Diagnosis and treatment of streptococcal toxic shock syndrome in the pediatric intensive care unit: a case report

Diagnóstico e tratamento da síndrome do choque tóxico estreptocócico em unidade de terapia intensiva pediátrica: relato de caso

INTRODUCTION

Group A *Streptococcus pyogenes* or β-hemolyticus is a naturally occurring gram-positive coccus found in the airways and skin of asymptomatic individuals and is one of the most common agents in several diseases affecting the pediatric age group.\(^1\)

The incidence of invasive *S. pyogenes* ranges from 0.3 to 4.8 cases per 100,000 inhabitants in developed countries. Darenberg et al. reported an 11% incidence of toxic shock syndrome (TSS) related to type A strains, of which 9.5% of cases developed necrotizing fasciitis. Its similarity to other forms of shock hinders early diagnosis and the selection of most appropriate antibiotic therapy and may delay the removal of the source of infection.\(^1,2\)

TSS is a systemic inflammatory process induced by immune mediators in response to certain infections caused by these agents, in which exotoxins act as superantigens, inducers of proliferation and activation of T lymphocytes and macrophages because they stimulate, without specificity, nearly 20% of the total shock that required intensive support.

ABSTRACT

Among the infections caused by *Streptococcus β hemolyticus* from the Lancefield serogroup A, toxic shock syndrome is perhaps the most severe, and its mortality rate is high. Its clinical similarity to other forms of shock, especially septic shock, can often confuse the evaluator and interfere with the selection of the most appropriate therapy. This report aims to inform readers of the need to add this syndrome as a differential diagnosis in cases of shock, especially those with no well-defined clinical manifestations. For this purpose, we present the case of an infant with common flu-like symptoms who progressed rapidly with a rash, a reduced level of consciousness and clinical and laboratory signs of shock that required intensive support. In addition to cultures indicating the etiological agent, the appearance of exanthema and necrotizing fasciitis led to the diagnosis. However, less than 50% of cases present classic clinical signs of this entity. Penicillins combined with aminoglycosides are still the therapy of choice and are supported by a high level of evidence. Despite the severity of this patient’s presentation, the progression was satisfactory.

Keywords: Shock, septic/diagnosis; Shock, septic/drug therapy; Intensive care units, pediatric; Exanthema; Fasciitis, necrotizing; Penicillins/therapeutic use; Aminoglycosides/therapeutic use; Combined modality therapy
population of T cells to bind directly to their receptors, instead of presenting to the major histocompatibility complex (MHC); this results in the massive release of cytokines, causing tissue injury and increased capillary permeability culminating in the dysfunction of multiple organs and shock, in addition to increasing the susceptibility to endotoxic shock due to gram-negative bacteria. (3,4)

This specificity is conferred by a streptococcal surface protein (M protein) that confers a high degree of resistance to heat and acidic pH and is responsible for promoting fixation in human epithelial cells, preventing complement opsonization and phagocytosis. Subtypes 1, 3 and 18 are related to invasive infections with a worse prognosis, reaching 50% mortality in cases that progress to TSS. (5,6)

Concentrated outbreaks have been reported since the first description of the disease 90 years ago and are related to reemerging conditions and soft tissue and respiratory tract infections, usually preceded by common and less-specific flu-like symptoms.

This report aimed to describe the peculiar characteristics of the syndrome, considering its severity, and to address need for specific and differential diagnoses to determine therapeutic targeting, remove the source of infection, and avoid the indiscriminate use of antibiotics in intensive care units. The legal guardian of the patient authorized the use of data from the medical records and the photos taken during hospitalization to prepare this report by signing the Informed Consent Form, which was subsequently submitted to the Research Ethics Committee through the Brazil Platform.

**CASE PRESENTATION**

A young female infant aged 1 year and 2 months, 9kg, previously healthy and eutrophic, presented hyaline coryza, nasal obstruction, dry cough and continuous fever between 38.5 and 39.4ºC and had been receiving antipyretics for 5 days. The rash emerged on the second day of symptoms and was accompanied by a decline in the general condition. The patient was admitted to the pediatric ward for investigation (Figures 1 and 2).

At the admission examination, the patient was in a regular general condition and was jaundiced, dehydrated and febrile, with generalized edema of the upper and lower limbs and face. Diffuse maculopapular exanthema was present on the lower and upper limbs, trunk, face, hands and feet; was rough, pruritic, with areas of petechiae; and more evident on the left arm and right leg.

Otoscopy found that the left auditory canal was hyperemic and the tympanic membrane was opaque, with a moderate quantity of fetid serous effusion. Oroscopy showed grade II tonsils, with mild hyperemia of the pillars without exudate. Cardiac auscultation detected a galloping heartbeat with a holosystolic murmur (3+/6+) in the mitral focus and tachycardia; blood pressure was 108 × 56mmHg. Lungs presented a bilaterally distributed vesicular murmur, coarse crepitations at the left base, no discomfort with eupnea and 95% saturation in room air. The liver was palpated 4cm from the right costal margin. Glasgow score was 11 with little contact and no neck stiffness or focal neurologic deficits.

On the ward, empiric antimicrobial treatment with amoxicillin and clavulanate at a dose of 100mg/kg/day was established according to the routine of the service. At the end of the first day of hospitalization, the patient evolved, developing toxemia, tachycardia, tachypnea, hypotension and prolonged capillary refill time, and the hypothesis of septic shock with an undefined source was suggested. The patient received a 20mL/kg crystalloid expansion in a single aliquot and was referred to the pediatric intensive care unit (ICU).

Upon admission to the ICU, functional echocardiography was performed, and the results indicated...

Figure 1 - Thorax and abdomen with diffuse erythematous rash.
After the initial shock support measures were provided, the participant maintained hypotension and central venous saturation < 70%; norepinephrine 1mg/kg/ min followed by hydrocortisone 100m/m2 body surface were administered. On the second day of ICU admission, the patient developed multiple organ dysfunction requiring blood transfusion (red blood cells and platelets) and vitamin K. The bedside transthoracic echocardiogram showed no intracardiac vegetation.

The patient progressed with hyperemia and generalized edema of the left upper limb, with a capillary refill time > 5 seconds and a weak radial artery pulse, diffuse petechiae and bruising in the lateral region of the contralateral limb suggesting necrotizing fasciitis, and bedside fasciotomy was performed. Cultures of the skin, subcutaneous tissue and muscles were collected (Figures 3 and 4).

Due to the severity of the condition and the worsening of the hematological and white blood cell status on the third day of hospitalization, the medical team had a clinical meeting and chose to schedule antibiotic therapy, suspending ceftriaxone and maintaining clindamycin combined with cefepime and vancomycin.

The results of the cultures collected at admission indicated only the presence of S. pyogenes in the otological secretions of the left ear. This ear was suppurative on the fourth day, when it was possible to titrate the vasoactive drug and the steroid, maintaining only 0.2mcg/kg/minute of epinephrine suspended together with vancomycin on the fifth day of intensive care.

The invasive ventilatory support was removed, followed by discharge to complete the therapeutic regimen on the ward from the sixth day of hospitalization. The patient remained afebrile, with furfuraceous desquamation of the limbs associated with intense pruritus in the folds. She was discharged from the hospital on the 14th day after completing treatment the cefepime and clindamycin regimen.

Figure 2 - Lower left limb with diffuse erythematous rash.

Figure 3 - Bedside fasciotomy due to necrotizing fasciitis.
DISCUSSION

Scarlet fever and sepsis during the puerperal period are historically the main causes of morbidity and mortality related to streptococcal TSS; they reached mortality rates of 30% at the end of the 19th century. After the 1900s, the incidence rate did not reach 2%; however, in the 1980s, there was a resurgence of severe infections caused by \textit{S. pyogenes}, with a return to the high incidence and mortality reported in the previous century. This variation can be explained by the natural variation in pathogen virulence.\(^{(7)}\)

As highlighted in table 1, the signs and symptoms comprising the diagnostic criteria for a syndrome attributable to \textit{S. pyogenes} are complex given that the need for a positive culture to determine the agent may hinder diagnosis and may underreport infection, either because of the sensitivity and specificity of the culture method used, the inappropriate harvesting or storage of cultures and the introduction of antimicrobial therapy prior to sample collection.

As in the case described, approximately 20% of patients experience a flu-like syndrome characterized by fever, myalgia, nausea, vomiting and diarrhea. Localized or diffuse abrupt and severe pain that precedes the inflammatory symptoms, together with the observation of an entryway for infection, are the main characteristics described in the literature.\(^{(9)}\)

Thus, organ dysfunction and shock, although similar to the presentation of septic shock, have specific clinical manifestations, such as rash, desquamation, gastrointestinal symptoms, muscle involvement, pharyngeal and conjunctival hyperemia, and renal failure, with rapid and aggressive progression.

Necrotizing fasciitis has often been associated with TSS. It is a diagnosis that should always be considered when a child exhibits erythema, heat and induration of the skin and soft tissues in association with persistent fever. Initial skin manifestations may hinder the diagnosis of necrotizing fasciitis; however, rapid progression and extension of the lesion, paresthesia, bruising, crackles, blistering or necrosis suggest the diagnosis.\(^{(10)}\)

Due to reports of a clinical syndrome similar to the toxic shock induced by \textit{Staphylococcus aureus} in 1993, an international working group linked to the Centers for Disease Control and Prevention (CDC) elaborated clinical and laboratory criteria to standardize the etiological diagnosis and provide support for specific treatment (Table 2).\(^{(8)}\)

The rapid institution of antibiotic therapy and fluid resuscitation are necessary and, when possible, should be guided by the epidemiological pattern of the unit and by noninvasive hemodynamic monitoring. Vasopressor, inotropic and respiratory support should be considered, as in any other form of shock.

Knowledge of the pathophysiology of this entity and the establishment of the most appropriate antibiotic for the condition are of great importance. Penicillin is still described as the treatment of choice, but in animal models with streptococcal myositis, there was a decrease in its efficacy given the low rate of replication of group A \textit{S. \textit{β} hemolyticus} when the inoculum is large. Therefore, the current recommended initial therapy is the combination of a beta-lactam antibiotic and some aminoglycosides.\(^{(11)}\)

Clindamycin is a semisynthetic antibiotic produced by the replacement of the 7 (R)-hydroxy group of a derivative of lincomycin, which binds to the 50S subunit of bacterial ribosomes and p the formation of peptide bonds, hindering the growth, reproduction and release of TSS-inducing toxins.\(^{(12)}\)
Diagnosis and treatment of streptococcal toxic shock syndrome

Table 1 - Streptococcal toxic shock syndrome: case definition (CDC 2011)

| Feature                      | Criteria                                                                 |
|------------------------------|--------------------------------------------------------------------------|
| Fever                        |greater than or equal to 38.9 ºC                                          |
| Rash                         |Diffuse macular erythema                                                  |
| Desquamation                 |1 - 2 weeks after the start of the rash                                   |
| Hypotension                  |Below the 5th percentile for age                                          |
| Multisystemic involvement    |Gastrointestinal: vomiting or diarrhea at the onset of disease           |
|                             |Muscular: severe myalgia or creatine kinase MB isoenzyme (CPMK) level at least twice the upper limit of normal |
|                             |Mucous membrane: vaginal, oropharyngeal or conjunctival hyperemia         |
|                             |Renal: urea and creatinine values at least twice the upper limit of normal to age |
|                             |Hepatic: total bilirubin, GOT and GPT values at least twice the upper limit of normal for age |
|                             |Hematologic: platelets ≤ 100,000/mm²                                      |
|                             |Neurological: disorientation or changes in the level of consciousness without focal neurological signs (when fever and hypotension are absent) |
| Isolation of *Streptococcus pyogenes* |Sterile site (blood, cerebrospinal fluid, peritoneal fluid and biopsy tissue) |
|                              |Nonsterile site (opharynx, sputum, vagina and surgical site)             |

Case classification

Probable: case that meets the clinical criteria in the absence of another etiology that might explain the clinical picture and the isolation of group A *Streptococcus* from a nonsterile site

Confirmed: case that meets the clinical criteria and with the isolation of group A *Streptococcus* from a normally sterile site

Table 2 - Difference between staphylococcal and streptococcal toxic shock syndrome

| Features                  | Staphylococcal TSS | Streptococcal TSS |
|---------------------------|--------------------|-------------------|
| Exotoxins                 | TSST-1, SEs A, B, C, D, E | SPEs A, G, H, J, SSA, MF, SMEZ |
| Predisposing factors      | Tampon, burns and wounds | Varicella, NSAIDs and wounds |
| Associated infection sites| Impetigo, burns, rashes, surgical wound | Abscesses, myositis, fascitis, surgical wound |
| Infection of soft tissues | Rare               | Common            |
| Acute pain                | Rare               | Common            |
| Rash                      | Very common        | Less common       |
| Diarrhea and vomiting     | Very common        | Less common       |
| Elevation of CPK          | Rare               | Common            |
| Bacteremia                | < 5%               | 60%               |
| Desquamation              | 7 to 14 days       | Less common       |
| Mortality                 | 3 to 5%            | 5 to 10%          |

TSS - toxic shock syndrome; TSST-1 - toxin from toxic shock syndrome; SEs - staphylococcal superantigens; SPE - streptococcal superantigens; NSAIDs - nonsteroidal anti-inflammatory drugs; CPK - creatine phosphokinase. Source: adapted from the Centers for Disease Control and Prevention. Toxic Shock Syndrome (Other Than Streptococcal): 2011 Case definition [internet]. [cited 2018 Mar 12]. Available from: https://wwwn.cdc.gov/nndss/conditions/toxic-shock-syndrome-other-than-streptococcal/case-definition/2011/.

The use of antibiotics during the acute phase of the disease eradicates the pathogen and prevents recurrence. Passive immunization with intravenous immunoglobulin is useful in severe cases and acts for weeks but does not induce active immunity.\(^{(11,12)}\)

**CONCLUSION**

We emphasize the importance of knowing the diagnostic criteria for this syndrome and its various spectra of presentation to establish appropriate antibiotic therapy. The initial shock support follows the same indications recommended for the other types of shock, but attention should be paid to the rapid evolution of the condition and the absence of clear focus of infection. Complications, such as the necrotizing fasciitis presented in this case, should be quickly resolved because they may contribute to hemodynamic imbalance in the patient.
RESUMO

Dentre as infecções causadas por *Streptococcus β hemolyticus* do grupo A de Lancefield, talvez a síndrome do choque tóxico seja a mais grave, com alto índice de mortalidade. A semelhança clínica com outras formas de choque, principalmente séptico, pode, muitas vezes, confundir o avaliador e interferir na escolha da terapêutica mais adequada. Esse relato tem o objetivo de auxiliar seus leitores quanto à necessidade de adicionar tal síndrome como diagnóstico diferencial, frente a quadros de choque, principalmente aqueles que não apresentam manifestações clínicas bem definidas. Para isso, apresentamos o quadro de um lactente com sintomas gripais comuns, que evoluiu rapidamente com exantema, rebaixamento do nível de consciência, sinais clínicos e laboratoriais de choque, com necessidade de suporte intensivo. Além das culturas indicando o agente etiológico, o aparecimento de exantema e fasciite necrosante levou ao diagnóstico, mas, em menos de 50% dos casos temos sinais clínicos clássicos dessa entidade. As penicilinas em terapia combinada com aminoglicosídeos ainda são a terapia de escolha e possuem alto nível de evidência. Apesar da gravidade a evolução foi satisfatória.

**Descritores:** Choque séptico/diagnóstico; Choque séptico/tratamento farmacológico; Unidades de terapia intensiva pediátrica; Exantema; Fasciite necrosante; Penicilinas/uso terapêutico; Aminoglicosídeos/uso terapêutico; Terapia combinada

REFERENCES

1. Souto BG, Riguetti M, Pellini AC, Lima GD, Oliveira ME. Surto concentrado de choque tóxico estreptocócico. ABCS Health Sci. 2013;39(2):75-80.
2. Darenberg J, Luca-Harari B, Jasir A, Sandgren A, Pettersson H, Schålén C, et al. Molecular and clinical characteristics of invasive group A streptococcal infection in Sweden. Clin Infect Dis. 2007;45(4):450-8.
3. Antunes R, Diogo M, Carvalho A, Pimentel T, Oliveira J. Síndrome do choque tóxico por Streptococcus Pyogenes. Acta Med Port. 2011;24(S3):617-20.
4. Ato M, Ikebe T, Kawabata H, Takemori T, Watanabe H. Incompetence of neutrophils to invasive group A streptococcus is attributed to induction of plural virulence factors by dysfunction of a regular. PLoS One. 2008;3(10):e3455.
5. Johansson L, Thulin P, Lov DE, Norby-Teglund A. Getting under the skin: the immunopathogenesis of Streptococcus pyogenes deep tissue infections. Clin Infect Dis. 2010;51(1):58-65.
6. Schmitz FJ, Beyer A, Charpentier E, Normark BH, Schade M, Fluit AC, et al. Toxin-gene profile heterogeneity among endemic invasive European group A streptococcal isolates. J Infect Dis. 2003;188(10):1578-86.
7. Lamagni TL, Darenberg J, Luca-Harari B, Siljander T, Efstratiou A, Henriques-Normark B, Vuopio-Varkila J, Bouvet A, Creti R, Ekelund K, Kolou M, Reinert RR, Stathi A, Strakova L, Ungureanu V, Schålén C; Strep-EURO Study Group, Jasir A. Epidemiology of severe Streptococcus pyogenes disease in Europe. J Clin Microbiol. 2008;46(7):2359-67.
8. Center for Disease Control and Prevention. Toxic Shock Syndrome (Other Than Streptococcocal): 2011 Case definition [internet]. [cited 2018 Mar 12]. Available from: https://wwwn.cdc.gov/nndss/conditions/toxic-shock-syndrome-other-than-streptococcal/case-definition/2011/.
9. Stevens DL, Tanner MH, Winship J, Swarts R, Ries KM, Schlievert PM, et al. Severe group A streptococcal infectious associated with a toxic shock-like syndrome and scarlet fever toxin A. N Engl J Med. 1989;321(1):1-7.
10. Ayala-Gaytán JJ, Guajardo-Lara CE, Valdovinos-Chávez SB. Fasciis necrotizante y choque tóxico en infección por estreptococo grupo A. Rev Med Inst Mex Seguro Soc. 2011;49(4):425-32.
11. Stevens DL, Yan S, Bryant AE. Penicillin-binding protein expression at different growth stages determines penicillin efficacy in vitro and in vivo: an explanation for the inoculum effect. J Infect Dis. 1993;167(6):1401-5.