Incidence of bloodstream infections and predictive value of qualitative and quantitative skin cultures of patients with overlap syndrome or toxic epidermal necrolysis: A retrospective observational cohort study of 98 cases

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Background: Epidermal necrolysis (EN) involving ≥10% of the body surface area (BSA) is often complicated by bacterial infections.

Objective: We sought to describe the epidemiology of bloodstream infections (BSIs) in EN involving a BSA ≥10% and the diagnostic performances of skin cultures for predicting the pathogen(s) isolated from BSIs.

Methods: This retrospective single-center observational study was conducted between 2009 and 2017. All patients referred at the acute phase for EN involving a BSA ≥10% were included. All clinical and bacteriologically relevant data were collected (blood and skin cultures results, number, and severity and time of BSI). Sensitivity, specificity, and predictive values of skin cultures and impact of the bacterial inoculum were investigated.

Results: Of 98 patients, 46 (46.9%) had ≥1 BSI episode during the hospital stay (BSIs were caused by *Staphylococcus aureus* [n = 17, 36.9%] and *Pseudomonas aeruginosa* [n = 17, 36.9%]). Skin cultures were concordant with blood cultures in 32 cases (71.1%). The positive and negative predictive values were 57.7% and 89.4% for *S aureus* and 50.0% and 80.9% for *P aeruginosa*, respectively. BSI increased with cutaneous inoculum of *S aureus*.

Limitations: This was a retrospective single-center design with a low total number of BSIs.

Conclusion: Skin cultures for *S aureus* and *P aeruginosa* may help predict the pathogens involved in BSIs. (J Am Acad Dermatol 2019;81:342-7.)

Key words: blood culture; bloodstream infection; epidermal necrolysis; Lyell syndrome; SJS-TEN overlap syndrome; skin culture.

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INTRODUCTION

Epidermal necrolysis (EN) is a life-threatening condition that is primarily caused by drugs. According to the percentage of body surface area (BSA) involved, patients are diagnosed with Stevens–Johnson syndrome (SJS, <10% BSA), SJS–toxic epidermal necrolysis (TEN) overlap (10-29% BSA), or TEN, also known as Lyell syndrome (≥30% BSA).[1] Mortality ranges from 10% to 40%.[2] The cornerstone of treatment is supportive care.[3]

Causes of mortality in EN include specific lung involvement[4] and invasive bacterial infections, the most frequent and life-threatening being bloodstream infections (BSIs). A relationship between BSIs and skin bacterial colonization was described in burns,[5,6] but data from EN remain scarce. We investigated the epidemiology of BSI in EN and assessed the ability of the qualitative and quantitative results of skin cultures to predict the pathogen(s) involved in BSI episodes.

CAPSULE SUMMARY

- Bloodstream infections are a frequent complication of epidermal necrolysis.
- Of 98 patients, 46 (46.9%) had bloodstream infections caused by *Staphylococcus aureus* (n = 17, 36.9%) and *Pseudomonas aeruginosa* (n = 17, 36.9%). Negative predictive values of skin cultures were 89.4% for *S aureus* and 80.9% for *P aeruginosa*.
- Skin cultures may help predicting the pathogens involved in bloodstream infections.

METHODS

This retrospective, single-center observational study included all patients admitted to the French reference center for EN between January 2009 and December 2017. Only patients with a final diagnosis of SJS-TEN overlap syndrome or TEN were included because BSIs are rare in SJS.[7] The diagnosis of EN was confirmed by previously published clinical criteria of EN and the histologic analysis of biopsy specimens.[2,8]

The following demographic, clinical, and biologic data were collected from medical files: age, gender, suspected drug, score of toxic epidermal necrosis,[9] baseline and maximal detached/detachable BSA, intensive care unit admission, cyclosporin treatment, antibiotics before and during hospitalization, time to reepithelialization, length of hospital stay, number of BSI episodes, septic shock, and hospital death.

According to French guidelines, routine management of wound care included skin antisepsis, consisting in the application of diluted chlorhexidine (bathing or spraying) once a day, without local antibiotics, and nonsticky dressings or white petroleum jelly. Prophylactic antibiotics were not recommended. Systemic antibiotics were prescribed in case of documented invasive infection or sepsis/septic shock.[3]

In our routine practice, skin colonization is investigated by repeated skin cultures performed every 3 days from admission to complete epithelialization, as recommended by French guidelines.[3] Skin cultures consist in applying sterile gauzes directly on the skin, on several places (usually 3) chosen among the most detached/severely injured areas, and then to put those gauzes on dedicated agar plates, which are subsequently incubated at 37°C. French guidelines also recommend daily blood cultures for all patients.

Only the first BSI episode, as defined by 1 (monomicrobial bacteremia) or >1 (polymicrobial bacteremia) pathogen(s) isolated from blood cultures, was considered for bacteriologic analysis. Strains of the first 3 skin cultures collected from admission to reepithelialization for several sites of detached skin were collected: *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, and exogenous enterobacteria (ie, non–*E coli* enterobacteria). Three semiquantitative classes of inoculum were defined: <100 (<10^2) colony-forming units (CFU)/cm^2, 101 to 10,000 (10^2-10^4) CFU/cm^2, and >10,000 (>10^4) CFU/cm^2. For patients with BSI, we investigated the results of the concomitant skin culture (ie, that performed at any time around the time of sampling the first positive blood culture, between 48 hours before and within 24 hours after). We considered that skin and blood cultures were concordant when the bacteria isolated in the BSI was also isolated in the corresponding skin culture (for monomicrobial BSI), or if ≥1 of the bacteria of the BSI was isolated in the corresponding skin culture (for polymicrobial BSI). Results are reported as percentages and medians (interquartiles [IQRs] 25-75%). The diagnostic performance of the concomitant skin culture for predicting the pathogen involved in the BSI was assessed by computing the sensitivity, the specificity, and the positive predictive value and negative predictive value of its qualitative results (presence or absence of the bacterium) for each pathogen involved. The odds ratios (ORs) and their 95% confidence intervals (CIs) of skin cultures growing *S aureus* and *P aeruginosa* for BSI episodes involving these pathogens were computed. The

Abbreviations used:

BSI: bloodstream infection
BSA: body surface area
CFU: colony-forming unit
EN: epidermal necrolysis
SJS: Stevens–Johnson syndrome
TEN: toxic epidermal necrolysis

impact of the inoculum was also assessed by computing the OR of developing a BSI for each skin inoculum category, with sterile skin cultures being the reference. Categorical data were compared using Fisher or chi-squared tests, as appropriate. Continuous data were compared using unpaired Student or Mann-Whitney tests, as appropriate. Two-sided P values were computed, and $P < .05$ was considered statistically significant.

The study was approved by the Hôpital Henri Mondor Institutional Review Board.

RESULTS

Among 166 patients referred for EN, we excluded 66 patients with SJS and 2 with missing data. Ninety-eight patients (55 female) were included, with a median age of 49.5 years (IQR 31.1-67.9 years), 40 (40.8%) with SJS-TEN overlap syndrome and 58 (59.2%) with TEN (Table I). The disease was drug-induced in 82 of 98 (83.7%) cases. The culprit drugs were antibiotics in 32 cases (32.6%), antiepileptic drugs in 22 cases (22.4%) and allopurinol in 14 cases (14.3%). No culprit drug was identified in 16 cases (16.3%).

Forty-six (46.9%) patients experienced ≥1 episodes of BSI during their hospital stay (85 total episodes) after a median of 7 days (IQR 0.8-13.2 days) after admission, resulting in an incidence of 33.3 BSIs per 1000 days of hospitalization per patient (Table I). Septic shock occurred in 24 of 46 cases (52.2%). Twelve patients with BSIs (26%) and 9 without (17.3%; $P = .29$) died. BSIs occurred more frequently in patients with TEN (n = 38/58, 65.5%) than in those with SJS-TEN overlap syndrome (n = 8/40, 20.0%; $P < .01$). Patients who received cyclosporin did not have a significantly higher BSI rate than those who did not.

Bacteria isolated from the first positive blood cultures were as follows (11/46 [23.9%] BSIs were polymicrobial): *S aureus* (n = 17/46, 36.9%), *P aeruginosa* (n = 17/46, 36.9%), exogenous enterobacteria (n = 7/46, 15.2%), *E coli* (n = 1/46, 2.2%), and others (n = 15, 32.6%). The median time elapsed between hospital admission and the first BSI episode ranged from 4.5 days (IQR 0-9 days) for methicillin-sensitive *S aureus* to 10 days (IQR 3-18 days) for *P aeruginosa* ($P = .004$).

Ninety-six patients had 1 skin culture performed, 68 had 2 skin cultures performed, and 34 had ≥3 skin cultures performed. The 3 skin cultures were performed after a median of 1.0 days (IQR 0.0-3.9 days), 6.5 days (IQR 1.5-11.5 days), and 12.0 days (IQR 6.8-14.2 days) after admission. The main bacteria isolated from the first skin culture were *S aureus* (36/96, 38%) and exogenous enterobacteria (36/96, 38%), whereas exogenous enterobacteria (23/34, 68%) and *P aeruginosa* (27/34, 79%) were predominant in the third skin culture (Fig 1).

Bacteria isolated from the concomitant cutaneous samples were concordant with those responsible for BSI in 32 of 45 (71.1%) cases (the skin culture was missing for 1 patient). Among those 32 skin cultures, 24 (75.0%) were performed during the 48 hours preceding the BSI and 8 (25.0%) during the 24 hours after. The concordance rate was 70.6% (24/34) for monomicrobial BSI and 72.7% (8/11) for polymicrobial BSI. Among the 13 patients with discordant blood and skin culture results, 9 (69.2%) had a negative skin culture and a positive blood culture, and 4 (30.7%) had a positive skin culture that did not match with the positive blood culture.

The diagnostic performance of skin cultures for predicting BSI episodes was as follows: skin cultures growing *S aureus* had a sensitivity of 88.2%, a specificity of 60.7%, a positive predictive value of 57.7%, and a negative predictive value of 89.4% for predicting *S aureus* BSIs; for *P aeruginosa*, the diagnostic performance was 75.0%, 58.4%, 50.0%, and 80.9%, respectively. Patients having ≥1 skin culture growing *S aureus* had an OR (95% CI) of having a BSI episode involving the same pathogen of 17.0 (95% CI 2.0-146.9; $P = .002$); for those having ≥1 *P aeruginosa*–positive skin culture, the OR was 8 (95% CI 1.9-36.4; $P = .005$). Post hoc analyses of the OR of developing a BSI for increasing bacterial inocula suggested that the risk of *S aureus* BSI gradually increased with the inoculum of skin culture, while that of *P aeruginosa* did not (Fig 2).

Concerning antibiotic susceptibility at admission (skin culture 1), 8 of 96 patients (8.3%) were colonized by methicillin-resistant *S aureus* and 0 of 96 (0.0%) by ceftazidime-resistant *P aeruginosa*. Twelve days after admission (skin culture 3), these rates rose to 8 of 34 (23.5%, $P = .03$) and 5 of 34 (14.7%, $P < .01$), respectively. The 8 patients with methicillin-resistant *S aureus* isolated on the third skin culture were not the same patients as the 8 who had a methicillin-resistant *S aureus* isolated on the first skin culture.

Table I. Characteristics and comparison of patients with and without a bloodstream infection

Patient characteristics	All patients, n = 98	Patients with BSI, n = 46	Patients without BSI, n = 52	*P* value
Female, n (%)	55 (56)	21 (45.6)	34 (65.4)	.049
Median age, y (range)	49.5 (15-99)	54.5 (15-99)	47.5 (18-83)	.23
Median SCORTEN at baseline (range)	2 (0-5)	2 (1-5)	2 (0-5)	.001
Median BSA involved at baseline, % (range)	15 (0-95)	20 (0-80)	10 (0-95)	.008
Median maximal BSA involved, % (range)	30 (10-100)	60 (10-100)	25 (10-100)	<.0001
Median time to cutaneous reepithelialization, days (range)	5 (0-19)	7 (2-19)	5 (0-11)	.07
Treatment with cyclosporin, n (%)	57 (58.1)	26 (56.5)	31 (67.4)	.75
Median length of hospitalization, days (range)	20 (4-116)	28.5 (4-116)	15 (4-43)	.0001
Antibiotics before admission, n (%)	67 (68.4)	30 (65.2)	37 (71.2)	.53
Antibiotics during hospitalization, n (%)	81 (82.7)	45 (97.8)	36 (69.2)	.0001
Intensive care unit admission, n (%)	49 (50)	34 (73.9)	15 (28.8)	<.0001
Hospital death, n (%)	21 (20.4)	12 (26)	9 (17.3)	.29

BSA, Body surface area; *BSI*, bloodstream infection; *SCORTEN*, SCOre of Toxic Epidermal Necrosis.

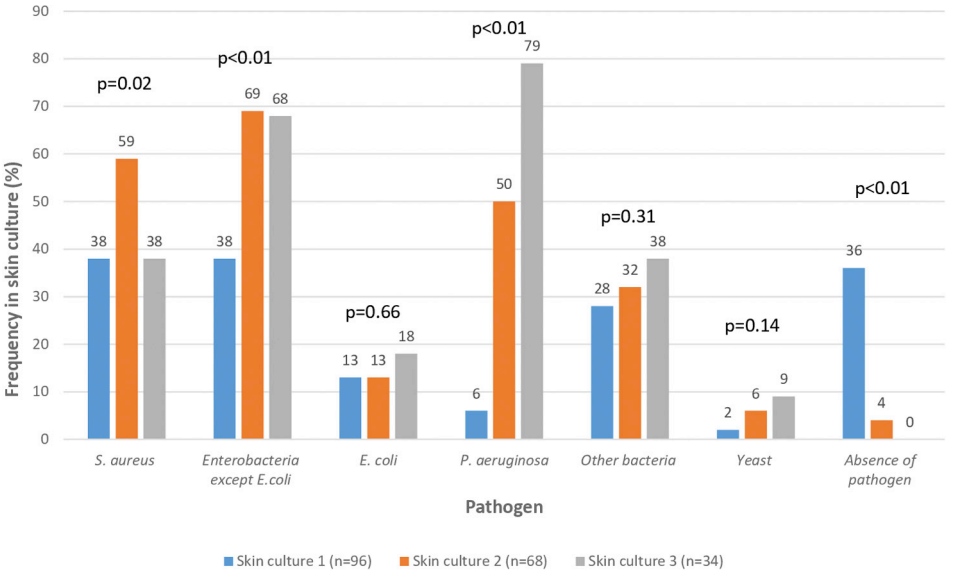

Fig 1. Percentage of skin cultures positive for the bacterial species of clinical interest. Percentages were compared for each bacterial species on skin cultures 1, 2, and 3 using the chi-squared test. $P < .05$ was considered statistically significant.

DISCUSSION

In the current series, we investigated the prevalence and characteristics of BSI episodes together with the performance of skin cultures in patients with SJS-TEN overlap syndrome and TEN. Our study adds important findings on the high frequency and severity of BSI in EN with >10% of BSA involved, especially in TEN. Our results also highlight the importance of monitoring the skin colonization by repeated skin cultures to target the bacteria most probably involved in BSI and adapt antibiotics accordingly, even before the positivity of blood cultures. We chose to focus our analysis on the first BSI episode typically occurring at the most acute phase of the disease, while the epidermis is not healed yet and therefore is more likely to be a direct consequence of skin detachment. Indeed, in these patients, multiple BSI episodes or other severe infections, such as pneumonias, can occur, even after healing, especially for the most severe cases that require intensive care unit admission and mechanical ventilation support.

We report on a high frequency of BSI in EN patients with a BSA >10% (46.9%) and highlighted the associated severity, illustrated by the occurrence of septic shock in nearly half of the cases. *S aureus* and *P aeruginosa* were the main bacteria responsible for BSI in EN, as previously reported.[7] Qualitative

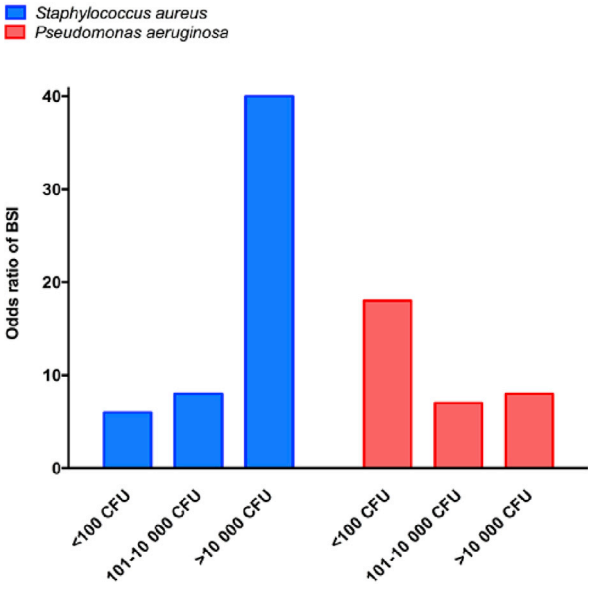

Fig 2. Odds ratio of developing *Staphylococcus aureus* and *Pseudomonas aeruginosa* bloodstream infections (BSIs) according to the inoculum of skin culture, expressed in colony-forming units (CFU) per cm^2. For *S aureus*, but not for *P aeruginosa*, odds ratios of BSIs increased with skin inoculum.

results of skin culture showed a good concordance with BSI (71.1%). The negative predictive value of the concomitant skin cultures were high for *S aureus* and *P aeruginosa*, showing that patients with negative skin cultures for these pathogens were unlikely to have a BSI involving these pathogens. We also showed the importance of monitoring skin cultures over time, as we observed a switch of skin colonization from Gram-positive cocci at baseline to Gram-negative bacilli during the hospital stay, as previously described for burn patients,[5-7,10] together with a significant decrease in the susceptibility patterns of the studied bacteria.

Our study added new data regarding the quantitative analysis of skin cultures. Indeed, skin colonization with *S aureus* or *P aeruginosa* was associated with a higher proportion of *S aureus* and *P aeruginosa* BSIs, respectively. In addition, for patients with *S aureus*–positive skin cultures, the OR of having a subsequent bacteremia increased with skin inoculum. Such dose-effect relationship was not observed with *P aeruginosa*, suggesting that different mechanisms might be involved. For *S aureus*, endogenous skin carriage is suggested, whereas for *P aeruginosa*, acquired skin colonization or digestive translocation because of specific involvement of EN is possible.[11,12] For other pathogens, such as *E coli* or other enterobacteria, digestive translocation is also suggested, as shown in patients with an altered digestive barrier, including those with burns.[13]

The strengths of our study, considering the rarity of EN, were the high number of patients included, the systematic process of repeated skin cultures as the standard of care, and the availability of complete qualitative and quantitative bacteriologic analyses. The main limitations include the retrospective and single-center design and the low number of BSI episodes, which limit definitive conclusions to be drawn. Skin cultures were sampled in routine practice on highly various anatomic sites according to the dermatologist's judgement. In addition, we did not collect all other microbiologic results, such as urine and catheter cultures. Finally, it can be argued that the skin cultures sampled after the first positive blood culture may be affected by antimicrobial treatment initiation. However, in the absence of any data, we hypothesized that the cutaneous colonization was only slightly impacted by parenteral antibiotics during the first 24 hours of their onset. Nevertheless, practices for skin care at the acute phase are heterogeneous according to centers, and a consensus is still needed for best topical antiseptic or antibiotic preventive treatments of skin colonization.[14]

According to French guidelines and our routine practice, we do not recommend initiating antibiotics on the sole basis of an isolated positive skin culture.[3] However, immediate and targeted antibiotics are mandatory for patients with EN as soon as invasive bacterial infection is suspected (ie, sepsis or septic shock). In that case, waiting for the complete results of BSI cultures and antibiograms (which can take ≤3 days), the choice of the antibiotics to be initiated should consider the susceptibility patterns of the bacteria carried by the patient, as shown by the results of the skin culture.

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