Epidemiology of severe drug hypersensitivity

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■ **Abstract**

Epidemiological studies of severe drug hypersensitivities are important to understanding the morbidity and mortality of this heterogeneous group of disorders. These insights also allow greater identification of at-risk patient groups. However, epidemiological studies of drug hypersensitivity reactions are challenging due to the variable diagnostic criteria applied and incomplete data sets studied. We review the epidemiology of severe drug hypersensitivity reactions with a particular focus on severe cutaneous adverse reactions (SCARs). SCAR diseases include: Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash eosinophilia and systemic symptoms, serum-sickness–like reaction and acute generalized exanthematous pustulosis.

The World Health Organization has defined an adverse drug reaction (ADR) as 'a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man.'[1] ADRs are typically subdivided into Type 1 reactions (approximately 80%), which are dose dependent, "on-target" and predictable, and Type 2 reactions (approximately 20%), which are "off-target" and idiosyncratic.

ADRs are associated with significant morbidity and mortality and have considerable economic implications. Clinical manifestations of an ADR are variable and may include cutaneous and/or systemic features. Severe cutaneous ADRs (also known by the terms drug-induced skin injury [DISI] and severe cutaneous adverse reactions [SCARs]) include: Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug-induced hypersensitivity syndrome (DIHS)/drug rash eosinophilia and systemic symptoms (DRESS), serum-sickness–like reaction and acute generalized exanthematous pustulosis (AGEP).[2] This chapter is a review of the incidence and prevalence of ADRs within select patient groups and a review of the data relating to specific clinical patterns of SCAR.

Hospitalized patients

It is important to note that for generalized data (eg, hospital, outpatient or emergency department) a significant proportion of the data is likely to reflect Type 1 (immediate type hypersensitivity) reactions. Approximately 10%-15% of hospitalized patients experience an ADR.[3] A 6-month prospective study in Boston (Boston Collaborative Drug Surveillance Program) studied ADRs occurring in admitted patients in 2 tertiary hospitals.[4] Over the study period, 247 ADRs plus a further 194 potential ADRs were recorded (6.5 events per 100 admissions). Of these ADRS, 30% were considered serious with a mortality rate of 1%. Interestingly, 42% of the life-threatening and serious ADRs were considered preventable. Further analysis of this cohort estimated that for every ADR the attributable cost was $2595 per episode.[5]

A meta-analysis of published data between 1966 and 1996 for ADRs within 39 US hospitals demonstrated serious ADRs occur in 6.7% of hospitalized patients with a fatality rate of 0.32%.[6] Similar studies have demonstrated comparable admission rates for ADRs in Swiss (3.3%), German (8.5%), Australian (2%-4%), British (6.5%), Singaporean (5.2%), and Korean (9.6%) studies.[7-12]

A French hospital-based study of all Cutaneous Adverse Drug Reactions (CADR) reported a prevalence of 3.6 per 1000 hospitalized patients.[13] In this study of 48 patients, the most common reaction reported was an exanthem (56%). Severe reactions accounted for 34% of cases and life-threatening reactions for 2%. In this study, an association with Human Immunodeficiency Virus (HIV) infection (19%), connective tissue disease (10%), and viral or autoimmune hepatitis (12%) was reported.[14] Hernandez-Salazar et al have also reported an association with SLE (14.6%), HIV (7.3%), and non-Hodgkin lymphoma (7.3%) in a 10-month prospective study of hospitalized patients in a hospital in Mexico.[14]

Discussed below is the epidemiology of SCAR-specific diseases.

Acute generalized exanthematous pustulosis

Acute generalized exanthematous pustulosis (AGEP) was first described in 1968 by Baker and Ryan but not attributed to the diagnostic label until 1980 by Beylot et al.[15,16]

Etiology

To date, there are more than 54 reported drugs implicated in AGEP including anti-infectives, analgesics and anticonvulsants (Table 1).[17,18] A relatively large case series has also implicated mercury in 17.4% of cases (n=11/63).[19] A recent review of EuroSCAR cases (collated from 5 countries) identified 7 drugs with a significantly elevated odds ratio >5: pristinamycin, ampicillin/amoxicillin, quinolones, (hydroxy)chloroquine, anti-infective sulfonamides, terbinafine, and diltiazem.[18] Interestingly, quinolones had not been highlighted before this publication as carrying a significant risk of precipitating disease.

While the majority of cases appear to be related to drugs (>90%), other factors have been implicated in disease development including Coxsackie B4, cytomegalovirus (CMV), Parvovirus B19 and the brown recluse spider bite.[20-23]

Frequency

The incidence of AGEP is difficult to accurately determine due to a rarity of cases and the potential for diagnostic uncertainty. The EuroSCAR project has aided in this regard with well-described diagnostic criteria to enable meaningful clinical review of cases of AGEP.[17] The estimated incidence of AGEP is 1-5 cases/million/year.[17] A smaller study of 11 cases in Israel reported an incidence

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TABLE 1 Drugs reported in association with acute generalized exanthematous pustulosis[17,19]

Drug Category	Drug name
Anti-infectives	Aminopenicillins,[a] Pristinamycin,[a] Quinolones,[a] Sulfonamides,[a] Cephalosporin, Chloramphenicol, Gentamicin, Imipenem, Isoniazid, Beta-Lactam antibiotics, Macrolides, Metronidazole, Nifuroxazide , Tetracyclines, Vancomycin, Terbinafine,[a] Griseofulvin, Itraconazole, Nystatin, Piperazine, Ethionamate
Anticonvulsants	Carbamazepine, Clobazam, Clozapine
Antidepressants	Amoxapine
Antihypertensive/ anti-anginal	Diltiazem,[a] Enalapril, Nifedipine
NSAIDs	Oxicam, NSAIDs
Miscellaneous	(Hydroxy)chloroquine,[a] Acetaminophen Allopurinol, Beta-adrenergic agonist (Buphenine, Fenoterol), Carbutamide, Chromium picolinate, Cimetidine, Clemastine, Corticosteroids, Eprazinone, Furosemide Lansoprazole, Mercury, Nadoxolol, Prostaglandin E1 Pneumococcal vaccine, Pyrimethamine, PUVA, Quinidine, Sulbutiamine, Thalidomide

[a]Greater risk of acute generalized exanthematous pustulosis.

of 0.35 cases/million/year but may reflect underreporting and a relatively small sample size (N = 11).[24]

Risk factors

The pathogenesis of AGEP is incompletely understood although initial reports suggested a link with psoriasis.[15] This is perhaps related to overlapping clinical and pathological features.[19] Interestingly, one of the largest retrospective studies published to date reported 11 of 63 patients had a past history of psoriasis.[19] More recently, the EuroSCAR data reported on 97 cases of probable or definite AGEP and found no such association.[17]

Genetic risk factors are a source of significant research interest but are less well developed than for other SCAR diseases. HLA genotypes appear to be influential in susceptibility; HLA-B51, -DR11 and –DQ3 have been implicated.[25]

Morbidity

The morbidity associated with AGEP is generally considered low with few reported cases of long-term sequelae following AGEP. A 10-year retrospective review of 58 patients identified systemic involvement in the acute phase of the disease in approximately 17%, including liver, kidney, bone-marrow and lung involvement.[26] Long-term outcomes are not established.

Mortality

The mortality associated with AGEP is difficult to ascertain due to the rarity of the disease. Studies have suggested a mortality of under 5%.[18,26,27]

Drug reaction eosinophilia and systemic symptoms

The nomenclature of this entity has caused considerable debate with proposed terms including drug hypersensitivity, drug induced hypersensitivity syndrome and drug induced delayed multiorgan hypersensitivity syndrome.

Etiology

DRESS was originally reported in association with sulfonamides and antiepileptic medication (particularly the aromatic anticonvulsants phenobarbital, phenytoin and carbamazepine).[28,29] It is now clear that DRESS may occur in response to a wide range of drugs (Table 2).[30] A recent review of 172 patients with DRESS identified 44 culprit drugs including carbamazepine (27%), allopurinol (11%), lamotrigine (6%), phenobarbital (6%), sulfasalazine (6%), and nevirapine (5%).[30] Another prospective study involving 8 countries registered with RegiSCAR (a European Commission funded registry for SCAR) enrolled 117 cases of DRESS between 2003 and 2009.[31] Within this cohort, a responsible medication was identified in 88% of cases (anticonvulsants 35%, allopurinol 18%, sulfonamide antimicrobials/dapsone 12% and other antibiotics 11%).

Frequency

Estimates of the frequency of DRESS in patients receiving relevant anticonvulsants are approximately 0.1-1 in 10,000 exposures.[32,33] A detailed record linkage study of patients receiving first or second prescriptions of anticonvulsants demonstrated a risk of DRESS as 2.3-4.5 per 10,000 for phenytoin and 1.0-4.1 per 10,000 for carbamazepine.[34] In this latter study, no episodes of DRESS occurred in patients receiving valproate. For other drugs implicated in the etiology of DRESS, the frequency is largely unknown.

Risk factors

Previously reported risk factors for DRESS include cranial irradiation, young age and HIV infection.[35] A study of 100 patients with HIV treated with anticonvulsants reported that 14% (n=12/87) of patients receiving phenytoin who also had HIV disease experienced a hypersensitivity reaction.[36] The authors did not report a relationship between viral or immune status and risk of DRESS remains to be fully elucidated.

In addition to HIV, several viral infections have been implicated in the pathogenesis of DRESS. A prospective study of 23 patients with DRESS reported viral reactivation in 30% of patients (Human Herpes Virus [HHV]-6, n=5; HHV-7, n=2).[20,37] Other viruses implicated in disease include Cytomegalovirus (CMV) and Epstein-Barr virus (EBV).[38,39] This is consistent with the recently reported RegiSCAR study which demonstrated a prevalence of HHV6 in 36% of patients that were tested (n=21/58).[31]

TABLE 2 Drugs reported in association with drug rash eosinophilia and systemic symptoms. [30]

Drug Category	Drug name
Anti-infectives	Abacavir,[a] Dapsone,[b] Sulfasalazine,[b] Ampicillin/amoxicillin, Cefotaxime, Ethambutol, Isoniazid, Linezolid, Metronidazole, Minocycline, Nevirapine,[a,b] Pyrazinamide, Quinine, Rifampin, Streptomycin, Trimethoprim-sulfamethoxazole, Vancomycin, Zalcitabine
Anticonvulsants	Carbemazepine,[a,b] Lamotrigine,[b] Phenobarbitol,[b] Phenytoin, Valproate, Zonisamide
Antidepressants	Bupropion, Fluoxetine
Antihypertensives	Amlodipine, Captopril
Biologics	Efalizumab, Imatinib
NSAIDs	Celecoxib, Ibuprofen
Miscellaneous	Allopurinol,[a,b] Epoetin alfa, Mexeltine, Ranitidine

[a]Used to denote drugs in which HLA association has been identified in select patient groups; [b]Greater risk of drug rash eosinophilia and systemic symptoms.

Human leukocyte antigen genotyping

The role of the human leukocyte antigen (HLA) in determining the risk of DRESS has proven to be a topic of significant interest. A Taiwanese study of 30 patients with allopurinol-induced DRESS demonstrated 100% prevalence of HLA-B*5801.[40] This has been confirmed in a patient population in Hong Kong.[41] A slightly weaker association was observed in a European study with 63.2% (n=12/19) of patients with allopurinol-induced DRESS carriers for HLA-B*5801.[42]

Current recommendations for use of allopurinol are dependent on country of practice. The American College of Rheumatology and Clinical Pharmacogenetics Implementation Consortium (CPIC) recommend screening all high risk populations for HLA-B*5801 prior to commencing allopurinol.[43,44] High risk populations include those of Han Chinese, Thai and Korean (with chronic kidney disease) descent. Within the Caucasian population, routine screening for HLA-B*5801 is not recommended due to the reduced association between HLA-B*5801 and allopurinol, and relatively low prevalence of HLA-B*5801.

Similar studies for individuals receiving abacavir therapy identified HLA-B*5701 as a risk for DRESS in white patients.[45,46] A clinical trial to evaluate the role of pretreatment screening HLA-B*5701, and avoidance of abacavir when appropriate, in a predominantly Caucasian population demonstrated a reduced incidence of DRESS and is now recommended as a screening test before initiating therapy.[47]

Other HLA genotypes are undergoing evaluation for a potential increased risk of DRESS (nevirapine and HLA-DRB1*0101; carbamazepine and HLA-A*3101).[48,49]

Enzyme polymorphisms

The role of genetic polymorphisms has also been proposed as a significant risk factor for DRESS. The cytochrome P450 system is essential in the metabolism of aromatic anticonvulsants to arene oxide metabolites and subsequent detoxification via epoxide hydroxylase. Polymorphisms of the epoxide hydroxylase have been implicated in toxic accumulation of metabolites and consequent immunological effects.[33] Slow N-acetylator phenotypes appear to also confer an increased risk of DRESS.[28] Assessment of genetic polymorphisms is predominantly a research tool and not evaluated routinely in clinical practice.

Polypharmacy

Polypharmacy may play a role in increasing risk of DRESS. A clinical trial involving concomitant valproate and lamotrigine demonstrated 1% (n=6/584) of patients were hospitalized for rash compared with 0.2% (n=4/2398) for those who received lamotrigine alone.[50] This may in part relate to competitive inhibition by valproate of an oxidative isoenzyme required for lamotrigine metabolism, significantly increasing the plasma half-life of lamotrigine.[51]

Morbidity

The morbidity associated with DRESS has recently been reviewed in a one-year follow up study of 52 affected patients. The study suggested autoimmune disease (including Graves' disease, Type 1 diabetes, alopecia areata, and autoimmune hemolytic anemia) and end organ disease (most commonly renal disease) as potential complications of disease.[52] Renal failure was observed in 2 patients, both of which had a premorbid history of hypertension, diabetes, and chronic renal disease. With respect to Type 1 diabetes, previous studies have suggested an association with HHV-6 and provide a potential mechanistic link between disease states.[53] In older patients with less functional reserve, the risk of end organ damage is thought to be more relevant.[52]

Mortality

The mortality of DRESS associated with anticonvulsant drugs has been estimated at 10%.[54,55] However, 3 recent studies, including a prospective (n=172), retrospective (n=39) and literature review (n=172), have reported mortality rates of 1.7%, 7.7% and 5% respectively.[30,31,56] Commonly reported causes of death relate to end organ failure or secondary infection.

Serum sickness-like reactions

Serum sickness-like reaction (SSLR) was described by Murray et al in 1980 and is most frequently drug-induced and characterized by the presence of fever, rash, and joint involvement.[57] The pathophysiology of SSLR is not fully understood, but it is not associated with circulating immune complexes, hypocomplementemia or vasculitis. Cefaclor is the most common cause of SSLR in children,[58] although many other drugs are also implicated,[59-64] including other cephalosporins,[60] penicillins,[61] minocycline,[62] insulin,[63] and infliximab.[64]

It is important to distinguish SSLR from serum sickness. Serum

sickness is a systemic immunologic disorder, considered a type III immune complex disease induced by the deposition of circulating immune complex in blood vessels and other tissues, complement activation and the subsequent inflammatory response.[65] This is most frequently induced by administration of foreign proteins such as antithymocyte globulin or horse serum (utilized as an antiserum to diphtheria, tetanus, or other organisms).[66] Serum sickness is very rare and is therefore not discussed further in this article.

Frequency

The incidence of SSLR is unknown. Cefaclor was found to induce 84.1% of SSLR cases.[67] Epidemiology studies in children suggest that the overall frequency of SSLR induced by cefaclor is 0.024%-0.2% per course of the drug.[68] Most reactions were reported in children under 5 years old, mainly during the second and third courses of therapy.[58]

Risk factors

Although the pathogenesis of SSLR is unknown, several mechanisms have been suggested. It has been postulated that in genetically susceptible hosts, a reactive metabolite binds with tissue proteins and elicits an inflammatory response, including elevation of acute phase reactants (erythrocyte sedimentation rate [ESR], C-reactive protein [CRP]).[69] In an in vitro lymphocyte-based cytotoxicity study, cefaclor-associated SSLR was suggested to be a unique adverse drug reaction that requires biotransformation of the parent drug, and results from inherited defects in the metabolism of reactive intermediates.[70] A recent study suggested a new mechanism by which cefaclor may alter the intestinal mucosal permeability and thereby increase the risk of SSLR.[67]

Clinical findings

The time between initiation of therapy and development of a reaction is usually 7-14 days (range 0-20 days).[67,69] The most frequent finding in SSLR is cutaneous involvement, including erythema that progresses to urticarial lesions (pruritic and migratory), urticarial wheals with dusky to purple centers ("purple urticaria") that morphologically resemble erythema multiforme,[58] and other cutaneous eruptions including morbilliform or scarlatiniform eruptions.[59]

The other primary clinical feature is joint involvement that may present with edema, decreased range of motion, warmth, pain, and difficulty walking. Polyarticular involvement is often observed, with involvement mainly of the wrists, ankles, hips and knees.[71] Some authors suggested that joint involvement may be related in part to increased fluid in the skin around affected joints due to urticarial eruption rather than arthritis.[58]

Fever, malaise, myalgia, lymphadenopathy are also reported. Neurologic involvement, gastrointestinal symptoms and renal complications are rarely documented.[60] Mucous membranes are not involved.[58] Notable laboratory abnormalities include an elevated ESR, CRP and leukocytosis.[60,72]

Diagnosis

The diagnosis of SSLR is based on clinical findings. Histology can be helpful in differentiating SSLR from acute hemorrhagic edema of infancy, which is characterized by vasculitis and may rarely affect internal organs.[73] The histological findings of SSLR appear to be in the spectrum of urticaria with no vasculitis.[73] The differential diagnosis also includes erythema multiforme and acute annular urticarial hypersensitivity syndrome in children.[74]

Outcome

Withdrawal of the offending agent and symptomatic treatment with oral antihistamines and topical corticosteroids is usually sufficient. A short course of oral corticosteroids may be required in patients with more severe symptoms.[59] Generally, the disease course is benign and resolves in a few days, although cases lasting several weeks have been described.[72] Re-exposure to the culprit drug should be avoided.[69] Cross-reaction of cefaclor with other beta-lactam antibiotics is rare; nevertheless, several authors recommend avoiding all beta-lactams antibiotics in patients with cefaclor-induced SSLR.[59] No long-term morbidity has been reported.[57]

Stevens-Johnson syndrome and toxic epidermal necrolysis

Stevens-Johnson syndrome (SJS) was first described by the physicians A.M. Stevens and F.C. Johnson in 1922.[75] The term toxic epidermal necrolysis (TEN) was coined in 1956 by A. Lyell.[76]

Frequency

SJS and TEN are rare severe cutaneous adverse reactions. The annual incidence of SJS and TEN is 1.2-6 and 0.4-1.2 per million individuals, respectively.[77,78] The annual incidence of SJS and/or TEN in HIV patients is estimated at 1-2 per 1000 individuals, approximately 1000-fold higher than that of the general population.[79] The incidence of SJS/TEN increases with age; children less than 15 years of age account for only 10% of the samples in most studies.[80] Women are 2 times more likely to be affected by TEN and SJS than men in the adult population,[79] while the male to female ratio is about equal in children.[80]

TEN may develop during pregnancy in the mother alone or simultaneously in the mother and fetus; it can be lethal for the fetus.[81]

Etiology

Drug exposure is the most common cause of SJS/TEN,[82] with more than 200 drugs identified,[83] including medications associated with high risk of SJS/TEN (Table 3),[80,84,85] and non-medications, implicated mainly in SJS.[86-91] These include infections, [86-90] contrast media[90] and vaccinations.[91] Infectious causes that have been reported include *Mycoplasma pneumoniae*,[86] dengue fever,[87] CMV,[88] and *Yersinia enterocolitica*.[89] A unique type of SJS that involves the mucosa without skin lesions is Fuchs syndrome,[92] which was reported to be associated with *Mycoplasma pneumoniae* mostly in children and adolescents.[92,93]

Genetic susceptibility for SJS/TEN has been studied in populations with a variety of ethnic backgrounds.[94,95] The genetic association can be specific to a drug, a phenotype, or an ethnic background.[96] Table 4[97] summarizes the unique and strong associations found between HLA genotype and SJS/TEN. The US Food and Drug Administration (FDA) recommends genetic screening for patients of Asian ancestry before initiation of carbamazepine or phenytoin although the increased risk does not span all Asians. Screening should also be performed in all patients prior to treatment with abacavir, and avoidance of the drug in the event of a positive result.[97]

TABLE 3 High-risk drugs in the etiology of Stevens Johnson syndrome/toxic epidermal necrolysis [80,84,85]

General population	Children	Africa[a]
Cotrimoxazole and other antibacterial sulfonamides	Antibacterial sulfonamides	Antibacterial sulfonamides[b]
Nevirapine	Phenobarbital	Nevirapine
Carbamazepine	Carbamazepine	Antiepileptics
Lamotrigine	Lamotrigine	Tuberculosis drugs
Phenobarbital		Analgesics
Phenytoin		Amino-penicillin
Oxicam, non-steroidal anti-inflammatory drugs		Non-steroidal anti-inflammatory drugs
Allopurinol[b]		Allopurinol
Sulfasalazine		

[a]Average age- 32.3±15.4.
[b]The drug with the highest incidence of inducing SJS/TEN in the population group.

ALDEN, an algorithm for the assessment of drug causality in SJS and TEN, was developed by the RegiSCAR study group[98] as a reference tool for assessing drug causality in the diseases. ALDEN includes 6 parameters that classify the patient's disease status as very unlikely, unlikely, possible, probable, and very probable.[98] SCORTEN is a scoring system developed to stratify severity of illness and predict mortality in patients with TEN. SCORTEN includes the following 7 independent risk factors: age, malignancy, tachycardia, initial body surface area of epidermal detachment, serum urea, serum glucose, and bicarbonate.[99]

Complications

Early and late physical complications are common among patients who survive SJS/TEN,[40,99-107] with some 80% experiencing long-term sequelae.[108] This figure led authors to suggest dividing SJS/TEN into acute and chronic disease, and patient organizations to refer to survivors as victims.[107] Only few studies have assessed these sequelae.[100,102-107] Complications may affect multiple organ systems including skin (including genital and mucosal sufaces), eyes (eg, visual loss, ectropion ± trichiasis, symblepharon), kidneys (eg, chronic kidney disease), gastrointestinal tract (eg, strictures, dysphagia) and respiratory system (eg, bronchiectasis, bronchiolitis obliterans). Ocular complications, which can lead to blindness, are the major long-term morbidity.[100] A recent case report of severe eye complications from SJS in an HIV-infected patient in Malawi[109] that resulted in blindness threw into question Malawi's recent adoption of the World Health Organization guidelines to begin antiretroviral therapy earlier in the course of HIV infection when the CD4 cell threshold for treatment initiation was increased from 250 to 350 cells/μL.[109] The risk of SJS/TEN related to CD4 count in patients with HIV remains to be fully elucidated.[106]

A few recent studies have dealt with the quality of life of patients surviving SJS/TEN.[102,110,111] The mean Dermatologic Life Quality Index (DLQI) in adult survivors of TEN after treatment in a burn center was found to be 9±11, and their Short Form-36 (SF-36) score representing overall health-related quality of life had declined in every domain from before hospitalization to follow-up 38±27 months after discharge. The SF-36 scores among TEN survivors at follow-up were significantly lower than those in the normal population in almost all domains, and a low rate of return to previous employment was documented.[102] Patients reported concerns about social interactions, fear of taking medications, and fear of contracting an illness necessitating medication.[111] Insufficient information and support for patients surviving SJS/TEN was also documented.[108,110,111] Unfortunately, because of the rarity of SJS/TEN, most physicians are not aware of the long-term complications of the diseases.[108]

TABLE 4 Drugs associated with Stevens-Johnson syndrome/toxic epidermal necrolysis and their corresponding human leukocyte antigen allele[95]

Drug	Clinical indication	Associated HLA allele	Population studied	The US Food and Drug Administration recommendations
Carbamazepine	Epilepsy	B*1502	Asian	Genotyping all Asians for the allele prior to treatment
Carbamazepine	Epilepsy	A*3101	Japanese and European descent	No recommendations
Allopurinol	Hyperuricemia	B*5801	Asian and European[a]	No recommendations
Abacavir	HIV/AIDS	B*5701	Caucasian and African-American	Genotyping all patients for allele prior to treatment

[a]In individuals of European descent, a much weaker association was found.

Mortality

The mortality rate of SJS and TEN is variable but may approach 30% for TEN.[83] The mortality rate for children with SJS or TEN is approximately 2%-7.5%.[80,104] In a large-scale population-based 1-year follow-up study of 460 SJS/TEN patients, the 6-week in-hospital mortality rate was 23%, the death rate in the time frame of 6 weeks to 1 year was 14%.[103] The mortality rate at 1 year was 24% for SJS, 43% for SJS/TEN overlap, and 49% for TEN. Several factors were found to affect mortality: age, severity of reaction, recent malignancy, pre-existing severe kidney or liver disorder, and recent infection. The last two, severe kidney or liver disease and recent infection, were recognized for the first time in this study as being independent risk factors for death. All other factors are part of the SCORTEN, a validated prognostic score for TEN.[99] The severity of the reaction was a major risk factor for death in the first few weeks, and severe co-morbidities and older age had major impact mortality after 6 weeks.[103]

Conclusion

Epidemiological studies of ADRs remain problematic due to the methodological challenges in capturing comprehensive data. Difficulties include the broad range of healthcare professionals providing care across a range of clinical environments. These limited data are further complicated by the inability of many studies to differentiate types of ADR (dose dependent and idiosyncratic).

Despite the challenge of studying ADRs, it remains important to do so to improve patient safety and preventive medicine within clinical practice. Understanding ADRs has further developed understanding of pharmacology, immunopathogenesis and the impact of genetic factors. The increasing use of pharmacogenomics provides an opportunity to develop personalized medicine and reduce ADRs further.

For SCAR specific diseases large-scale, multi-center studies afford an opportunity to evaluate epidemiology, risk factors, morbidity and mortality. This is of great importance to informing clinicians involved in managing SCARs and improving clinical care.

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