

COMPREHENSIVE REVIEW ON STREPTOCOCCAL TOXIN SHOCK SYNDROME(STSS) AND MECHANISM OF ACTION OF CLINDAMYCIN AND IVIG

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ABSTRACT

An extremely dangerous side effect of group A Streptococcus infection is streptococcal toxic shock syndrome, which has a high fatality rate. When treating these individuals, prompt identification, early intensive care assistance, and surgical management are crucial. The care of patients with streptococcal toxic shock syndrome depends on early detection and interdisciplinary management, which includes prompt determination of the infectious source or sources, surgical surgery, and appropriate and intensive support of failing organs. The identification and reporting of necrotizing fasciitis and other extremely invasive group A streptococcal infections linked to organ failure and shock. Streptococcal toxic-shock syndrome has been the term used to describe such extreme occurrences. The potentially fatal infection called necrotizing fasciitis damages the fat and fascia beneath the skin. A deadly infection known as neonatal sepsis can develop within the first 28 days of a neonate's life or, in the case of preterm newborns, up to 4 weeks after the anticipated due date. Neonatal sepsis is linked to a few factors. These include immune system immaturity, low birth weight, and preterm. A consequence of an invasive Streptococcus pyogenes

infection (IGAS), streptococcal toxic shock syndrome (STSS) is characterized by hypotension and end-organ failure, frequently accompanied by immunological symptoms like rash[6]. Though perspectives differ on whether clindamycin should only be used in cases of streptococcal toxic shock syndrome (STSS), it is currently generally advised for usage in conjunction with a beta lactam antibiotic for severe iGAS infections. Intravenous immunoglobulin (IVIG) therapy has been proposed as a treatment adjunct that can reduce mortality. Our goal is to further demonstrate the clinical effectiveness of IVIG therapy provided to well-defined STSS patients in a comparative observational analysis. Group A gram-positive, beta-haemolytic bacterium is *Streptococcus* (GAS). From minor ailments like pharyngitis and impetigo to more serious conditions like necrotizing fasciitis and streptococcal toxic shock syndrome [STSS], it can cause a wide range of illnesses.

Keywords: *Streptococcal Toxic Shock Syndrome, Intensive care assistance, Streptococcal infection, Necrotizing fasciitis, Neonatal sepsis, Clindamycin, IVIG, Group A gram-positive, Adverse Effects of Clindamycin and IVIG.*

1.Introduction:

Streptococcal toxic shock syndrome (STSS) is a serious, potentially fatal illness that exacerbates invasive streptococcal infections, primarily caused by group A streptococcus. Infections with streptococci are common and can cause a wide range of illnesses, from self-limited pharyngitis to serious conditions such as bacteraemia, pneumonia, meningitis, endocarditis, sinusitis, arthritis, and deep soft tissue infections like necrotizing fasciitis and myositis. The STSS is a serious side effect of group A streptococcal infections, which are primarily invasive, however other streptococcal species can also cause it less frequently [Schmitz, Roux, Huttner and Pugin et.al.2018]. A severe consequence of a streptococcus infection, streptococcal toxic shock syndrome (STSS) typically develops quickly and leads to multi-organ failure. Even in healthy people, it has a high death rate and is commonly linked to group A streptococcus infection. High fever, hypotension, generalized erythematous rash, and numerous

organ dysfunction are among the clinical signs, which can quickly escalate to severe and uncontrollable shock. Although the exact mechanism underlying this illness is unknown, it is thought to be a mix of enterotoxins with superantigen activity and the host's reaction to the streptococcal infection[Miguel Silva et.al.2022]. In 40–50% of individuals, renal impairment occurs prior to hypotension (8). Upon admission and during the hospital stay, hypoalbuminemia and hypocalcaemia are linked. Deeper soft-tissue infections can be identified with the help of the serum creatinine kinase level. Emerging Infectious Diseases Necrotizing fasciitis or myositis are strongly correlated with elevated or growing levels. The mean percentage of immature neutrophils (including band forms, metamyelocytes, and myelocytes) is a startling 40% to 50%, even though the preliminary laboratory results only show mild leucocytosis[L. Stevens et.al.1995]. Because of laboratory findings showing potentially positive benefits, such as neutralization of superantigens and improved bacterial clearance, some specialists advocate Polyspecific intravenous immunoglobulin (IVIG) as an adjuvant treatment for STSS. Clinical evaluation of IVIG for STSS has been challenging, nevertheless; the sole randomized controlled study (RCT) was terminated early because of sluggish recruitment. The interpretation of these findings is confounded by the inherent risk of bias, the varying inclusion criteria, and the uneven use of clindamycin, which is commonly recommended as an adjuvant to penicillin, despite the tiny number of non-randomized studies that have been reported. We conducted a comprehensive evaluation of studies that assessed the use of adjunctive IVIG in STSS, both randomized and non-randomized[Parks, Wilson, Curtis, Norrby-Teglund and Sriskandan et.al.2018].

2. Diseases Caused by Streptococcal Toxin Syndrome:

Necrotizing fasciitis :

An acute, potentially fatal infection of the soft tissue and fascia beneath the skin is called necrotizing fasciitis. Depending on the bacteria involved, the microbiologic incubation duration can range from one to four days. Although necrotizing fasciitis can be brought on by a single or a combination of virulent aerobic

and anaerobic bacteria, Group A beta-haemolytic *Streptococcus pyogenes* is responsible for most of the infection's morbidity and mortality. GAS-induced necrotizing fasciitis, either by itself or in conjunction with other organisms, is categorized as Type II, while Type I necrotizing fasciitis is defined as the presence of at least one group of streptococci (apart from group A) along with facultative anaerobes, anaerobic species, and/or *Enterobacteriaceae* sp. member [Larose-Pierre, J.Scrivens, Norwood and Rappa et.al.2002]. The affected area turns bluish purple and bullae appear, causing the skin and subcutaneous tissue to necrotize. Patients with multiple organ involvement, such as disseminated intravascular coagulation (DIC), acute renal failure, and liver failure, may advance to STSS [J.Cawley, Briggs, R.Haith, J.Reilly , E.Guilday, R.Braxton and Patton et.al.1999].

Neonatal sepsis:

The symptoms of neonatal sepsis include lethargy, fever, hypothermia, bradycardia, apnoea, abdominal distention, lethargy, and neutropenia. Neonatal sepsis can be categorized as either late-onset (4–90 days of life) or early-onset (0–3 days of life). While late-onset sepsis happens to infants who contract the bacterial pathogen via a healthcare worker or the hospital environment, early-onset sepsis happens to infants who contract bacteria from moms who are infected and those who are not. Even if neonatal sepsis mortality has decreased because of existing preventative strategies [Al-Haqan, S.Boswihi, Pathan and E. Udo et.al.2020]. Magnetic resonance imaging (MRI) and/or computed tomography (CT) scans are typically helpful in determining the soft tissue origins of GAS infection and in distinguishing between fasciitis and skin infections. When in doubt, a fascia biopsy should be used for surgical revision; in cases of infection should be used, respectively [Schmitz, Roux, Huttner and Pugin et.al.2018].

3.Adverse Events:

• Neuroautoimmune Disorders :

Headache, abducens nerve palsy, posterior reversible encephalopathy syndrome (PRES), aseptic meningitis, and seizures are among the neurological conditions linked to

immunoglobulin therapy. A headache after IVIG is a typical side effect. Headaches occur in over 50% of individuals following immunoglobulin treatment.

[L. Geller and Hackner et.al.2005]

- **Renal Impairment :**

Serious adverse effects from IVIG include haemolytic anaemia, thrombosis, arrhythmia, aseptic meningitis, renal impairment, and transfusion-related acute lung injury (TRALI). These negative effects are linked to individual variations and certain immunoglobulin formulations.

[L. Geller and Hackner et.al.2005]

- **Cardiovascular Disorder :**

Many investigations have documented arrhythmias that develop during or after immunoglobulin infusion. These arrhythmias can include bradycardia and supraventricular tachycardia, and most of these people had a history of heart illness. Due to the small sample size and potential bias in patient selection, the overall incidence IVIG-related headache in patients with a history of migraine was low among these studies.

[Darenberg, Ihendyane, Sjölin, Aufwerber, Haidl, Follin Andersson and Norrby-Teglund et.al.2003].

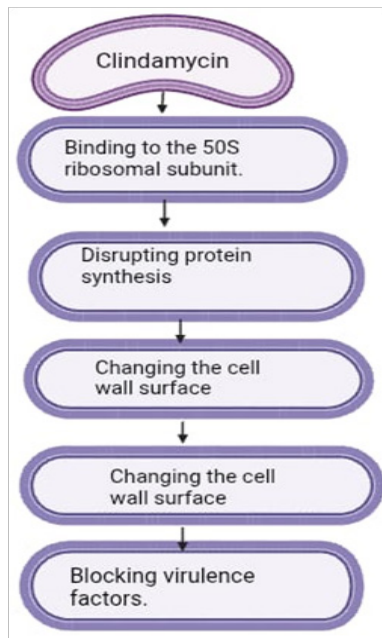
- **Haemolytic anaemia:**

Red blood cells can't be produced as quickly as they can be destroyed. The red blood cells' rupture. The spleen is where this most frequently happens, however it can also happen mechanically or in the reticuloendothelial system. Increased bilirubin excretion into the biliary tract might result from it, potentially leading to gallstones. Continuous free hemoglobin release has been connected to the onset of pulmonary hypertension, which in turn causes chest discomfort, syncope episodes, and increasing dyspnea. Eventually, pulmonary hypertension leads to right ventricular heart failure, which manifests as ascites and peripheral oedema. **[Schmitz, Roux, Huttner and Pugin et.al.2018].**

4. Mechanism Of Action:

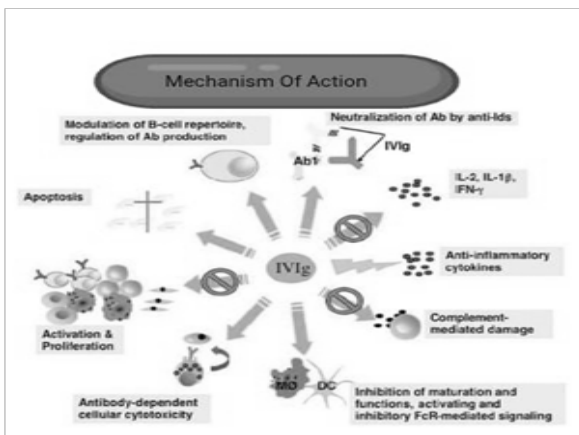
- **Clindamycin:**

Clindamycin suppresses the transcription and synthesis of several streptococcal proteins, including pyrogenic exotoxin superantigens, especially when given during early-log-phase growth. Clinical benefit in humans has only been demonstrated in retrospective case studies. As determined by the presence of STSS, length of hospital stay, and ICU admission, clindamycin-treated subjects were younger and had more severe disease than clindamycin-untreated cases. [Carapetis, Jacoby, Carville, Jeol Ang, Curtis and Andrews et.al.2014]. A statistically significant decrease in mortality is linked to the delivery of adjunctive IVIG to patients with STSS receiving clindamycin. Importantly, our research separates the effects of IVIG and clindamycin, which has occasionally been troublesome [Parks, Wilson, Curtis, Norrby-Teglund and Sriskandan et.al.2018].



- **IVIG :**

Some specialists suggest Polyspecific intravenous immunoglobulin (IVIG) as an adjuvant treatment for STSS, in part due to laboratory studies showing potentially positive outcomes such as improved bacterial clearance and neutralization of superantigens. However, clinical evaluation of IVIG for STSS has been challenging; the sole RCT was terminated early because of sluggish recruitment . Even though there are only a few non-randomized trials available, the interpretation of these results is made more difficult by the possibility of bias, the varying inclusion criteria, and the uneven application of clindamycin, which is frequently recommended as a penicillin adjuvant. We conducted a comprehensive evaluation of studies that assessed the use of adjunctive IVIG in STSS, both randomized and non-randomized. [Parks, Wilson, Curtis, Norrby-Teglund and Sriskandan et.al.2018]. Intravenous immunoglobulin (IVIG) stimulates leukocytes, neutralizes superantigens and toxins, and lowers excessive immunological responses in streptococcal toxic shock syndrome (STSS).IVIg neutralizes the superantigens that the STSS-causing invasive streptococcus infection produces.T-cell proliferation and cytokine production are inhibited by IVIg. IVIg causes leukocytes to respond. IVIg has an all-encompassing anti-inflammatory action. [Carapetis, Jacoby, Carville, Joel Ang, Curtis and Andrews et.al.2014].



5.Conclusion :

A high death rate and extremely severe clinical condition, STSS is thought to be partially caused by group A *Streptococcus*'s superantigen activity. This illness is deadly in part because of the patients' quick decline into multiple-organ failure, which necessitates intense care and organ support. Prompt antibiotic medication, surgical debridement, immunoglobulins, and hemoperfusion are some potential future therapeutic approaches that could help lower the high death rate.[**Miguel Silva et.al.2022**].IVIG seems to be a significant supplement to the usual treatment plan, even if the patient's favorable outcome was undoubtedly influenced by several clinical interventions and their young age. [**J.Cawley, Briggs, R.Haith, J.Reilly , E.Guilday, R. Braxton and Patton et.al.1999**]. Antibiotic resistance and immunological response (CRP) did not correlate. It advanced our knowledge of how virulence factors that cause newborn bacteraemia are carried in the central nervous system and antibiotic resistance[**Al-Haqan, S.Boswihi, Pathan and E. Udo et.al.2020**]. In summary, these findings imply that routine antibiotic prophylaxis for household contacts of cases is strongly supported, and that expanding the indications and putting policies in place to promote the use of clindamycin and IVIG in iGAS illness may lower mortality. [**Miguel Silva et.al.2022**].

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