STEVENS-JOHNSON AND TOXIC EPIDERMAL NECROSIS SJS AND TEN

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AIMS

- To update the use of IVIG and CORTICOIDS IN management of SJS/ TEN
- To remind Doctors being careful when giving drugs to patients.

BACKGROUND

- SJS is an immune-complex-mediated hypersensitivity complex.
- SJS and TEN are the different manifestations of the same disease.
- SJS typically involves the skin and the mucous membrane: Oral, nasal, eye, vaginal, urethral, gastrointestinal and lower respiratory tract mucous membranes.

EPIDEMIOLOGY

- From two to seven cases per million people per year.
- SJS is more common, outnumbering TEN by as much as 3/1.
- The incidence of SJS/TEN is approximately 100-fold higher among HIV-infected individuals than in the general population.
- SJS/TEN can occur in patients of any age. It is more common in women than in men, with a male/female ratio of 0.6.
- The overall mortality rate among patients with SJS/TEN is ranging from approximately 10% for SJS to > 30% for TEN.
- Mortality continues to increase up to 1 year after disease onset.

CLASSIFICATION

- SJS (A minor form of TEN): <10% BSA detachment. Mucous membranes are affected in over 90% of patients, usually at two or more distinct sites (ocular, oral, and genital).
- Overlapping SJS/ TEN: 10-30% BSA detachmnent
- TEN: >30% detachment. Mucous membranes are involved in the majority of cases.

CAUSES

- **Medications-** Most often associated with SJS/TEN are sulfonamide antimicrobials, phenobarbital, carbamazepine, and lamotrigine. Others: acetaminophen, PNC,NAIDS …
- **Infection** -*Mycoplasma.pneu,* CMV infections are the next most common trigger of SJS/TEN, Group A beta Streptococcus, Diptheria , Typhoid, HSV, AIDS, EBV, hepatitis, influenza, Cocsakie, Mumps, Rickettsia Coccidioidomycosis, Histoplasmosis, malaria and Trichomoniasis
- SJS is idiopathic in 25-50%

PREDISPOSING FACTORS

Risk factors for SJS/TEN include HIV infection, genetic factors, underlying immunologic diseases, and possibly physical factors.

PRODROME

Fever, often exceeding 39°C (102.2°F), influenza-like symptoms precede by 1 to 3 days the development of mucocutaneous lesions.

- Pain on swallowing may be early symptoms of mucosal involvement. Malaise, myalgia, and arthralgia…
- Eye: Red eye, tearing, dry, itching, pain eye; heavy eyelid and decrease vision, photophobia and conjunctival itching or burning…
- Skin: Erythroderma, facial edema or central facial involvement, skin pain, palpable purpura…
- Mucous membrane erosion and crusting, swelling of tongue

PHYSICAL

- Skin: Rashes-> macules, papules, vesicles, bullae, urticarial plaques, denuded skin.
- Mucosal involvement: edema, sloughing, blistering , ulceration and necrosis.
- Others: tachycardia, hypotension, epitaxis, conjunctivitis, corneal ulceration, balanitis, erosive vulvovaginitis, seizure, coma…

LABORATORY ABNORMALITIES

- Hematologic abnormalities, particularly anemia and lymphopenia, are common in SJS/TEN. Eosinophilia is unusual; neutropenia is present in about one-third of patients, and is correlated with a poor prognosis. However, the administration of systemic corticosteroids can cause demarginalization and mobilization of neutrophils into the circulation, and this may obscure neutropenia.

LABORATORY ABNORMALITIES

- Hypoalbuminemia, electrolyte imbalance, and increased blood urea nitrogen and glucose may be noted in severe cases, due to massive transdermal fluid loss and hypercatabolic state. Serum urea nitrogen >10 mmol/L and glucose >14 mmol/L are considered markers of disease severity. Mild elevations in serum aminotransferase levels (2 to 3 times the normal value) are present in about one-half of patients with TEN.

CLINICAL COURSE

- The acute phase of SJS/TEN lasts 8 to 12 days and is characterized by persistent fever, severe mucous membrane involvement, and epidermal sloughing that may be generalized and result in large, raw, painful areas of denuded skin.
- Reepithelialization may begin after several days, and typically requires two to four weeks. Skin that remained attached during the acute process may peel gradually and nails may be shed.

Diagnosis and Differential Diagnosis

- Skin biopsy is the definitive diagnosis.
- Skin biopsy specimens demonstrate that the bullae are subepidermal. Epidermal cell may be noted. Perivascular areas are infiltrated with Lymphocytes.
- Differential Diagnosis: Burn, conjunctivitis, dermatitis, scleritis, sarcoidosis, Sjogren, 4S, irradiation, trauma, scleroderma…

COMPLICATIONS

- Acute phase - In severe cases with extensive skin detachment, acute complications may include massive loss of fluids through the denuded skin, electrolyte imbalance, hypovolemic shock with renal failure, bacteremia, sepsis and septic shock, insulin resistance, hypercatabolic state, and multiple organ dysfunction syndrome. Abdominal compartment syndrome secondary to excessive replacement fluid therapy has been reported in a few patients.

COMPLICATIONS

- Pulmonary complications(eg, pneumonia, interstitial pneumonitis), the risk of progression to acute respiratory distress syndrome.
- Gastrointestinal complications may result from epithelial necrosis of the esophagus, small bowel, or colon. (Diarrhea, melena, small bowel ulcerations, colonic perforation, and small bowel intussusception…)

Long-term sequelae

- Ophthalmologic sequelae develop in approximately 50 to 90% of patients include dry eye, photophobia, ingrown eyelashes, neovascularization of the cornea, keratitis, and corneal scarring leading to visual impairment and rarely blindness.
- Oral and dental sequelae are not rare and include mouth discomfort, xerostomia, gingival inflammation and synechiae, caries, and periodontal disease. Severe dental growth abnormalities, such as dental agenesia, root dysmorphia…
- Dermatologic sequelae are common and include irregular pigmentation, eruptive nevi, abnormal regrowth of nails, alopecia, scarring.

Criteria for admission

- Minor may be treated as outpatient with topical steroid->daily follow-up
- Major : must be hospitalized.
- Transfer criteria would be the same as for the patients with thermal burns (grade 2C)
- a SCORTEN score of 0 or 1, and disease that is not rapidly progressing may be treated in nonspecialized wards. Patients with more severe disease and a SCORTEN score ≥2 should be transferred to intensive care units or burn units if available.

Prognosis-Scorten score(Grade 2C)

- Age>=40
- Malignancy : yes
- BSA detached>= 10%
- Tarchycardia>= 120/min
- Serum urea>=10mmol/l
- Serum glucose>=14mmol/l
- Serum bicarbonate<20mmol/l
- Mortality rates are as follows:(0-1;3,2%) (2;>=12,1%) (3;>=35,3%) (4;>=58,3%) (>=5;>=90%)
- Use on days one and three of hospitalization for SJS/TEN

Treatment

- No specific drug treatment has been consistently shown to be beneficial in the treatment of SJS. The best management is supportive care.
- Supportive care: wound care, fluid and electrolyte managemnet, nutrition support, ocular care, temperature and pain control, monitoring for/treatment of superinfection.
- Corticoid, IVIG, plasmapheresis, TNF inhibitors
- Evaluate the extent of epidermal detachment daily by percentage of BSA.

ANTIBIOTICS

- Antimicrobials are indicated in cases of urinary tract or cutaneous infections, either of which may lead to bacteremia
- Prophylactic systemic antibiotics are not useful esp. in the current of multiple-drug resistance

CORTICOID.1

- A large multicenter European study, suggested that a short course of moderate to high dose of systemic corticosteroids(eg, prednisone 1 to 2 mg/kg/ day for 3 to 5 days) may not be harmful and may have a beneficial effect if given early in the course of the disease(ie, within 24 to 48 hours of symptom onset).

CORTICOID.2

- In a systematic review of treatment of SJS/TEN in children, including 31 case series with 128 patients, 20 patients received either prednisolone or prednisone (1 mg/kg/d) or methylprednisolone (4 mg/kg/d) for 5 to 7 days. No deaths were reported; complications occurred in five patients (mild skin infections in three children and bronchiolitis in two).

CORTICOID.3

- In a retrospective analysis of 281 patients with SJS/TEN from France and Germany enrolled in the EuroSCAR study, 159 patients received variable doses of corticosteroids (ranging from 60 mg to 250 mg per day of prednisone equivalents), 75 IVIG (40 in association with corticosteroids), and 87 supportive care alone. The mortality rate was 18 percent in the corticosteroid group, 25 percent in the IVIG group, and 25 percent in the supportive care group. The odds ratio of death for patients treated with corticosteroids compared with patients treated with supportive care alone was 0.6 (95% CI 0.3-1.0), suggesting a potential benefit.

CORTICOID.4

- subsequent analysis of 442 patients from the RegiSCAR cohort did not find a survival advantage for patients treated with systemic corticosteroids, compared with patients treated with supportive therapy only (hazard ratio 1.3, 95% CI 0.8-1.9).
- In a systematic review of 439 patients with SJS/TEN, the mortality rate was 22 percent among patients treated with systemic corticosteroids and 27 percent among those treated with supportive measures only. In both groups, mortality rates were similar to those predicted by the SCORTEN score, without any significant difference related to the type of treatment.

CORTICOID.5

- Case-control study examined the effect of previous corticosteroid therapy on the course and outcome of SJS/TEN. The study included 92 SJS/TEN patients who were on corticosteroid therapy before the onset of disease and 321 randomly selected SJS/TEN patients not previously exposed to corticosteroids. The exposure to corticosteroids before the onset of SJS/TEN did not affect the disease severity and mortality; however, corticosteroids prolonged the latency (time from drug initiation to onset of disease) and progression of disease

CORTICOID.6

- Taken together, the results of these studies do not support the use of systemic corticosteroids for the treatment of SJS/TEN. In addition, since corticosteroids theoretically increase the risk of sepsis and protein catabolism and decrease the rate of epithelialization, their use in patients with extensive skin detachment is contraindicated. (**Grade 2C**)

Intravenous immune globulin.1

- Review of case series with at least 9 patients evaluated the outcome of 156 patients (22 with SJS and 134 with TEN or SJS/TEN overlap) treated with IVIG. The mean total dose of IVIG ranged from 1.6 to 3.9 g/kg. Treatment was started 3.5 to 9.2 days after the disease onset and given for 2 to 4 days. The average mortality rate was 20.5 % (range 0 to 42 %), with higher rates in centers where lower doses of IVIG were used or the time to treatment was longer.

IVIG.2

- In a series of 281 patients with SJS/TEN from the EuroSCAR cohort study, 35 patients were treated with IVIG alone and 40 with IVIG plus systemic corticosteroids. The dose of IVIG ranged from 0.7 to 2.3 g/kg and was given in 1 to 7 days. The mortality rate was 34 % in the group treated with IVIG alone, 18 % in the group treated with IVIG and corticosteroids, and 18 % in a group of 87 patients treated with supportive measures alone.

IVIG.3

- A systematic review and meta-analysis of 17 studies including 113 patients treated with IVIG and 130 with supportive care only found no difference in the risk of death between the two groups (odds ratio 1.00; 95% CI 0.58-1.75). However, a subgroup analysis showed a statistically nonsignificant reduction in the mortality risk for patients treated with high-dose IVIG (total dose ≥2 g/kg) compared with those treated with <2 g/kg (odds ratio 0.49; 95% CI 0.11–2.30).

IVIG.4

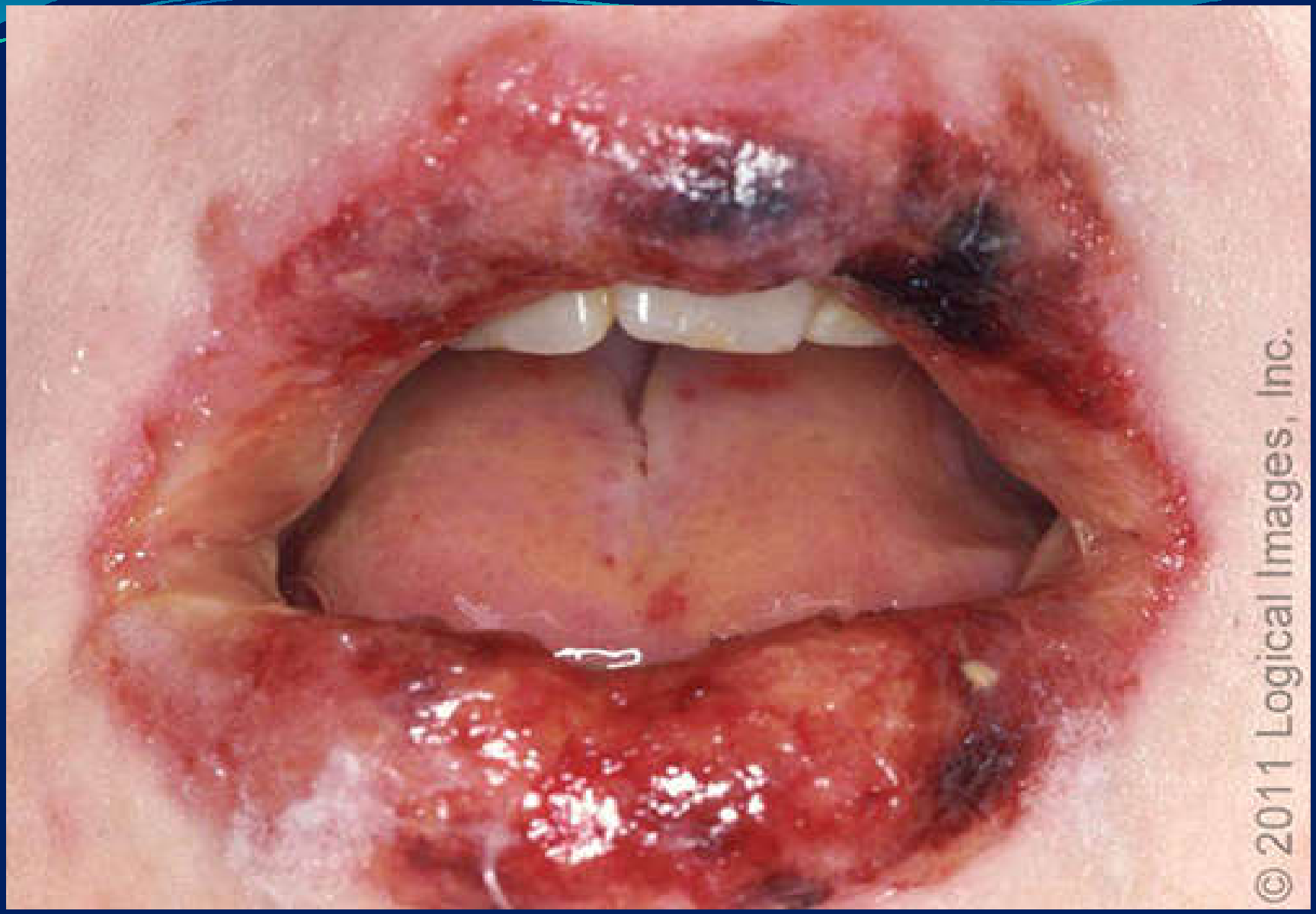
- In a systematic review of treatment of SJS/TEN in children including 31 case series (128 patients), 57 children were treated with IVIG 0.25 to 1.5 g/kg/day for 1 to 5 days. No deaths were reported in the IVIG group, whereas 2 of 33 patients treated with supportive therapy alone died. Poor quality and heterogeneity of the studies included did not allow a statistical analysis of pooled data.
- In a systematic review of 439 patients with SJS/TEN, the mortality rate was 24 % among patients treated with IVIG and 27 % among those treated with supportive measures only. The observed mortality rate in the IVIG group was slightly lower than that predicted by the SCORTEN score

IVIG.5

- In summary, there is no high quality evidence supporting the use of IVIG in SJS/TEN. However, if a decision is made to use IVIG for individual patients with severe disease, a dose of 1 g/kg per day may be given for three consecutive days (total dose 3 g/kg) in the early phase of the disease (ie, within 24 to 48 hours of symptom onset). (**Grade 2C**).

References

- UpToDate
- The Cochrane library
- Nelson textbook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