2013) Guidance for industry: acute bacterial skin and skin structure infections developing drugs for treatment. www.fda.gov/downloads/Drugs/Guidances/ucm071185.pdf. Accessed 24 August 2016
4. Sartelli M, Malangoni MA, May AK, Viale P, Kao LS, Catena F et al (2014) WSES guidelines for management of SSTI. World J Emerg Surg 9:57
5. Kamath RS, Sudhakar D, Gardner JG, Hemmige V, Safar H, Musher DM (2018) Guidelines vs actual management of skin and soft tissue infections in the emergency department. Open Forum Infect Dis 5(1):ofx188
6. Jenkins TC, Knepper BC, Moore SJ, O'Leary ST, Caldwell B, Saveli CC et al (2014) Antibiotic prescribing practices in a multicenter cohort of patients hospitalized for acute bacterial skin and skin structure infection. Infect Control Hosp Epidemiol 35(10):1241–1250
7. Lazzarini L, Conti E, Tositti G, Lalla F (2005) Erysipelas and cellulitis: clinical and microbiological spectrum in an Italian tertiary care hospital. J Inf Secur 51(5):383–389
8. Lipsky BB, Napolitano LM, Moran GJ, Vo L, Nicholson S, Kim M (2014) Inappropriate initial antibiotic treatment for complicated skin and soft tissue infections in hospitalized patients: incidence and associated factors. Diagn Microbiol Infect Dis 79(2):273–279
9. Walsh TL, Chan L, Konopka CI, Burkitt MJ, Moffa MA, Bremmer DN et al (2016) Appropriateness of antibiotic management of uncomplicated SSTIs in hospitalized adult patients. BMC Infect Dis 16(1):721
10. Roger PM, Demonchy E, Risso K, Courjon J, Leroux S, Leroux E et al (2017) Medical table: a major tool for antimicrobial stewardship policy. Med Mal Infect 47(5):311–318
11. Smieja M (1998) MD FRCPC DTM&H, Current indications for the use of clindamycin: a critical review. Can J Infect Dis 9(1):22–28
12. Gunderson CG, Martinello RA (2012) A systematic review of bacteraemia in cellulitis and erysipelas. J Inf Secur 64(2):148–155
13. Pulido-Cejudo A, Guzmán-Gutierrez M, Jalife-Montaño A, Ortiz-Covarrubias A, Martínez-Ordaz JL, Noyola-Villalobos HF et al (2017) Management of acute bacterial skin and skin structure infections with a focus on patients at high risk of treatment failure. Ther Adv Infect Dis 4(5):143–161
14. Halilovic J, Heintz BH, Brown J (2012) Risk factors for clinical failure in patients hospitalized with cellulitis and cutaneous abscess. J Inf Secur 65(2):128–134
15. Figtree M, Konecny P, Jennings Z, Goh C, Krilis SA, Miyakis S (2010) Risk stratification and outcome of cellulitis admitted to hospital. J Inf Secur 60(6):431–439
16. Corey GR, Stryjewski ME (2011) New rules for clinical trials of patients with acute bacterial skin and skin-structure infections: do not let the perfect be the enemy of the good. Clin Infect Dis 52(Suppl. 7):S469–S476
17. Joukhadar C, Klein N, Frossard M, Minar E, Stass H, Lackner E et al (2001) Angioplasty increases target site concentrations of ciprofloxacin in patients with peripheral arterial occlusive disease. Clin Pharmacol Ther 70(6):532–539
18. Roger PM, Cua E, Courjon J, Landraud L, Carles M, Bernard E (2014) The impact of bacteraemia on the outcome of bone infections. Med Mal Infect 44(8):380–386
19. Vazquez-Grande G, Kumar A (2015) Optimizing antimicrobial therapy of sepsis and septic shock: focus on antibiotic combination therapy. Semin Respir Crit Care Med 36(1):154–166