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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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1 **Incidence of bloodstream infections and predictive value of qualitative and quantitative**
2 **skin cultures of patients with overlap syndrome or toxic epidermal necrolysis: a**
3 **retrospective observational cohort study of 98 cases.**

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47 bloodstream infection, blood culture

48

49 **Capsule summary**

- 50
- 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%)
51 and *P. aeruginosa*, n=17 (36.9%)]. Negative predictive values of skin cultures were
52 89.4% and 80.9%, respectively.
 - Skin cultures may help predicting the pathogens involved in bloodstream infections.
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64 **Abstract**

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

67 **Objective:** To describe the epidemiology of bloodstream infections (BSIs) in EN involving a
68 $BSA \geq 10\%$ and the diagnostic performances of skin cultures for predicting the pathogen(s)
69 isolated from BSIs.

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

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

80 **Limitations:** Retrospective monocentric design and few total number of BSI.

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

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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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106 **Introduction:**

107 Epidermal necrolysis (EN) is a life-threatening condition, mainly due to drugs. According to
108 the body surface area (BSA) involved, patients are categorized as Stevens-Johnson syndrome
109 (SJS, <10% BSA), SJS-TEN overlap (10-29% BSA), or toxic epidermal necrolysis (TEN, or
110 Lyell syndrome, \geq 30% BSA).¹ Mortality ranges from 10 to 40%.² The cornerstone of
111 treatment is supportive care.³

112 Causes of mortality in EN include specific lung involvement⁴ and invasive bacterial
113 infections, the most frequent and life-threatening being bloodstream infections (BSI). A
114 relationship between BSI and skin bacterial colonization was described in burns,^{5,6} but data
115 from EN remain scarce. Here, we aimed to investigate the epidemiology of BSI in EN and
116 assess the ability of the qualitative and quantitative results of skin cultures to predict the
117 pathogen(s) involved in BSI episodes.

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128 **Materials and methods:**

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

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

139 According to the French guidelines, routine management of wound care included skin
140 antiseptics, consisting in the application of diluted chlorhexidine (bathing or spraying) once a
141 day, without local antibiotics, and non-sticky dressings or white petroleum jelly. Prophylactic
142 antibiotics were not recommended. Systemic antibiotics were prescribed in case of
143 documented invasive infection or sepsis/septic shock.³

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

150 Only the first BSI episode, as defined by one (monomicrobial bacteremia) or more
151 (polymicrobial bacteremia) pathogen(s) isolated from blood cultures, was considered for

152 bacteriological analysis. Strains of the first three skin cultures collected from admission to re-
153 epithelialization for several sites of detached skin were collected: *Staphylococcus aureus*,
154 *Pseudomonas aeruginosa*, *Escherichia coli*, and exogenous enterobacteria (*i.e.* non-*E. coli*
155 enterobacteria). Three semi-quantitative classes of inoculum were defined: <100 (<10²)
156 colony-forming units (CFU)/cm², 101-10,000 (10²-10⁴) CFU/cm², and >10,000 (>10⁴)
157 CFU/cm². For patients with BSI, we investigated the results of the concomitant skin culture,
158 *i.e.*, that performed at any time around the time of sampling the first positive blood culture,
159 between 48h before and within the 24h after. We considered that skin and blood cultures were
160 concordant when the bacteria isolated in the BSI was also isolated in the corresponding skin
161 culture (for monomicrobial BSI), or if at least one of the bacteria of the BSI was isolated in
162 the corresponding skin culture (for polymicrobial BSI).

163 Results are reported as percentages and medians (interquartiles [IQR] 25-75). The diagnostic
164 performance of the concomitant skin culture for predicting the pathogen involved in the BSI
165 was assessed by computing the sensitivity, the specificity, and the positive (PPV) and
166 negative (NPV) predictive values of its qualitative results (presence or absence of the
167 bacterium) for each pathogen involved. The odds ratio (OR), and their 95% confidence
168 interval, of skin cultures growing *S. aureus*, and *P. aeruginosa* for BSI episodes involving
169 these pathogens were computed. The impact of the inoculum was also assessed by computing
170 the OR of developing a BSI for each skin inoculum category, sterile skin cultures being the
171 reference. Categorical data were compared using Fisher or chi-2 tests, as appropriate.
172 Continuous data were compared using unpaired Student tests or Mann-Whitney tests, as
173 appropriate. Two-sided p values were computed and p<0.05 was considered significant.

174 The study was approved by the Institutional Review Board Mondor (IRB00011558,
175 2018/09/20).

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177 Results:

178 Among 166 patients referred for EN, we excluded 66 patients with SJS and two with missing
179 data. Ninety-eight patients (55 female) were included, with a median age of 49.5 years (IQR
180 31.1-67.9), 40 (40.8%) with SJS-TEN overlap syndrome and 58 (59.2%) with TEN (Table 1).
181 The disease was drug-induced in 82/98 (83.7%) cases. Culprit drugs were antibiotics in 32
182 cases (32.6%), antiepileptic drugs in 22 cases (22.4%) and allopurinol in 14 cases (14.3%).
183 No culprit drug was identified in 16 cases (16.3%).

184 Forty-six (46.9%) patients experienced one or more episodes of BSI during their hospital stay
185 (total=85), after a median of seven days (IQR 0.8-13.2) following admission, resulting in an
186 incidence of 33.3 BSI/1000 days of hospitalization/patient (Table 1). Septic shock occurred in
187 24/46 cases (52.2%). Twelve patients with BSI (26%) and nine without (17.3%, $p=0.29$) died.
188 BSI occurred more frequently in patients with TEN ($n=38/58$, 65.5%) than in those with the
189 SJS-TEN overlap syndrome ($n=8/40$, 20.0%; $p<0.01$). Patients who received cyclosporin did
190 not show a significantly higher BSI rate than those who did not.

191 Bacteria isolated from the first positive blood cultures were as follows (11/46 [23.9%] BSIs
192 were polymicrobial): *S. aureus* ($n=17/46$, 36.9%), *P. aeruginosa* ($n=17/46$, 36.9%),
193 exogenous enterobacteria ($n=7/46$, 15.2%), *E. coli* ($n=1/46$, 2.2%), and others ($n=15$, 32.6%).
194 The median time elapsed between hospital admission and the first BSI episode ranged from
195 4.5 days (0-9) for methicilline-sensitive *S. aureus* to 10 days (3-18) for *P. aeruginosa*
196 ($p=0.004$).

197 Ninety-six patients had one skin culture performed, 68 had two, and 34 had three or more.
198 The three skin cultures were performed after a median of 1.0 (0.0-3.9), 6.5 (1.5-11.5), and
199 12.0 (6.8-14.2) days following admission. The main bacteria isolated from the first skin
200 culture were *S. aureus* (36/96, 38%) and exogenous enterobacteria (36/96, 38%), whereas

201 exogenous enterobacteria (23/34, 68%) and *P. aeruginosa* (27/34, 79%) were predominant in
202 the third skin culture (Figure 1).

203 Bacteria isolated from the concomitant cutaneous samples were concordant with those
204 responsible for BSI in 32/45 (71.1%) cases (skin culture missing for one patient). Among
205 those 32 skin cultures, 24 (75.0%) were performed during the 48 hours preceding the BSI and
206 8 (25.0%) during the 24 hours after. The concordance rate was 70.6% (24/34) for
207 monomicrobial BSI and 72.7% (8/11) for polymicrobial BSI. Among the 13 patients with
208 discordant blood and skin culture results, 9 (69.2%) had a negative skin culture and a positive
209 blood culture, and 4 (30.7%) had a positive skin culture that did not match with the positive
210 blood culture.

211 The diagnostic performance of skin cultures for predicting BSI episodes was as follows: skin
212 cultures growing *S. aureus* had a sensitivity of 88.2%, a specificity of 60.7%, a PPV of
213 57.7%, and an NPV 89.4% for predicting *S. aureus* BSIs; for *P. aeruginosa*, the diagnostic
214 performance was 75.0%, 58.4%, 50.0%, and 80.9%, respectively. Patients having ≥ 1 skin
215 culture growing *S. aureus* had an odds ratio (OR [95% confidence interval]) of having a BSI
216 episode involving the same pathogen of 17.0 [2.0-146.9] ($p=0.002$); for those having ≥ 1 *P.*
217 *aeruginosa*-positive skin culture the OR was 8 [1.9-36.4] ($p=0.005$). *Post-hoc* analyses of the
218 OR of developing a BSI for increasing bacterial inocula suggested that the risk of *S. aureus*
219 BSI gradually increased with the inoculum of skin culture, while that of *P. aeruginosa* did not
220 (Figure 2).

221 Concerning antibiotic susceptibility at admission (skin culture 1), 8/96 patients (8.3%) were
222 colonized by methicillin-resistant *S. aureus* and 0/96 (0.0%) by ceftazidime-resistant *P.*
223 *aeruginosa*. Twelve days after admission (skin culture 3), these rates rose to 8/34 (23.5%,
224 $p=0.03$) and 5/34 (14.7%, $p<0.01$), respectively. The 8 patients with methicillin-resistant *S.*

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

227 **Discussion:**

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

240 We report on a high frequency of BSI in EN patients with a BSA>10% (46.9%) and
241 highlighted the associated severity, illustrated by the occurrence of septic shock in nearly half
242 of the cases. *S. aureus* and *P. aeruginosa* were the main bacteria responsible for BSI in EN, as
243 previously reported.⁷ Qualitative results of skin culture showed a good concordance with BSI
244 (71.1%). The NPV of the concomitant skin cultures were high for *S. aureus* and *P.*
245 *aeruginosa*, illustrating that patients with negative skin cultures for these pathogens were
246 unlikely to have a BSI involving these pathogens. We also showed the importance of
247 monitoring skin cultures over time, as we observed a switch of skin colonization from gram-
248 positive cocci at baseline to gram-negative bacilli during the hospital stay, as previously

249 described for burn patients,^{5-7,10} together with a significant decrease in the susceptibility
250 patterns of the studied bacteria.

251 Our study added new data regarding the quantitative analysis of skin cultures. Indeed, skin
252 colonization with *S. aureus* or *P. aeruginosa* was associated with a higher proportion of *S.*
253 *aureus* and *P. aeruginosa* BSIs, respectively. Furthermore, for patients with *S. aureus*-
254 positive skin cultures, the odds ratio of having a subsequent bacteremia increased with skin
255 inoculum. Such dose-effect relationship was not observed with *P. aeruginosa*, suggesting
256 different mechanisms might be involved. For *S. aureus*, endogenous skin carriage is
257 suggested, whereas for *P. aeruginosa*, acquired skin colonization and/or digestive
258 translocation due to specific involvement of EN is possible.^{11,12} For other pathogens, such as
259 *E. coli* or other enterobacteria, digestive translocation is also suggested, as shown in patients
260 with an altered digestive barrier, including those with burns.¹³

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

274 According to French guidelines and our routine practice, we do not recommend initiating
275 antibiotics on the sole basis of an isolated positive skin culture.³ However, immediate and
276 targeted antibiotics are mandatory for EN patients, as soon as invasive bacterial infection is
277 suspected (*i.e.*, sepsis, septic shock). In that case, waiting for the complete results of BSI
278 cultures and antibiograms (that can last up to three days), the choice of the antibiotics to be
279 initiated should consider the susceptibility patterns of the bacteria carried by the patient, as
280 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.

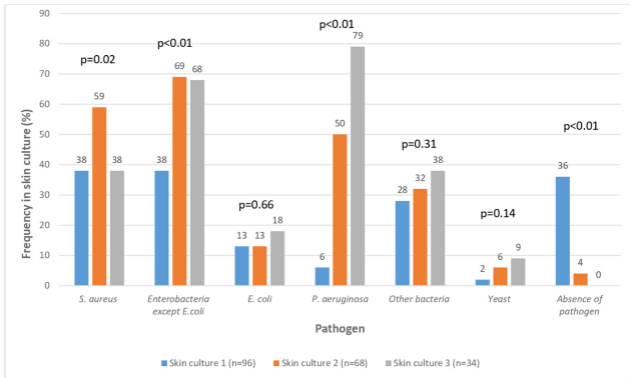
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Patient characteristics	All patients n = 98	Patients with bloodstream infection n = 46	Patients without bloodstream infection n = 52	P-value
Female, n (%)	55 (56)	21 (45.6)	34 (65.4)	0.049
Median age, years (range)	49.5 (15-99)	54.5 (15-99)	47.5 (18-83)	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*

369

Figure 1:



■ *Staphylococcus aureus*
■ *Pseudomonas aeruginosa*

