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Mini Review

Bacteremia in Stevens Johnson Syndrome and Toxic Epidermal Necrolysis: Main Pathogens and Risk Factors: A Mini Review

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Abstract

Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are hypersensitivity reaction, mainly to drugs, characterized by skin detachment. They are dermatological emergencies, and bacteremia is the main cause death, especially in patients with extensive cutaneous involvement.

We reviewed and summarized the large retrospective studies that focused on the risk factors and main pathogens involved in patients with SJS and TEN who developed bacteremia. Our results showed that the risk factors include a Total Body Surface Area (TBSA) higher than 10%, higher Severity-of-Illness Score For Toxic Epidermal Necrolysis (SCORTEN), hypertension, previous opiate use, White Blood Cells (WBC) > 10000/mL; C-Reactive Protein (CRP) > 100mg/mL; procalcitonin (PCT) ≥ 1µg/L; and skin colonization with *P. aeruginosa*, *S. aureus*, and methicillin-resistant *S. aureus* (MRSA). The most frequently isolated pathogens from blood cultures were *S. aureus*, *E. faecalis*, *P. aeruginosa*, *Enterobacter spp*, and *A. baumannii*.

The identification and consideration of these variables on each patient with SJS and TEN could result in an earlier diagnosis, proper management and even prevention of bacteremia in this population.

Keywords: Stevens johnson syndrome; Toxic epidermal necrolysis; Bacteremia; Infection; Emergency

Abbreviations

SJS: Stevens Johnson Syndrome; TEN: Toxic Epidermal Necrolysis; BSI: Blood Stream Infections; WBC: White Blood Cells; CBC: Complete Blood Count; MRSA: Methicillin-Resistant *Staphylococcus Aureus*; TBSA: Total Body Surface Area; LOS: Length of Hospital Stay; CRP: C-Reactive Protein; PCT: Procalcitonin.

Introduction

SJS and TEN are potentially life-threatening, severe drug reactions. They both present with cutaneous and mucosal involvement, characterized by epidermal detachment and mucosal erosions [1]. They represent a disease continuum and are classified according to the TBSA affected. SJS is characterized by a TBSA involvement of 10% or less, whereas in TEN the TBSA involved is 30% or more and SJS/TEN overlap involves more than 10% but less than 30% TBSA [2].

The terms bacteremia and Blood Stream Infection (BSI) are sometimes used interchangeably; however, bacteremia refers to the presence of viable bacteria in the bloodstream that could progress to BSI if there is an impaired or oversaturated immune response [3].

The mortality of patients with SJS and TEN depends on the extent of TBSA affected; which is why TEN has the highest mortality rate, and sepsis is the major cause of death in this population [1]. Also, bacteremia has been identified as a major risk factor associated with the need for mechanical ventilation, along with shock or multiorgan failure on admission [4].

We performed a literature search for articles focusing on bacteremia and/or BSI in patients with SJS and/or TEN. We included large retrospective studies with more than 20 patients published in the last 10 years. Our objective was to identify the main risk factors associated with the development of bacteremia and the most common pathogens involved.

In Table 1, we briefly summarize the important findings previously described in large retrospective studies focusing on bacteremia.

Main Pathogens

Regarding the pathogens involved with bacteremia, the most frequently isolated were S. aureus, *E. faecalis*, *P. aeruginosa*, *Enterobacter* and *A. baumannii*. These pathogens vary in frequency, in accordance with the local epidemiology of different medical institutions, as well as the region´s environment. The most frequently reported single organism was *Staphylococcus aureus* [1,2,4-8].

A. baumannii is considered an emerging nosocomial microorganism especially in tropical regions [7]. The main factors associated with multidrug-resistant *A. baumannii* infection included invasive procedures, ICU admission, mechanical ventilation, and the use of broad-spectrum antibiotics [7].

There seems to be a relationship between bacteria isolated from skin and blood cultures. Lecadet et al found that the same pathogen responsible for BSI was also isolated from skin cultures in up to 71% of their patients with SJS/TEN, and *S. aureus*, *P. aeruginosa*, and

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Table 1: Risk factors and main culprits for bacteremia from large retrospective studies.

Study	Patients studied	BSI	Pathogens	Risk factors	Comorbidities	Time elapsed to bacteremia
de Prost N, et al.	N: 179 · SJS 29.6% · SJS/TEN 33.02% · TEN 36.9%	26.80%	*S. aureus* 32.8% *P. aeruginosa* 21.4% *Enterobacteriaceae* 24.3% *Polymicrobial 13.4%	· >40 years · WBC>10, 000/mm^3 · TBSA detached of 30% · Skin colonization with *Pseudomonas aeruginosa* and MRSA	None	5 days after admission; 11 days from onset of first symptoms
Koh HK, et al.	N: 176 · SJS 33.5 % · SJS/TEN 29% · TEN 37.5%	29.50%	*A. baumannii* 27.7% *S. aureus* 21.4% Other Gram + 18.8% *Enterobacteriaceae* 15.2% *Polymicrobial 11.4%	· TBSA ≥ 10%, · Hemoglobin ≤ 10 g/dL · Hypothermia · C-reactive protein ≥ 100 mg/L · Procalcitonin ≥ 1 ug/L	· Cardiovascular disease · Hypertension	9 days from the onset of disease
Lecadet A, et al.	N: 98 · SJS/TEN 40.8% · TEN 59.2%	46.90%	*S. aureus & P. aeruginosa* 36.9% each. Exogenous enterobacteria 15.2% *E. coli* 2.2% Other 32.6% *Polymicrobial 23.9%	· TBSA > 10% · Skin colonization with *S. aureus* and *P. aeruginosa*	None reported	• 7 days after admission • 4.5 days for MRSA • 10 days for *P. aeruginosa*
Lipový B, et al.	N: 38 · 100% TEN	38%	*Culture from any site. Coagulase neg *Staphylococcus* *E. faecalis* *P. aeruginosa* *Blood cultures · G+ 78% · G- 21%	· Higher SCORTEN after 15 days of hospitalization · Longer LOS	None reported	>15 days from admission
Mahar PD	N:27 · 100% TEN	14.80%	*P. aeruginosa* *S. aureus* *Enterococcus faecalis*	Previous opiate use	None reported	15 days from admission
Diao M, et al.	N: 125 · 72% SJS · 28% TEN	3.20%	*S. aureus* and *E. coli* 100%	· Longer LOS · High SCORTEN	Hypertension	Not specified

SJS: Stevens Johnson Syndrome; TEN: Toxic Epidermal Necrolysis; WBC: White Blood Cells; MRSA: Methicillin-Resistant Staphylococcus Aureus; TBSA: Total Body Surface Areal; LOS: Length of Hospital Stay.

Enterobacteriaceae species were the ones that showed this correlation [5] Similarly, de Prost et al identified *P. aeruginosa* and MRSA from qualitative skin cultures as being predictive of bacteremia.

Risk Factors

Authors agree that a TBSA >10%, higher SCORTEN and preexisting health conditions are indicators of a worse prognosis. In this review, we found that hypertension was the only statistically significant and consistent comorbidity associated with a higher risk of bacteremia [6,7]. Additional risk factors identified were: age above 40 years, previous opiate use (six weeks prior), time elapsed between the onset of symptoms and longer hospital stays [1,9], although the latter may be more a consequence of infection than a cause for bacteremia.

It has also been identified that there is a general higher risk for late-onset infectious complications by Gram-positive bacteria in patients who used antibiotics immediately before TEN onset, compared to patients without any recent antibiotic use [10]. Lipovy et al attributed this finding to the fact that this subset of patients received antibiotic therapy due to the presence of an infection before the onset of TEN, as well as possible dissemination caused by treatment interruption [11].

The laboratory findings on admission that might be useful to predict the risk for developing bacteremia are WBC > 10 000/mL; CRP > 100mg/mL; PCT ≥ 1μ/L; and skin colonization with *P. aeruginosa*, *S. aureus*, and MRSA [1,7].

Pro-inflamatory cytokines including TNF-a, IL-6 and IL-8 induce the release of procalcitonin in the setting of bacterial infection [12]. Wang et al found that PCT levels were significantly higher in patients with systemic bacterial infections compared to those without infection or with superficial skin infection. PCT could be more accurate in identifying systemic bacterial infection in SJS/TEN than CRP, since the latter can be influenced by high doses of glucocorticoids, one of the standard treatments for SJS/TEN [12].

Avoidance of prophylactic antibiotics is encouraged; [5-7,9] in cases of high suspicion of infection, antibiotic selection should be based on local microbiota, and cultures should be obtained before their administration [9]. Furthermore, antibiotic administration has been associated with longer hospital stays and antibiotic resistance [7].

It is important to point out that authors who described treatment modalities in their population did not find a higher risk for infection in those treated with immunomodulators or systemic corticosteroids [9,11].

Discussion

From the short review above, key findings emerge:

The main pathogens causing bacteremia in SJS and TEN are *S.*

aureus, *E. faecalis*, *P. aeruginosa*, *Enterobacter* and *A. baumannii*. The prevalence of these microorganisms varies in frequency depending on the local microbiological characteristics and emerging nosocomial agents, depending on the region´s climate.

Clinical risk factors for bacteremia include TBSA > 10%, higher SCORTEN, hypertension and previous opiate use. Laboratory markers include WBC > 10000/mL, CRP > 100mg/mL, and PCT ≥ 1μg/L. However, PCT has shown to be a more reliable marker than CRP for bacteremia. Skin colonization with *P. aeruginosa*, *S. aureus*, and MRSA have also shown to have a correlation with bacteremia development. Moreover, contrary to general belief, the use of immunomodulators did not increase the risk for bacteremia, and prophylactic antibiotics is repeatedly discouraged.

Taken together, these findings suggest that a thorough medical history and laboratory work up that includes the tests, as well as regular skin cultures could aid in the early detection of bacteremia in patients with SJS and TEN.

Conclusion

Over the past decade, physicians have made efforts to identify risk factors involved in the development of bacteremia, as well as the more commonly associated pathogens, since research has consistently demonstrated that a higher SCORTEN leads to a higher risk for bacteremia, both leading to an increased mortality rate.

Bacteremia is one of the leading causes of death in patients with SJS and TEN. Different factors contribute to its development, and these vary among patient populations, regions, and local microbiota. The identification of these risk factors may aid timely diagnosis and prompt treatment. Prospective studies are needed to further establish recommendations, which could be generalized.

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References

1. de Prost N, Ingen-Housz-Oro S, Duong T, Valeyrie-Allanore L, Legrand P, Wolkenstein P, et al. Bacteremia in Stevens-Johnson syndrome and toxic epidermal necrolysis: epidemiology, risk factors, and predictive value of skin cultures. Medicine (Baltimore). 2010; 89: 28-36.
2. Roujeau JC. The spectrum of Stevens-Johnson syndrome and toxic epidermal necrolysis: a clinical classification. J Invest Dermatol. 1994; 102: 28S-30S.
3. Christaki E, Giamarellos-Bourboulis EJ. The complex pathogenesis of bacteremia: from antimicrobial clearance mechanisms to the genetic background of the host. Virulence. 2014; 5: 57-65.
4. Phan K, Oh LJ, Issler-Fisher A, Rao A, Wong EH, Maitz P. Ventilatory support in Stevens-Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. J Dermatolog Treat. 2020:1-6.
5. Lecadet A, Woerther PL, Hua C, Colin A, Gomart C, Decousser JW, et al. 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. J Am Acad Dermatol. 2019; 81: 342-347.
6. Diao M, Thapa C, Ran X, Ran Y, Lv X. A retrospective analysis of infections and antibiotic treatment in patients with Stevens-Johnson syndrome and toxic epidermal necrolysis. J Dermatolog Treat. 2020; 31: 61-65.
7. Koh HK, Chai ZT, Tay HW, Fook-Chong S, Choo KJL, Oh CC, et al. Risk factors and diagnostic markers of bacteremia in Stevens-Johnson syndrome and toxic epidermal necrolysis: A cohort study of 176 patients. J Am Acad Dermatol. 2019; 81: 686-693.
8. Tocco-Tussardi I, Huss F, Presman B. Microbiological findings and antibacterial therapy in Stevens-Johnson syndrome/toxic epidermal necrolysis patients from a Swedish Burn Center. J Cutan Pathol. 2017; 44: 420-432.
9. Mahar PD, Wasiak J, Cleland H, Paul E, Gin D, Watters DA, et al. Secondary Bacterial Infection and Empirical Antibiotic Use in Toxic Epidermal Necrolysis Patients. Journal of Burn Care & Research. 2014; 35: 518-524.
10. Lipový B, Holoubek J, Hanslianová M, Cvanová M, Klein L, Grossová I, et al. Toxic epidermal necrolysis data from the CELESTE multinational registry. Part I: Epidemiology and general microbiological characteristics. Burns. 2018; 44: 1551-1560.
11. Lipový B, Holoubek J, Hanslianová M, Cvanová M, Klein L, Grossová I, et al. Toxic epidermal necrolysis data from the CELESTE multinational registry. Part II: Specific systemic and local risk factors for the development of infectious complications. Burns. 2018; 44: 1561-1572.
12. Wang Q, Tian XB, Liu W, Zhang LX. Procalcitonin as a diagnostic indicator for systemic bacterial infections in patients with Stevens-Johnson syndrome/toxic epidermal necrolysis. J Dermatol. 2018; 45: 989-993.