Intensive Care Med
DOI 10.1007/s00134-015-3861-7

Jason P. Burnham
Marin H. Kollef

Understanding toxic shock syndrome

Received: 13 April 2015
Accepted: 4 May 2015

This work was performed at Barnes-Jewish Hospital, St. Louis, MO.

J. P. Burnham
Division of Medical Education, Washington University School of Medicine, St. Louis, MO, USA

M. H. Kollef (✉)
Division of Pulmonary and Critical Care Medicine, Washington University School of Medicine, St. Louis, MO, USA
e-mail: mkollef@dom.wustl.edu

Epidemiology

Toxic shock syndrome (TSS) is a fulminant Gram positive infection, typically due to *Staphylococcus aureus* or *Streptococcus pyogenes*, though small series have described similar syndromes in closely related pathogens, including group B, C, and G streptococci. The annual incidence of staphylococcal TSS (SaTSS) is about 0.5/100,000 and about 0.4/100,000 for streptococcal TSS (SeTSS), though local rates may vary [1, 2]. Mortality rates are below 5 % for menstrual SaTSS, 5–22 % for non-menstrual SaTSS, and 30–70 % for SeTSS [2–5].

Clinical presentation and diagnosis: SaTSS

The initial presentation of SaTSS is non-specific with fever, malaise, gastrointestinal symptoms, myalgias, confusion, and refractory hypotension, which can be difficult to differentiate from septic shock and other conditions such as Rocky Mountain spotted fever, rubeola, leptospirosis, drug toxicities, and viral exanthems. SaTSS is classically associated with diffuse erythroderma that starts on the trunk and spreads to the extremities (including the palms and soles), conjunctival hyperemia, and strawberry tongue. Desquamation occurs 1–2 weeks after disease onset. No single criterion is sufficient for the diagnosis and a high index of suspicion must be maintained. Laboratory findings are also non-specific and generally reveal the extent of critical illness. The Centers for Disease Control and Prevention (CDC) recently updated the diagnostic criteria for SaTSS, though strict application of these criteria likely underestimates the incidence of the syndrome [6]. Menstrual cases are related to vaginal colonization by toxic shock syndrome toxin-1 (TSST-1) producing *S. aureus* and the presence of a tampon. Menstrual SaTSS cases peaked in the 1980s before the recognition that super-absorbent tampons introduced oxygen in an otherwise anaerobic vaginal environment which facilitated production of TSST-1. Non-menstrual cases may result from surgical wound colonization with or without infection, burns, nasal packing, post-influenza pneumonia, postpartum infections, insulin pump infusion sites, or no source may be identified. Interestingly, invasive infection is not required for development of SaTSS; the syndrome can develop in patients colonized with superantigen-producing strains of

Published online: 14 May 2015

S. aureus. SaTSS only develops in people without antibodies to TSST-1; serologic studies estimate that over 85 % of US adults have these antibodies [7].

Clinical presentation and diagnosis: SeTSS

SeTSS presents similarly to SaTSS, with some important differences. SeTSS often has positive blood cultures (up to more than 90 % of cases), whereas blood cultures are positive in less than 5 % of cases of menstrual SaTSS and only about 50 % of non-menstrual SaTSS [4, 8]. SeTSS almost always occurs as a result of an invasive infection, predominantly M types 1 or 3. SeTSS can have a rash, though less commonly than SaTSS and typically in a scarlatiniform pattern. Vesicles, blistering, and bullae occur more commonly in SeTSS than SaTSS, but are still uncommon. Pain out of proportion to examination is a classic finding for streptococcal necrotizing fasciitis (NF) and may be seen in SeTSS resulting from NF. SeTSS occurs in about half of the cases of streptococcal NF. While case definitions were recently updated, no single diagnostic criterion is sufficient for diagnosis [9]. SeTSS is most commonly associated with NF, myositis, or cellulitis, but can be seen with pneumonia, peritonitis, osteomyelitis, myometritis, or can occur in the setting of minimal trauma without a clear entry point. The reasons for development of fulminant shock in some, but not all patients with streptococcal infections are not well understood, but SeTSS may be more likely to develop in patients with low level antibody titers to superantigens and M proteins [10]. Patients with HIV, cancer, diabetes, cardiopulmonary disease, varicella zoster infection, alcohol abusers, and intravenous drug users are all at increased risk of developing SeTSS. Emerging data show that staphylococci may cause TSS with NF that presents similarly to SeTSS [11].

SaTSS and SeTSS are reportable and have CDC definitions for confirmed and probable cases (Fig. 1) [6, 9]. A diagnosis of TSS is difficult and a high index of suspicion is necessary.

Pathophysiology

SaTSS and SeTSS are the result of induction of T cells by superantigens TSST-1, enterotoxins B or C (staphylococci), or pyrogenic exotoxin A or B (streptococci). Superantigens bypass normal antigen processing by antigen presenting cells (APCs) and stimulate clonal T cell proliferation by direct linkage of major histocompatibility complex class II molecules on APCs to T cell receptors. This leads to massive production of interferon-gamma, interleukin-1, interleukin-6, tumor necrosis factor alpha, and tumor necrosis factor beta, the so-called cytokine storm. Superantigens cause T cell proliferation (20–30 % of all T cells) three orders of magnitude greater than that which occurs via normal antigen processing. In addition to cytokine storm, TSST-1 causes direct vascular injury and has synergistic effects with lipopolysaccharide from normal flora, resulting in capillary leak and hypotension. Individuals that do not develop TSST-1 antibodies are susceptible to recurrence. Menstrual SaTSS cases are typically caused by TSST-1, whereas non-menstrual cases are caused by TSST-1 in about half of cases and enterotoxins in the other half [12, 13]. In some centers, PCR tests may be available to detect superantigenemia, though these are not in widespread use [1].

Treatment

All patients with TSS require general resuscitative measures in accordance with individual institutions' protocols for management of septic shock. Aggressive source control is also paramount, which may include surgical debridement, removal of invasive devices, or vaginal examination in the case of menstrual TSS.

When TSS is suspected, empiric therapy must cover for drug-resistant infections. Expert opinion based on retrospective studies and in vitro data highlight vancomycin and clindamycin or linezolid alone as possible treatment regimens [14–17]. Nafcillin or oxacillin is a good choice for methicillin-sensitive SaTSS, but must be used in combination with clindamycin as naficillin alone can increase toxin production [16]. Clindamycin or linezolid is essential in treatment as it reduces superantigen production in both SaTSS and SeTSS [15–17]. When susceptibilities are available, antibiotics should be de-escalated while still including an agent that suppresses toxin production.

Intravenous immunoglobulin (IVIG) nonspecifically binds and inactivates superantigens, limiting cytokine storm, though the clinical benefits are controversial. As a result of the rarity of TSS, recruitment for randomized controlled trials of IVIG has been difficult [18]. A recent prospective observational study found a significantly improved mortality in patients that received IVIG or clindamycin for SeTSS [19]. IVIG is even less studied in SaTSS, though in a recent study, five patients with confirmed SaTSS received IVIG and none expired [20]. IVIG can be considered in patients with TSS, though specific

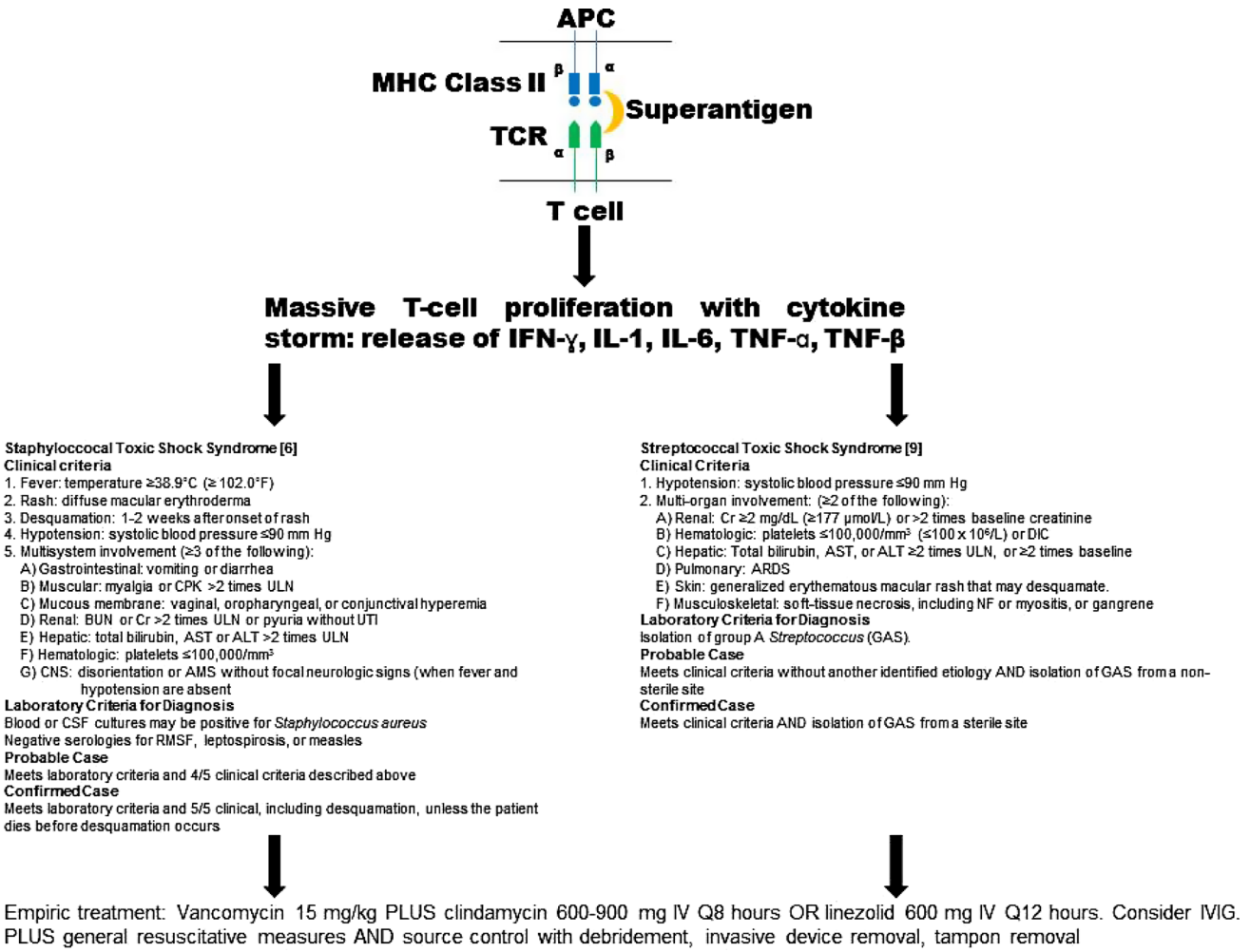

Fig. 1 From pathophysiology to diagnosis to treatment of staphylococcal and streptococcal toxic shock syndrome. *ALT* alanine aminotransferase, *AMS* altered mental status, *APC* antigen presenting cell, *ARDS* acute respiratory distress syndrome, *AST* aspartate aminotransferase, *BUN* blood urea nitrogen, *CNS* central nervous system, *CPK* creatine phosphokinase, *Cr* creatinine, *CSF* cerebrospinal fluid, *DIC* disseminated intravascular coagulation, *IFN* interferon, *IL* interleukin, *IVIG* intravenous immunoglobulin, *MHC* major histocompatibility complex, *NF* necrotizing fasciitis, *RMSF* Rocky Mountain spotted fever, *TCR* T cell receptor, *TNF* tumor necrosis factor, *ULN* upper limit of normal, *UTI* urinary tract infection

dosing regimens have not been well studied. Currently, the only method of TSS prevention is annual influenza vaccination to limit post-influenza TSS.

Conflicts of interest Dr. Burnham has no conflicts of interest to report. Dr. Kollef's effort was supported by the Barnes-Jewish Hospital Foundation.

References

1. DeVries AS, Lesher L, Schlievert PM, Rogers T, Villaume LG, Danila R, Lynfield R (2011) Staphylococcal toxic shock syndrome 2000–2006: epidemiology, clinical features, and molecular characteristics. PLoS One 6:e22997
2. Lamagni TL, Darenberg J, Luca-Harari B, Siljander T, Efstratiou A, Henriques-Normark B, Vuopio-Varkila J, Bouvet A, Creti R, Ekelund K, Koliou M, Reinert RR, Stathi A, Strakova L, Ungureanu V, Schalen C, Jasir A (2008) Epidemiology of severe *Streptococcus pyogenes* disease in Europe. J Clin Microbiol 46:2359–2367
3. Kain KC, Schulzer M, Chow AW (1993) Clinical spectrum of nonmenstrual toxic shock syndrome (TSS): comparison with menstrual TSS by multivariate discriminant analyses. Clin Infect Dis 16:100–106

4. Descloux E, Perpoint T, Ferry T, Lina G, Bes M, Vandenesch F, Mohammedi I, Etienne J (2008) One in five mortality in non-menstrual toxic shock syndrome versus no mortality in menstrual cases in a balanced French series of 55 cases. Eur J Clin Microbiol Infect Dis 27:37–43
5. Hajjeh RA, Reingold A, Weil A, Shutt K, Schuchat A, Perkins BA (1999) Toxic shock syndrome in the United States: surveillance update, 1979 1996. Emerg Infect Dis 5:807–810
6. Centers for Disease Control and Prevention (2011) Toxic shock syndrome (other than streptococcal) (TSS); 2011 case definition. http://wwwn.cdc.gov/nndss/conditions/toxic-shock-syndrome-other-than-streptococcal/case-definition/2011/. Accessed 3 Apr 2015
7. Parsonnet J, Hansmann MA, Delaney ML, Modern PA, Dubois AM, Wieland-Alter W, Wissemann KW, Wild JE, Jones MB, Seymour JL, Onderdonk AB (2005) Prevalence of toxic shock syndrome toxin 1-producing *Staphylococcus aureus* and the presence of antibodies to this superantigen in menstruating women. J Clin Microbiol 43:4628–4634
8. Davies HD, McGeer A, Schwartz B, Green K, Cann D, Simor AE, Low DE (1996) Invasive group A streptococcal infections in Ontario, Canada. Ontario Group A Streptococcal Study Group. N Engl J Med 335:547–554
9. Centers for Disease Control and Prevention (2010) Streptococcal toxic-shock syndrome (STSS) (*Streptococcus pyogenes*); 2010 case definition. http://wwwn.cdc.gov/nndss/conditions/streptococcal-toxic-shock-syndrome/case-definition/2010/. Accessed 3 Apr 2015
10. Holm SE, Norrby A, Bergholm AM, Norgren M (1992) Aspects of pathogenesis of serious group A streptococcal infections in Sweden, 1988–1989. J Infect Dis 166:31–37
11. Miller LG, Perdreau-Remington F, Rieg G, Mehdi S, Perlroth J, Bayer AS, Tang AW, Phung TO, Spellberg B (2005) Necrotizing fasciitis caused by community-associated methicillin-resistant *Staphylococcus aureus* in Los Angeles. N Engl J Med 352:1445–1453
12. Schlievert PM (1986) Staphylococcal enterotoxin B and toxic-shock syndrome toxin-1 are significantly associated with non-menstrual TSS. Lancet 1:1149–1150
13. Lee VT, Chang AH, Chow AW (1992) Detection of staphylococcal enterotoxin B among toxic shock syndrome (TSS)- and non-TSS-associated *Staphylococcus aureus* isolates. J Infect Dis 166:911–915
14. Stevens DL, Wallace RJ, Hamilton SM, Bryant AE (2006) Successful treatment of staphylococcal toxic shock syndrome with linezolid: a case report and in vitro evaluation of the production of toxic shock syndrome toxin type 1 in the presence of antibiotics. Clin Infect Dis 42:729–730
15. Carapetis JR, Jacoby P, Carville K, Ang SJ, Curtis N, Andrews R (2014) Effectiveness of clindamycin and intravenous immunoglobulin, and risk of disease in contacts, in invasive group a streptococcal infections. Clin Infect Dis 59:358–365
16. Stevens DL, Ma Y, Salmi DB, McIndoo E, Wallace RJ, Bryant AE (2007) Impact of antibiotics on expression of virulence-associated exotoxin genes in methicillin-sensitive and methicillin-resistant *Staphylococcus aureus*. J Infect Dis 195:202–211
17. Coyle EA, Cha R, Rybak MJ (2003) Influences of linezolid, penicillin, and clindamycin, alone and in combination, on streptococcal pyrogenic exotoxin a release. Antimicrob Agents Chemother 47:1752–1755
18. Darenberg J, Ihendyane N, Sjolin J, Aufwerber E, Haidl S, Follin P, Andersson J, Norrby-Teglund A (2003) Intravenous immunoglobulin G therapy in streptococcal toxic shock syndrome: a European randomized, double-blind, placebo-controlled trial. Clin Infect Dis 37:333–340
19. Linner A, Darenberg J, Sjolin J, Henriques-Normark B, Norrby-Teglund A (2014) Clinical efficacy of polyspecific intravenous immunoglobulin therapy in patients with streptococcal toxic shock syndrome: a comparative observational study. Clin Infect Dis 59:851–857
20. Matsushima A, Kuroki Y, Nakajima S, Sakai T, Kojima H, Ueyama M (2014) Low level of TSST-1 antibody in burn patients with toxic shock syndrome caused by methicillin-resistant *Staphylococcus aureus*. J Burn Care Res. doi:10.1097/BCR.0000000000000128