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RESEARCH ARTICLE

Profiles of Stevens-Johnson syndrome and Toxic Epidermal Necrolysis in A General Hospital in Singapore

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Abbreviations: SJS: Stevens Johnson Syndrome; TEN: Toxic Epidermal Necrolysis; ICD: International Classification of Diseases; HAS: Health Sciences Authority; CBZ: Carbamazepine; ED: Emergency Department

Introduction

Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are severe reactions which involve the skin and mucosa. They are characterized by mucocutaneous necrosis and detachment of the epidermis. The majority of cases of SJS and TEN are drug-induced. Other possible causes include infections, immunizations, environmental chemicals and radiation therapy. SJS and TEN can have a significant impact on public health because of high morbidity and mortality.

Objectives

The aim of this study was to determine the (i) epidemiology of this disease in Singapore, (ii) the most common offending agents, (iii) treatment measures and (iv) Duration of hospitalization. Correlating clinical severity, treatment measures and outcome may serve as a guide to identifying cases that could potentially be treated outpatient thus reducing admission rates.

Methodology

A retrospective review of medical records of patient's admitted with medical diagnosis of SJS/TEN was done. Patients were identified through searching for their International Classification of Diseases (ICD-9) code. All adult patients aged 18 years and above with the diagnosis of Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN) between 01 January 2009 and 01 January 2015 in a tertiary hospital were included.

Results

46 cases of SJS, 10 cases of SJS/TEN overlap and 31 cases of TEN were identified. There were 41 males and 46 females with a mean age of 56.5 years. Omeprazole, Allopurinol and Sulfonamides were the most common offending agents causing SJS and TEN. Specifically, Carbamazepine and Trimethoprim/Sulfamethoxazole were the most commonly implicated drugs for SJS. Omeprazole was the most common offending agent in TEN. Although treatment primarily involves the discontinuation of causative agents, 71.7% of SJS and 94.0% of TEN patients were treated with corticosteroids, cyclosporine or intravenous immunoglobulin (IVIG). None of the patients experienced adverse events of IVIG such as anaphylaxis or acute renal failure. 10 patients with TEN died (32.3%). The mean duration of hospitalization was 8.1 and 24.9 days for SJS and TEN respectively.

Discussion: Common Offending Drugs

A. Omeprazole Sensitivity- An Emerging Phenomenon?

Over prescription of PPIs has been reported in many Western countries, whereby up to 70% of patients on PPIs had no clinical indication or did not meet their country's criteria for taking these drugs [1]. The Health Sciences Authority (HSA), Singapore subsequently presented updated statistics in 2014 identifying 6 cases of omeprazole-induced SJS/TEN [2]. Majority of cases occurred within 6 weeks of commencing omeprazole. This study contributes further evidence to suggest the possibility of an emerging trend of over prescription of omeprazole locally. The primary prevention of SJS/TEN involves limiting exposure to high- risk drugs by prescribing only when indicated and using safer alternatives wherever possible. Hence, local data regarding prevalence and indication of prescription of PPIs should be further investigated.

B. Allopurinol

The high prevalence of allopurinol- induced adverse reactions in this study closely mirrors previously published local data [3]. Genetic susceptibility for SJS/TEN has been proposed and

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HLA-B*5801 is strongly associated with allopurinol-induced SJS/TEN in the European, Japanese, Han Chinese and Thai populations [4, 5]. Prescription of allopurinol for appropriate and justified indications can help limit the occurrence of SJS/TEN.

C. Anticonvulsants: Carbamazepine (CBZ), Phenytoin & Lamotrigine

Other commonly implicated drugs were anti-convulsants. CBZ has been reported as the most common culprit drug for SJS and TEN and a strong association between HLA-B*1502 and CBZ-induced SJS/TEN has been reported in Han Chinese, Thai, Indian and Malay patients [6, 7]. Hung et al [8] conducted a case-control study and concluded that phenytoin, lamotrigine and oxcarbazepine, which possess an aromatic ring like that of CBZ, share a common risk allele and should be avoided in the B*1502 carrier. The implementation of HLA-B*1502 genotype screening as standard of care for new carbamazepine patients of Asian ancestry was commenced on 30 April 2013 locally [9]. In view of forward measures, the prevalence of adverse events may be expected to decrease.

D. Trimethoprim-Sulfamethoxazole and Its Use in HIV/AIDS Patients

There were 4 HIV/AIDS patients and trimethoprim–sulfamethoxazole was implicated in 3 cases of SJS and 1 case of TEN. The average duration of drug ingestion prior to onset was 20.0 days and the patients were hospitalized for a mean duration of 16.5 days. There was no reported mortality. These results were comparable to Western countries, whereby most cases of ADR in HIV infected patients were related to antibacterial sulphonamides. Male sex, history of syphilis, CD4:CD8 ratio < 0.10, and low CD 4 cell count have been implicated as positive independent predictors of the development of hypersensitivity [10].

Treatment

Immediate cessation of the suspected causative drug is key to the management of SJS/TEN. The controversy over whether systemic corticosteroids should be used to curtail progression remains unresolved. Su et al [11] reported that 87.5% of patients with severe cutaneous drug reactions received systemic steroids with resolution of symptoms. There has also been renewed interest in cyclosporine, with an ongoing phase 3 clinical trial exploring its effect on clinical outcomes when used as an adjuvant treatment to supportive management [12]. An open, phase II trial to determine the safety and possible benefit of cyclosporine in 29 patients showed that cyclosporine 3 mg/kg/d for 10 days and tapered over a month, when given early, stabilized epidermal detachment, and was not associated with any mortality in SJS, SJS/TEN and TEN [13]. Comparably in this study, 10.9% of SJS and 22.0% of TEN patients were treated with cyclosporine with good recovery and nil reports of mortality. A recent local study that appraised the efficacy of IVIG reported that its use was not associated with a reduction in mortality [14]. 4.3 % of SJS and 61.0% of TEN patients were treated with IVIG. This included 9 patients who eventually died. The high mortality rates may reflect greater severity of disease compounded by a lack of efficacy of IVIG. In view of the above, the role of IVIG in future management could become obsolete.

Could SJS be Managed Outpatient?-Need for Escalation of Care and Duration of Hospitalization among SJS Patients

Among the patients with SJS, only 1 required escalation to a burns intensive care unit due to the progression of disease. There were no reported mortalities and the average duration of hospitalization was 8.1 days. Noskin et al [15] described the successful outpatient management of 4 patients with drug-induced SJS using oral corticosteroids. However, the severity of disease (e.g. body surface area) and complications were not reported. They proposed that outpatient management could be considered in patients with mild to moderate symptoms and recommended oral prednisolone be commenced at 60-80mg a day with close follow-up. The authors recognized that outpatient treatment would only be feasible in patients with good home support services and those who are able to return for frequent reviews. It is considerable that SJS be managed outpatient but this would need to be borne out in larger, collaborative, prospective studies.

Admitting Diagnosis at the Emergency Department (ED)

Severe life-threatening dermatological diseases require prompt recognition and treatment to reduce morbidity and mortality. Overall diagnostic concordance of the ED diagnosis with the dermatologist in one of the local tertiary hospitals was reported as 57.5%, with a discordance rate of 42.5% [16]. Comparably, in this study the accurate diagnosis of SJS/TEN was established in 55.1% of patients at the ED, with a similarly high discordance of 44.9%. High discordance rates are not unexpected as skin disorders frequently pose a diagnostic challenge due to the broad spectrum of clinical manifestations. Hence, future consideration of teledermatology may be beneficial in evaluating urgent dermatologic complaints in the ED, whereby digital photographs of the patient's skin lesions are transmitted electronically to a dermatologist for an opinion.

Conclusion

Overall, Omeprazole, Allopurinol and Sulfonamides were the most common offending agents causing SJS and TEN. The most common complications included sepsis, conjunctivitis and transaminitis. Corticosteroids and Cyclosporine show good clinical response. The role of IVIG has become obsolete and should be discontinued. It is considerable that SJS be managed outpatient but this would need to be borne out in larger, collaborative, prospective studies. Accuracy of diagnosis at the emergency department and timely withdrawal can prevent delays in treatment and improve outcome.

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