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Overview of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

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This knowledge-based activity is targeted for all pharmacists and is acceptable for 1.0 hour (0.1 CEU) of continuing education credit. This course requires completion of the program evaluation and at least a 70 percent grade on the program assessment questions.

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Objectives

After completion of this program, the reader should be able to:

1. Discuss the impact of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).
2. Describe the three most commonly proposed immunological mechanisms underlying SJS and TEN.
3. List medications commonly implicated in causing SJS and TEN.
4. Discuss commonly used therapies for SJS and TEN and the controversy surrounding them.

Abstract

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are immunologic reactions that typically present due to drug hypersensitivity. These reactions present with serious mucocutaneous manifestations that can lead to significant morbidity and mortality. The pathogenesis of SJS and TEN have yet to be clearly elucidated, but three potential immunologic mechanisms have been defined in literature: granulysin, Fas-FasL, and perforin and granzyme B. Medications have been immunologically linked as the primary causative agents of SJS/TEN. Corticosteroids, intravenous immunoglobulin administration (IVIG) and cyclosporine have been employed as treatments; however, none have resulted in consistent positive outcomes. Pharmacists have a significant role in identifying and discontinuing the offending agent and recommending pharmacotherapy for treatment.

Overview

Drug hypersensitivity reactions are major clinical complications that can result in serious and life-threatening conditions. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe immunologic reactions that clinically present with a widespread, cutaneous rash, target-like lesions and skin detachment.¹ Stevens-Johnson syndrome and toxic epidermal necrolysis are rare occurrences with only one to two cases per one million individuals reported annually.² The characteristic rash and lesions tend to localize in the facial region, upper trunk and extremities of afflicted individuals especially as the severity of the reaction pro-

gresses (Figure 1). However, as a practicing pharmacist, it is important to note that a majority of these cases are precipitated by a hypersensitivity reaction to certain medications. Therefore, SJS and TEN are typically classified as severe cutaneous adverse drug reactions (SCARs).³ Common medications that elicit such a violent response from the body are discussed below.

Patients who develop SJS/TEN may present with a variety of symptoms. Initial symptoms, which often precede cutaneous involvement, can be non-specific and include fever, sore throat and stinging eyes.² While the level of epidermal skin detachment is utilized to determine the extent of the reaction, any of the mucous membranes in the body can be impacted.³ All major organ systems containing mucosal membranes can be drastically impacted; gastrointestinal, ocular, nasal, respiratory and genital membranes may potentially inflame and scar.⁴ In severe cases, the scarring of organs results in a complete, irreversible loss of function that can contribute to mortality.⁴ It is also common for patients to experience secondary infections of the skin or other organs during the course of the syndrome.⁵ Frequently, survivors of SJS/TEN will experience ophthalmologic sequelae based on the extent of ocular membrane damage incurred by the reaction.¹ These potential complications illustrate that SJS/TEN can result in both significant morbidity and mortality.

Stevens-Johnson syndrome and toxic epidermal necrolysis have similar pathophysiology and clinical presentation but are differentiated based on severity of disease.⁶ Stevens-Johnson syndrome is classified as presenting with skin detachment that affects 10 percent or less of the body.⁶ A patient will be diagnosed with TEN when 30 percent or more of the skin becomes detached. This separation of the epidermis from the underlying dermis is the direct result of immune-mediated keratinocyte apoptosis, and the extent of apoptosis determines the total percentage of skin impacted.⁵ Overlap of SJS and TEN can result when 10 to 30 percent of the body is visibly impacted, making a distinct diagnosis difficult.⁶ Stevens-Johnson syndrome/toxic epidermal necrolysis can be assessed with the SCORTEN (SCORE of Toxic Epidermal Necrolysis) system, a set of criteria utilized to predict mortality outcomes for diagnosed individuals.⁷ Such criteria include patient age, serum bicarbonate levels, heart rate and the presentation of malignancies.⁷

Immunologic Mechanism

Although the pathogenesis of SJS and TEN are not fully understood, the processes are known to be due to an immune response. Re-challenging with the offending stimulus hastens the onset and provokes a more severe reaction; therefore re-challenging is not recommended. The majority of cells that

present in this immunological reaction are CD8+ Cytotoxic T-lymphocytes (CTL), CD3+ T Cells, CD56+ Natural Killer (NK) cells and Natural Killer T-lymphocytes (NKT).³ The cytotoxic response of CD8+ T cells in the skin is induced by the recognition of the human leukocyte antigen (HLA) class I molecules that bind the drug or endogenous antigen promoting clonal expansion of the cytotoxic lymphocytes. These cells migrate to the skin and produce inflammatory mediators, such as granulysin, perforin and granzyme B. These mediators then promote apoptosis of keratinocytes which causes the separation of the epidermis from the dermis.⁶ There have been recent findings that certain genotypes of the HLA-I molecules may be associated with this reaction.⁵ The complete mechanism of this reaction has not been clearly defined in the literature, but there are currently three major theories proposed to explain the mechanism.

Figure 1. Male presenting with SJS along chest, hands and mucosal tissue around the mouth



http://missinglink.ucsf.edu/lm/DermatologyGlossary/stevens_johnson_syndrome.html
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The first proposed mechanism is granulysin as a mediator of SJS and TEN. Granulysin is a cytolytic cationic protein stored in the granules of CTLs and NK cells that is cytotoxic for tumor cells, bacteria, fungi and parasites. In SJS and TEN granulysin is released and binds to the keratinocyte surface via its charge, promoting ion flux. Ion flux within the keratinocytes causes increased permeability of the mitochondrial membrane resulting in mitochondrial damage and cytochrome-c release, which in turn promotes apoptosis. Granulysin is a chemo-attractant and pro-inflammatory activator of T cells and monocytes, thus recruiting more cells to amplify this reaction.³ In one study, granulysin was found to be a key molecule responsible for keratinocyte death with a direct correlation between amount of granulysin and severity of tissue destruction.³ Granulysin levels in serum were suggested to have clinical significance by acting as a potential marker for predicting the prognosis, monitoring the progression and evaluating the therapeutic response for SJS/TEN.⁵

Activation of the apoptosis-inducing surface receptor Fas by its corresponding ligand (FasL) has also been suggested as a proposed mechanism of keratinocyte apoptosis. Fas is a death domain receptor expressed on the surface of a wide

array of other cells including keratinocytes. FasL, which is prominently expressed by activated CTLs, binds and activates Fas to promote the trimerization of Fas receptors which then activate Fas-associated death domain protein (FADD). Fas-associated death domain protein causes the nucleation of inactive procaspase 8 allowing autoactivation of procaspase 8 molecules to active caspase 8. Caspase 8, in turn, activates the caspase cascade activating executioner caspases which cause the degradation of cytoskeletal proteins and DNA.⁵ The IVIG treatment strategy to prevent further apoptosis of keratinocytes is based upon the Fas-FasL hypothesis.⁶

The perforin and granzyme B pathway is the last mechanism proposed to produce the keratinocyte apoptosis. Activated CTLs and NK cells produce perforin and secrete it into the keratinocyte membrane. Perforin is a transmembrane protein that binds and forms a pore through the cell membrane. Granzyme B is a protease released to enter the keratinocyte activating the caspase cascade resulting in apoptosis. It has been proposed that increasing levels of perforin, granzyme B, TNF-alpha and FasL have been observed to be related to disease severity of drug hypersensitivity (from mild maculopapular rashes to severe TEN).⁵

Although the exact immune mechanism is unknown, medications have been immunologically linked as the primary causative agents of this hypersensitivity reaction. Up to 77 to 95 percent of cases are directly associated with specific medication use and more than 100 drugs have been associated with SJS/TEN.¹ Table 1 illustrates some of the most common medications causing SJS and TEN. Other potential causative agents are *Mycoplasma pneumoniae*, viruses and one study implicated vaccines specifically for smallpox, anthrax and tetanus.^{8,9}

Table 1. Summary of Commonly Implicated Medications of SJS and TEN.

Antibiotics	Cephalosporins, fluoroquinolones, macrolides, sulfamethoxazole and trimethoprim, penicillins
Anticonvulsants	Phenytoin, carbamazepine,* ⁵ valproic acid, Phenobarbital
NSAIDs	acetaminophen, ibuprofen, nimesulide, diclofenac
Gout	Allopurinol* ⁵
Other	Thiazides, multivitamins, ranitidine

*data currently recommending genotype testing before use of this medication

Treatment Strategies

Finding an ideal therapeutic treatment option for SJS/TEN patients has proven to be difficult. Due to the rarity of the disease, obtaining and producing a case-controlled clinical

trial with a large sample size of patients is a daunting task. However, based on limited clinical data, the outcome of SJS/TEN patients is largely dependent on three management measures: supportive care, withdrawal of the suspecting drug and active treatment.

First, SJS/TEN patients have an improved chance of survival depending upon how quickly they are transferred to a burn unit for supportive care. Aggressive skin care is available in this setting, including critical fluid resuscitation, electrolyte balance and enteral nutrition maintenance. Body temperature and other signs of infection and sepsis should be closely monitored. Due to the potential eye complications, early ophthalmologic evaluation of these patients is critical.⁷ Visual acuity and scarring can be protected and prevented with application of short-term topical corticosteroids (fluorometholone ointment 0.1 percent, applied every one to two hours), use of amniotic membranes and coverage of the ocular surface with symblepharon rings.^{7,10} Moreover, patients are often unable to eat or drink due to oral and esophageal mucosa involvement from the disease. Viscous lidocaine or other topical oral local anesthetics can be used before meals, making food intake more tolerable.^{7,8} Finally, wound care and skin treatment are necessary. Wounds should be treated conservatively using nonadhesive dressings.² Avoid topical sulfa containing medications and skin debridement, as blistered skin favors re-epithelialization.²

Second, upon diagnosis of SJS/TEN, the causative drug(s) should be rapidly identified and withdrawn.¹¹ In concordance with identifying the risk drug within a patient's recent history, analysis of drug intake and development of symptoms is necessary. The most likely offending drug that should be suspected as a causative drug for SJS/TEN is one that has been newly administered in the past four weeks.¹¹ Refer to Table 1 for a summary of commonly implicated medications of SJS and TEN.

Lastly, initiating an active treatment is a recommended measure. However, there is no agreement as to which, if any, treatment shortens the course of the disease.¹¹ Current active modulating therapies for SJS/TEN include: corticosteroids, intravenous immunoglobulin administration (IVIG) and cyclosporine.

Systemic corticosteroids are the most widely used for the treatment of SJS/TEN. Yet, they are also the most controversial. High doses of systemic corticosteroids are administered

with the intent to suppress the intensity of immune reaction, control the extension of the necrolytic process, decrease the injury area, reduce fever and discomfort, and prevent damage to internal organs in the early stages of SJS/TEN.⁵ Doses of 1 mg to 2.5mg/kg/day for three days of oral methylprednisolone have been used.^{8,11} However, the use of corticosteroids with their robust immunosuppressive actions also poses concern for increased risk of infection. Decreased host resistance, increased morbidity and complications (sepsis, leukemia, gastrointestinal ulcerations) and prolonged recovery for skin healing are additional concerns; therefore, an antibacterial treatment is recommended. Bacterial and fungal cultures should be taken two to three times a week from skin and mucosal erosions.¹¹ A prophylactic antibacterial treatment (sodium penicillin, 10 million units twice daily) should be administered immediately and adjusted according to the culture and sensitivity results.¹¹ Stevens-Johnson syndrome/toxic epidermal necrolysis patients should be closely monitored for the aforementioned potential complications, and further controlled studies will be required to substantiate whether systemic corticosteroids are ultimately beneficial.

The theory behind IVIG therapy is that IVIG may be able to block immune mediators of SJS/TEN reactions.⁵ Intravenous immunoglobulin administration is a promising strategy for reducing disease progression, based on the Fas-FasL hypothesis: that blocking FasL binding to the Fas receptor will interfere with the apoptotic signal, preventing cell death.⁶ Therapeutic doses have been set from 2 to 3.9g/kg, infused over a two-, four-, or five-day period.¹² Further randomized controlled studies are needed to support IVIG as a standard therapy option.

Cyclosporine, a powerful anti-inflammatory and immunosuppressive agent, has not been closely studied but has been shown to be beneficial in various case studies.⁷ Cyclosporine affects cytotoxic T-lymphocyte mediated actions and inhibits the inflammation caused by FasL, NK-kB, and TNF- α .⁵ In addition to nephrotoxicity and hepatotoxicity, other potential complications secondary to cyclosporine therapy, such as hypomagnesemia and reversible posterior leukoencephalopathy, should also be carefully monitored.⁵

Recent advances in pharmacogenomic studies suggest a possible prevention strategy for the future cases of SJS/TEN. Studies have found a strong genetic association between certain HLAs and specific drug-induced SJS/TEN.⁵ Particular HLA alleles were recognized as being main genetic determi-

Table 2. Associations Between Drug Hypersensitivity Reactions and HLA Alleles.⁵

Causative Drug	HLA Allele(s)	Hypersensitivity Reaction(s)
Abacavir	B*57:01	Abacavir hypersensitivity
Allopurinol	B*58:01	SJS/TEN/DRESS
Carbamazepine	B*15:02	SJS/TEN
Carbamazepine	B*15:11	SJS/TEN
Carbamazepine	A*31:01	SJS/TEN/DRESS/MPE
Methazolamide	HLA-B*59:01	SJS/TEN
Nevirapine	DRB1*01:01	MPE/DRESS
Oxicam NSAIDs	A2, B12	TEN
Sulfonamide	A29, B12, DR7	TEN

nants of SJS/TEN in combination with specific causative drugs. For example, HLA-B*15:02 is strongly associated with carbamazepine (CBZ)-induced SJS/TEN.⁵ Table 2 outlines further associations between drug hypersensitivity reactions and HLA alleles. Chung *et al.* suggested that the strong genetic association between HLAs and specific drug-induced SJS/TEN makes preventive screening tests prior to drug intake a possible practice to prevent SJS/TEN.⁵

Conclusion

Stevens-Johnson syndrome and toxic epidermal necrolysis are significant cutaneous reactions often caused by medications due to an immune response. Although there is a low incidence of SJS and TEN, these conditions have high rates of morbidity and mortality. Pharmacists may have a significant role in the prevention and treatment of SJS and TEN. Pharmacists can identify medications with potential to evoke this immunological reaction as well as recommend HLA testing for high risk drugs such as allopurinol and carbamazepine. Additionally, pharmacists are foremost in ability to perform medication review, an integral step in the treatment process. Pharmacists may also recommend pharmacotherapy, as there is a great deal of controversy surrounding treatment. Further studies need to be performed to help distinguish drug causes, the immunopathologic reaction and treatment options to prevent and successfully improve patient outcomes.

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Assessment Questions

Overview:

1. SJS/TEN presents clinically with:
 - A. Myocardial infarction
 - B. Cutaneous rash
 - C. Excitability
 - D. Abnormal hair loss
2. What percentage of epidermal detachment is associated exclusively with SJS?
 - A. <10%
 - B. >30%
 - C. >55%
 - D. 10-30%
3. The SCORTEN system:
 - A. Aids in determining what agent elicited the immunologic response
 - B. Does not include age as a criterion
 - C. Assesses mortality outcomes
 - D. Is a computer system that tracks all patients who currently have SJS/TEN

Immunology and Causative Drugs:

4. True or False: Re-challenging with the offending stimulus is not recommended due to a faster and more severe response to the causative agent.
 - A. True
 - B. False
5. Which immunological mediator is appropriately matched to its mechanism of keratinocyte death?
 - A. Granulysin-Cation that creates ion flux resulting in damage of the mitochondrial membrane resulting in apoptosis
 - B. Fas-FasL-death domain receptor trimerization which activates the caspase cascade resulting in apoptosis
 - C. Perforin, granzyme B- released by keratinocytes to stimulate their own apoptosis
 - D. All of the above
 - E. Two of the above
6. Potential causative agents of SJS and TEN
 - A. Allopurinol
 - B. Acetaminophen
 - C. Cephalosporins
 - D. Phenytoin
 - E. All of the above

7. Pharmacists can have a role in:
 - A. Identifying and discontinuing offending agent
 - B. Recommending treatment options
 - C. Drug information regarding treatment options
 - D. Recommending HLA testing for carbamazepine and allopurinol
 - E. All of the above

Treatment:

8. The outcome of SJS/TEN patients is dependent on which management measure?
 - A. Supportive care
 - B. Withdrawal of the suspecting drug
 - C. Active treatment
 - D. All the above
9. Prophylactic measures should be taken when administering systemic corticosteroids as treatment of SJS/TEN due to the possible risk of:
 - A. Seizures
 - B. Fatigue
 - C. Infection
 - D. Diarrhea
10. IVIG therapy can be used as a treatment option for SJS/TEN because of its immunologic binding activity of which mediator?
 - A. TNF- α
 - B. FasL
 - C. INF- γ
 - D. Granzyme B
11. The HLA*B 15:02 allele was recognized as being main genetic determinant of SJS/TEN in combination with which specific causative drug?
 - A. Carbamazepine
 - B. Methazolamide
 - C. Nevirapine
 - D. Allopurinol



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Program Content:	Strongly Disagree			Strongly Agree	
The program objectives were clear.	1	2	3	4	5
The program met the stated goals and objectives:					
Discuss the impact of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).	1	2	3	4	5
Describe the three most commonly proposed immunological mechanisms underlying SJS and TEN.	1	2	3	4	5
List medications commonly implicated in causing SJS and TEN.	1	2	3	4	5
Discuss commonly used therapies for SJS and TEN and the controversy surrounding them.	1	2	3	4	5
The program met your educational needs.	1	2	3	4	5
Content of the program was interesting.	1	2	3	4	5
Material presented was relevant to my practice.	1	2	3	4	5

Comments/Suggestions for future programs:

Thank you!

Answers to Assessment Questions—Please Circle Your Answer

- | | | | |
|------------|--------------|--------------|-------------|
| 1. A B C D | 4. A B | 7. A B C D E | 10. A B C D |
| 2. A B C D | 5. A B C D E | 8. A B C D | 11. A B C D |
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