

12-4-2015

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Recommended Citation

Hart, Sharon K. and Frerichs, Dawn, "Stevens Johnson Syndrome: How Diagnosis Impacts Disease Course" (2015). *Graduate Research Projects*. 78.

<https://knowledge.e.southern.edu/gradnursing/78>

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December 4, 2015

Translational Evidence Based Practice Manuscript with Matrix

A Paper Presented to Meet Partial Requirements

For NRSG-527-A

Nursing Research

Southern Adventist University

School of Nursing

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Stevens Johnson Syndrome: How Diagnosis Impacts Disease Course

Stevens Johnson syndrome (SJS) is a rare, potentially life threatening, severe adverse drug reaction involving the skin and mucous membranes. SJS affects only one to five patients per million annually (Rehmus, n.d.), therefore providing a challenge to medical providers for timely diagnosis and appropriate treatment. Even after the patient battles SJS for their lives, their struggle is long from over. Complications of SJS include living with scars and complications related to eye injury and corneal tears that their bodies sustained from this rare condition. By facilitating the knowledge base of the Advanced Practice Nurse (APN), an expedient diagnosis of SJS may be achieved in order to prevent delay in diagnosis that can increase complications from infections and mortality.

Background

SJS was first noted in 1922 as an acute mucocutaneous syndrome in which cell death causes the epidermis to separate from the dermis (Harr & French, 2010). Two American physicians named Stevens and Johnson first noted this syndrome in two young boys with symptoms “described as an acute mucocutaneous syndrome characterized by severe purulent conjunctivitis and severe stomatitis with extensive mucosal necrosis” (Naveen, Pai, Rai, & Athanikar, 2013, p. 80). Presenting symptoms typically include fever, sore throat, and fatigue that can be misdiagnosed and treated with a course of antibiotics, which could possibly continue or worsen the condition. Any mucosal membrane has the potential of being affected. SJS has been linked to agents including NSAIDS (non-steroid anti-inflammatory drugs), allopurinol, phenytoin, carbamazepine, barbiturates, anticonvulsants, and sulfa antibiotics, but almost any medication can be a cause (DeClerck, Jhun, Bright & Herbert, 2015). Individuals who experience SJS have usually completed a course of antibiotics or drug therapy and present with a

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rash, fever, lesions in the mouth, and/or eye irritation. Unlike typical allergic drug reactions, the presentation of SJS is delayed by one to four weeks after the initiation of the medication.

SJS and Toxic Epidermal Necrolysis (TEN) present as severe mucosal erosions with widespread erythematous, cutaneous macules or atypical targets (Ghislain & Roujeau, 2002), SJS and TEN are considered to be the same syndrome, but on opposite ends of the spectrum. SJS differs from TEN by the degree of body surface involvement. In SJS the detachment of the epidermis is less than 10%, with the SJS/TEN overlap skin detachment range is 10-30%, and more than 30% of body surface involvement happens with TEN. When there is more skin surface involvement there is a corresponding higher mortality rate. The mortality rate for SJS is 5-15% and 30-35% for TEN (Ghislain & Roujeau, 2002). Risk factors for both SJS and TEN are increased when there is continued exposure to the predisposing factor, an autoimmune disorder, or a human leukocyte antigen (HLA)-linked genetic susceptibility. This HLA-linked factor affects individuals of Asian descent and makes them more susceptible to SJS. “The genetic variations most strongly associated with SJS/TEN occur in the *HLA-B* gene” (Genetics Home Reference, n.d.). The HLA complex helps the body to tell the difference between proteins the body makes and proteins that are foreign substances like those made by viruses and bacteria. When the body has a reaction to drugs, a substance called granulysin is released by the immune cells cytotoxic T cells and natural killer (NK) cells which destroys skin and mucous membrane cells (Genetics Home Reference, n.d.). When the cells are destroyed or die that is what causes the peeling and blistering skin associated with SJS/TEN patients.

Research Question

Due to SJS being a rare reaction, it is crucial to provide primary and emergency care providers with the appropriate tools to aid in early recognition of SJS symptoms. Early

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recognition and subsequent diagnosis along with removal of the offending pharmacological agent will assist in minimizing mucocutaneous damage. Many SJS and TEN patients present with skin lesions that are inflamed and resemble partial thickness burns or scalded skin. Primarily, the goal of treatment is to reduce the devastating impact of SJS while minimizing avoidable long-term effects of therapy. Does early diagnosis shorten the disease course in patients with SJS? Ultimately, a strong working knowledge by the Advanced Practice Nurse regarding SJS is imperative in order to reduce additional risks and facilitate a return of homeostasis by the patient.

Literature Review

The focus of this literature review is to provide information regarding how diagnosis impacts the disease course in patients with SJS and to facilitate understanding regarding current treatment plans. Even though SJS and TEN affect only a small number of individuals, it is important for health care providers to understand what can be done to improve the process in diagnosing these individuals, improve the recovery time and eliminate any lasting injury from the disease process. The following eight literature reviews attempt to determine what current evidence shows regarding how diagnosis from time of symptom onset impacts the disease process and additional long-term effects from SJS.

One study by Naveen, Pai, Rai & Athanikar supported that “early identification of the drug will help in prompt withdrawal of the drug thus reducing mortality and morbidity among the patients with SJS/TEN” (Naveen, et al., 2013, p. 80). A focus of the study was to help those prescribing and treating patients to use caution when prescribing medications and to understand the risk of the drugs that cause the life threatening reactions. In this retrospective analysis, anti-epileptics, antibiotics, antipsychotics, analgesics and antiretrovirals were the causal drugs. More

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patients were affected by antiepileptics in this study (50%) followed by antibiotics. The drug that had a higher morbidity and mortality rate was ofloxacin instead of the anti-epileptic that had a higher usage rate. The drug ofloxacin had a longer recovery time of 9.6 days and anticonvulsants had 6 days. The study emphasized drugs that were the possible trigger of SJS/TEN.

With polypharmacy becoming more common it is important to find the culprit drugs early to ensure removal is performed accurately and to avoid removing effective drug therapies. The importance of this study will help APNs and physicians to understand which drugs could be possible triggers of SJS/TEN and what treatment plans could be effective. Another aspect that came out of this study was the use of steroids and how steroids could affect the outcomes of SJS/TEN if given early in the treatment process. The limitations of the study are that it had a small sample size of 22 individuals, 14 males and 8 females. The age group that was most affected in this study was 20-40 years old, but the mean age in other studies varied, so age could play a factor in reaction times of the offending drugs.

In a multicenteric, retrospective study completed by Barvaliya, Sanmukhani, Patel, Paliwal, Shah, & Tripathi (2011) data for patients with SJS and TEN were evaluated to “find out the proportion of individual drugs involved, major complications, and cost of management” (p.116) associated with these diagnoses. Of the 32 cases included, antimicrobials were the most common causative drug followed by nonsteroidal anti-inflammatory drugs (NSAIDS) and antiepileptic drugs. Secondary infections were the most common complication and the cost of management was higher in patients with a SJS/TEN overlap or TEN diagnoses in comparison to other adverse drug reactions (ADR's) while SJS remained similar in cost. Barvaliya et al. (2011)

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also compared SCORTEN scores with actual patient mortality. The research findings showed a higher mortality rate with a higher SCORTEN score.

Limitations noted within this study include 13 patients with co-existing HIV and a small sample size. Patients with co-existing HIV decrease generalizability of the findings while enhancing the knowledge of potential causes of SJS in this vulnerable population. The findings increase knowledge concerning the most common causative drugs in patients with SJS and TEN for the stated population and continue to validate the value of SCORTEN for predicting mortality.

A small study by Mehta, Prajapati, Mittal, Joshi, Sheth, Patel, & Goyal (2009) examined the association of human leucocyte antigen (HLA)-B*1502 allele and carbamazepine induced SJS in Indian patients. This research was based on the strong association between the HLA-B*1502 allele and carbamazepine induced SJS in Han Chinese patients. Previous research suggests that carbamazepine induced SJS and its association with the HLA-B*1502 allele is ethnicity specific for Asian patients.

Carbamazepine is a commonly prescribed antiepileptic in India and is responsible for many cases of SJS/TEN in Indian patients. Mehta et al. (2009) found that six of the eight Indian patients with carbamazepine induced SJS had the HLA-B*1502 gene, while none of the ten patients in the control group had the gene. The association between the HLA-B*1502 gene is not as strong in Indian patients in comparison to Han Chinese patients, but this research does show a significant association ($P=0.0014$) between the HLA-B*1502 allele and carbamazepine induced SJS in Indian patients.

The main limitation within this study was the small sample size. The findings suggest the need for more research concerning genetic susceptibility and its association with the

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development of SJS/TEN. This research promotes knowledge concerning potential causes of SJS in Indian patients which is useful for any health care provider caring for an ethnically diverse group of patients. All providers should have an understanding of genetic susceptibility when prescribing medications for ethnically diverse patients.

Bansal, Garg, Sardana, and Sarkar (2015) completed an analysis on the predictive value and accuracy of the SCORE of Toxic Epidermal Necrolysis (SCORTEN) scale in predicting disease severity and patient prognosis. SCORTEN was developed and validated in 2000 by Bastuji-Garin et al. as a way for health care providers to predict disease severity and mortality based on seven parameters in patients with SJS and TEN (Bansal et al., 2015).

This study evaluated SCORTEN values on days 1, 3, and 5 following diagnosis and compared them to actual mortality. Of the 60 patients in the study, the discriminative ability of SCORTEN values was appropriate at each time point with day 5 being the most significant ($P < 0.001$). Bansal et al. (2015) also reported that of the SCORTEN parameters only heart rate, blood urea, and serum bicarb were statistically significant ($P < 0.05$) concerning mortality. Other risk factors including delayed hospitalization, hypernatremia, and skin colonization were evaluated and did not show statistical significance with patient mortality. The researchers shared how the first eight to twelve days of SJS/TEN is considered the acute phase during which the disease progresses. During this phase, time of symptom onset influences SCORTEN's predictive ability greater than length of hospital stay. Ethnicity must also be considered when evaluating patients with SJS/TEN due to the noted differences in causative factors, genetics and comorbidities. All 60 patients received conservative treatment which included "withdrawal of the causative agent, fluid replacement, nutritional support, temperature regulation, provision of daily dressings and prophylactic antibiotics" (Bansal et al, 2015, p. e19). The mortality rate of

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16.7% noted in this study presents conservative treatment, as previously described, as a valid option for SJS/TEN.

Limitations noted in this research included a participant mean age of 23.3 years (Bansal et al.) while the original study, completed by Bastuji-Garin et al., had a mean age of 42.3 years. With the SJS and TEN being a rare reaction, 60 participants is a large number therefore strengthening the validity of this study. SCORTEN's predictive value remains valid and continues to be a useful tool for providers when caring for patients with SJS.

A large cohort study of 513 patients with SJS or TEN from six countries Austria, France, Germany, Israel, Italy, and the Netherlands were enrolled in EuroSCAR from a network of about 1800 hospitals. This is a registry of a multinational collaborative research team that was established in 1988 to study severe cutaneous adverse reactions (SCAR), recently changed to RegiSCAR-group. Collaborating members include specialists in dermatology, epidemiology, genealogy and immunology where they studied three different varieties of SCAR, which include SJS/TEN. The majority of enrolled patients (80%) were from France and Germany. There were 379 patients that had confirmed diagnosis of SJS or TEN who developed a reaction outside the hospital. The patients were classified by any treatment after hospitalization that used systemic corticosteroids, intravenous immunoglobulin (IVIG) or immunosuppressive agents. The study analyzed differences in outcomes from three different drug treatment plans in relation to earlier and later treatment of a combination of IVIG only, IVIG and corticosteroids or corticosteroids only. The research supports that age is an important factor in mortality with the death rate being lower in children than adults. Other factors in this study that contributed to a "poor prognosis", were related to new diagnosis of cancer or other possible underlying diseases like "hyperglycemia, elevated urea, and decreased bicarbonates" (Schneck et al., 2007, p. 33). The

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SCORTEN scale which is a predictor of mortality and severity of illness was not used in this study because not enough data were collected in the EuroSCAR study. There were 134 patients with SJS (35%), 136 patients with SJS/TEN overlap (36%), and 109 patients with TEN (29%). Authors concluded that the mortality rate was 21% or 81 patients who did not survive their disease process. There was a strong correlation of death risk related to the patient's age and severity of disease.

The limitation of this study were differences in two main countries, France and Germany, and there were no significant benefit from any one medication treatment, neither was there any difference in outcomes related to early or late treatment. The study pointed out that there were many challenging aspects to control in this study to get a definitive answer on treatment plans of corticosteroid and IVIG medication benefits. Another study would be necessary to observe a uniform treatment plan especially studying a low or high dose regimen to provide a better outcome analysis and the effects on the disease course of SJS/TEN.

The importance of the study was the finding that no treatment modality was better in treating SJS/TEN, than simple early detection and removal of the offending drug and starting supportive care early. The strengths of the study include a well-defined population, the largest ever studied. Patients were assessed by an expert committee and information was obtained in a way to assure correct classification of the disease stage.

A study examined by Kardaun and Jonkman (2007) found Dexamethasone Pulse Therapy (DPT), if given early in the treatment process, can possibly reduce the mortality risk. DPT is the administration of large doses of drugs in an intermittent manner to enhance the therapeutic effect and reduce side effects ("What is Pulse Therapy, n.d.). DPT was started early and contributed to a relatively quick stabilization and healing, may even have halted the process of apoptosis or cell

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death. If DPT is given for longer periods of time it increases the risk of infection. On the other hand corticosteroids usually are not given because it can delay wound healing and cause sepsis. DPT is used with corticosteroids in severe, sometimes autoimmune, diseases. The only definitive way to diagnose SJS/TEN is to take a skin biopsy that verifies sub epidermal involvement. In this study, DPT treatment was started as soon as a definitive diagnosis was made.

The strength of the study showed that using DPT early in the disease course could possibly stop the cell damage and could reduce mortality in SJS/TEN patients. The limitations were a small sample size of 12 patients over a 10 year period and it was difficult to show statistical relevance because of the small number of patients.

Another retrospective study of treating patients with IVIG therapy was completed by Gravante, Delogu, Marianetti, Trombetta, Esposito and Montone in 2007. The study consisted of understanding how late referral to their center increased the risk of mortality in patients because IVIG therapy treatment was not started early and the risk of infection increased. There was a 10 day delay in referral in starting the IVIG therapy and supportive care. “This delay of referral increased mortality probability of 416.5 times, with the absence of IVIG therapy of 67.5 times and more than 2-types of bacteria 84 times” (Gravante, et al., 2007, p. 121). Late referral and total body surface area of detached skin are two factors that contributed to an increased death rate. Out of 35 patients that had an initial diagnosis of TEN, 32 patients were included in this study. The 32 patients that were evaluated, there was one case of SJS and seven patients with SJS/TEN overlap. This made up 25% with SJS involvement and a total mortality rate of 34.4% which is 11 out of 32 patients studied (Gravante, et al., 2007).

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The limitations in this retrospective study show that it is difficult to determine how sick patients were at time of referral. This could have an impact on mortality rates and what the treatment regimens were at the time of the study. Another limitation was the small sample size. The importance of the study showed that septicemia played an important role in mortality, and if there were more than three different bacteria present during hospitalization than this increased the risk of death for patients. This study showed an encouraging outcome of giving IVIG even if there is late referral to treatment. Further studies are recommended to understand current treatment modalities and the specific effect on IVIG therapy. Even though IVIG therapy is not well established for SJS/TEN in this study, the delay in introducing specific immunoglobulin-blocking therapy and specific support therapy contributed to an increased risk of death.

A study completed by Singh, Chatterjee, and Verma (2013) compared the use of cyclosporine versus steroids for treatment of patients with SJS and TEN. The researchers reported a significant reduction in the amount of time to the arrest of progression of SJS/TEN ($P = 0.04282$), total re-epithelization time ($P = 0.009956$) and hospitalization stay ($P = 0.02597$) in those treated with cyclosporine in comparison to those treated with corticosteroids. There were no statistically significant differences noted between the cyclosporine and corticosteroid groups concerning age, total body surface area (TBSA) and onset of disease to admission time. Singh et al. also reported on other studies showing that early withdrawal of the causative drug positively influenced prognosis and causative drugs with a long half-life increase the risk of mortality. Identification of the causative drug can be challenging in patients receiving multiple medications that have the potential to cause SJS/TEN.

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This research was conducted over a one year time span on eleven patients who has SJS or TEN. Once again the number of participants is small for research purposes, but when combined with other studies, the evidence does promote the use of cyclosporine in uncomplicated cases of SJS and TEN. Timely diagnosis from onset of symptoms and removal of the causal agent combined with cyclosporine treatment provides hope for providers who aim to decrease mortality in patients with SJS and TEN.

Recommendations

One recommendation to practice is to have a better understanding of how certain medications are a leading cause of SJS and TEN in over 75% of cases affecting both adults and children. When patients present with symptoms resembling SJS, a thorough drug history and identification of any causative medications must be identified. The causative agent should be eliminated and supportive care started immediately following diagnosis. If the reaction resulted from a sulfonamide, early diagnosis will provide avoidance of drugs that have a sulfa-base, such as silver sulfadiazine ointment, which is commonly used for burn patients. The Advanced Practice Nurse must have a strong working knowledge of SJS/TEN symptoms and causative medications to reduce additional risks and facilitate early treatment plans for the patient.

Conclusion

The reviewed literature consistently stated that apart from intensive supportive therapy, there is no accepted guideline for treatment or standard practice that exists besides supportive care. Most of the literature states that larger cohorts need to be studied and that there still is a lack of information regarding SJS/TEN and the benefits of IVIG, cyclosporine and corticosteroid treatment. When there is a delay in early diagnosis, there is an increased risk in mortality because the causative drug is still triggering injury and supportive care has not been initiated.

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In order to advance knowledge about SJS/TEN and prevent delay in diagnosis, it is important to have concise drug information given to all physicians and primary care providers. Adverse drug reactions are the leading cause of SJS and TEN and a multidisciplinary approach is needed to manage any complications of the syndrome. More than 100 drugs are associated with SJS/TEN, and an improved system of warnings is needed in drug dictionaries regarding any associated risk. It is important for health care providers to understand what can be done to improve the process of diagnosing these individuals, shorten their disease course and eliminate lasting injury from the disease process.

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(See Appendix A for Matrix Evaluation Table for Stevens Johnson Syndrome)