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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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Capsule summary

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

Abstract

Background: Epidermal necrolysis (EN) involving $\geq 10\%$ body surface area (BSA) is often complicated by bacterial infections.

Objective: To describe the epidemiology of bloodstream infections (BSIs) in EN involving a BSA $\geq 10\%$ 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 $\geq 10\%$ were included. All clinical and bacteriological relevant data were collected (blood and skin cultures results, number, severity and time of BSI). Sensitivity, specificity, and predictive values of skin cultures and impact of the bacterial inoculum were investigated.

Results: Out of 98 patients, 46 (46.9%) had ≥ 1 BSI episode during the hospital stay [*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: Retrospective monocentric design and few total number of BSI.

Conclusion: Skin cultures for *S. aureus* and *P. aeruginosa* may help in predicting the pathogens involved in bloodstream infections.

86 **Abbreviations and acronyms list:**

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88 BSI = bloodstream infection

89 BSA = body surface area

90 CFU = colony forming unit

91 EN = epidermal necrolysis

92 NPV = negative predictive value

93 OR = odds ratio

94 *P. aeruginosa* = *Pseudomonas aeruginosa*

95 PPV = positive predictive value

96 *S. aureus* = *Staphylococcus aureus*

97 SJS = Stevens-Johnson syndrome

98 TEN = toxic epidermal necrolysis

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Introduction:

Epidermal necrolysis (EN) is a life-threatening condition, mainly due to drugs. According to the body surface area (BSA) involved, patients are categorized as Stevens-Johnson syndrome (SJS, <10% BSA), SJS-TEN overlap (10-29% BSA), or toxic epidermal necrolysis (TEN, or Lyell syndrome, $\geq 30\%$ 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 involvement⁴ and invasive bacterial infections, the most frequent and life-threatening being bloodstream infections (BSI). A relationship between BSI and skin bacterial colonization was described in burns,^{5,6} but data from EN remain scarce. Here, we aimed to investigate the epidemiology of BSI in EN and assess the ability of the qualitative and quantitative results of skin cultures to predict the pathogen(s) involved in BSI episodes.

Materials and methods:

This retrospective single-center observational study included all patients admitted to the French reference center for EN between 01/2009 and 12/2017. Only patients with a final diagnosis of SJS-TEN overlap syndrome or TEN were included, as BSIs are rare in SJS.⁷ Diagnosis of EN was confirmed by previously published clinical criteria of EN and skin biopsy histological analysis.^{2,8}

The following demographic, clinical, and biological data were collected from medical files: age, gender, suspected drug, SCORTEN,⁹ baseline and maximal detached/detachable BSA, intensive care unit admission, cyclosporin treatment, antibiotics before and during hospitalization, time to re-epithelialization, length of hospital stay, number of BSI episodes, septic shock, and hospital death.

According to the 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 non-sticky 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 three days from admission to complete epithelialization, as recommended by the French guidelines.³ Skin cultures consist in applying sterile gauzes directly on the skin, on several places (usually three) 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 one (monomicrobial bacteremia) or more (polymicrobial bacteremia) pathogen(s) isolated from blood cultures, was considered for

bacteriological analysis. Strains of the first three skin cultures collected from admission to re-epithelialization for several sites of detached skin were collected: *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, and exogenous enterobacteria (*i.e.* non-*E. coli* enterobacteria). Three semi-quantitative classes of inoculum were defined: <100 ($<10^2$) colony-forming units (CFU)/cm², 101-10,000 (10^2 - 10^4) CFU/cm², and $>10,000$ ($>10^4$) CFU/cm². For patients with BSI, we investigated the results of the concomitant skin culture, *i.e.*, that performed at any time around the time of sampling the first positive blood culture, between 48h before and within the 24h 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 at least one of the bacteria of the BSI was isolated in the corresponding skin culture (for polymicrobial BSI).

Results are reported as percentages and medians (interquartiles [IQR] 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 (PPV) and negative (NPV) predictive values of its qualitative results (presence or absence of the bacterium) for each pathogen involved. The odds ratio (OR), and their 95% confidence interval, of skin cultures growing *S. aureus*, and *P. aeruginosa* for BSI episodes involving these pathogens were computed. The impact of the inoculum was also assessed by computing the OR of developing a BSI for each skin inoculum category, sterile skin cultures being the reference. Categorical data were compared using Fisher or chi-2 tests, as appropriate. Continuous data were compared using unpaired Student tests or Mann-Whitney tests, as appropriate. Two-sided p values were computed and $p<0.05$ was considered significant.

The study was approved by the Institutional Review Board Mondor (IRB00011558, 2018/09/20).

Results:

Among 166 patients referred for EN, we excluded 66 patients with SJS and two with missing data. Ninety-eight patients (55 female) were included, with a median age of 49.5 years (IQR 31.1-67.9), 40 (40.8%) with SJS-TEN overlap syndrome and 58 (59.2%) with TEN (Table 1). The disease was drug-induced in 82/98 (83.7%) cases. 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 one or more episodes of BSI during their hospital stay (total=85), after a median of seven days (IQR 0.8-13.2) following admission, resulting in an incidence of 33.3 BSI/1000 days of hospitalization/patient (Table 1). Septic shock occurred in 24/46 cases (52.2%). Twelve patients with BSI (26%) and nine without (17.3%, $p=0.29$) died. BSI occurred more frequently in patients with TEN ($n=38/58$, 65.5%) than in those with the SJS-TEN overlap syndrome ($n=8/40$, 20.0%; $p<0.01$). Patients who received cyclosporin did not show 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 (0-9) for methicilline-sensitive *S. aureus* to 10 days (3-18) for *P. aeruginosa* ($p=0.004$).

Ninety-six patients had one skin culture performed, 68 had two, and 34 had three or more. The three skin cultures were performed after a median of 1.0 (0.0-3.9), 6.5 (1.5-11.5), and 12.0 (6.8-14.2) days following 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 (Figure 1).

Bacteria isolated from the concomitant cutaneous samples were concordant with those responsible for BSI in 32/45 (71.1%) cases (skin culture missing for one 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 PPV of 57.7%, and an NPV 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 odds ratio (OR [95% confidence interval]) of having a BSI episode involving the same pathogen of 17.0 [2.0-146.9] ($p=0.002$); for those having ≥ 1 *P. aeruginosa*-positive skin culture the OR was 8 [1.9-36.4] ($p=0.005$). *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 (Figure 2).

Concerning antibiotic susceptibility at admission (skin culture 1), 8/96 patients (8.3%) were colonized by methicillin-resistant *S. aureus* and 0/96 (0.0%) by ceftazidime-resistant *P. aeruginosa*. Twelve days after admission (skin culture 3), these rates rose to 8/34 (23.5%, $p=0.03$) and 5/34 (14.7%, $p<0.01$), respectively. The 8 patients with methicillin-resistant *S.*

aureus isolated on the third skin culture were not the same patients than the 8 who had a methicillin-resistant *S. aureus* isolated on the first skin culture.

Discussion:

In the current series, we investigated the prevalence and characteristics of BSI episodes together with the performances 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 more than 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 thus 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 requiring 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 results of skin culture showed a good concordance with BSI (71.1%). The NPV of the concomitant skin cultures were high for *S. aureus* and *P. aeruginosa*, illustrating 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. Furthermore, for patients with *S. aureus*-positive skin cultures, the odds ratio of having a subsequent bacteremia increased with skin inoculum. Such dose-effect relationship was not observed with *P. aeruginosa*, suggesting different mechanisms might be involved. For *S. aureus*, endogenous skin carriage is suggested, whereas for *P. aeruginosa*, acquired skin colonization and/or digestive translocation due to 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

Strengths of our study, considering the rarity of EN, were the high number of patients included, the systematic process of repeated skin cultures as standard of care, and the availability of complete qualitative and quantitative bacteriological analyses. The main limitations include the retrospective and monocentric design and 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. Furthermore, we did not collect all other microbiological results, such as urine and catheter cultures. Last, it can be argued that the skin cultures sampled after the first positive blood culture may be affected by antimicrobial treatment initiation. However, in 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 EN patients, as soon as invasive bacterial infection is suspected (*i.e.*, sepsis, septic shock). In that case, waiting for the complete results of BSI cultures and antibiograms (that can last up to three 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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Legends of Figures:

Figure 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 Chi2 test. Differences with $p < 0.05$ were considered significant.

Figure 2:

Odds ratio of developing *S. aureus* and *P. aeruginosa* bloodstream infections (BSI) according to the inoculum of skin culture, expressed in colony-forming units (CFU)/cm².

For *S. aureus*, but not for *P. aeruginosa*, odds ratios of BSIs increased with skin inoculum.

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366 **Table 1:** Characteristics and comparison of patients with and without a bloodstream infection.

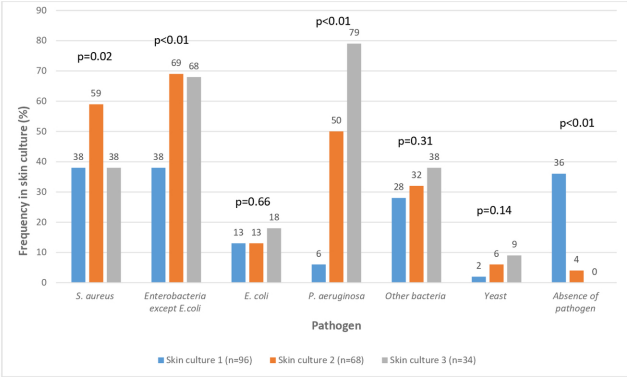
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Patient characteristics	All patients n = 98	Patients with bloodstream infection n = 46	Patients without bloodstream infection n = 52	P-value
Female, n (%)	55 (56)	21 (45.6)	34 (65.4)	0.049
Median age, years (range)	49.5 (15-99)	54.5 (15-99)	47.5 (18-83)	0.23
Median SCORTEN at baseline (range)	2 (0-5)	2 (1-5)	2 (0-5)	0.001
Median BSA involved at baseline, % (range)	15 (0-95)	20 (0-80)	10 (0-95)	0.008
Median maximal BSA involved, % (range)	30 (10-100)	60 (10-100)	25 (10-100)	< 0.0001
Median time to cutaneous re- epithelialization, days (range)	5 (0-19)	7 (2-19)	5 (0-11)	0.07
Treatment with cyclosporin, n (%)	57 (58.1)	26 (56.5)	31 (67.4)	0.75
Median length of hospitalization, days (range)	20 (4-116)	28.5 (4-116)	15 (4-43)	0.0001
Antibiotics before admission, n (%)	67 (68.4)	30 (65.2)	37 (71.2)	0.53
Antibiotics during hospitalization, n (%)	81 (82.7)	45 (97.8)	36 (69.2)	0.0001
Intensive care unit admission, n (%)	49 (50)	34 (73.9)	15 (28.8)	< 0.0001
Hospital death, n (%)	21 (20.4)	12 (26)	9 (17.3)	0.29

368 *BSA: body surface area*

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Figure 1:



■ *Staphylococcus aureus*
■ *Pseudomonas aeruginosa*

