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REVIEW ARTICLE

Drugs Implicated, Mortality and Use of Corticosteroids in Toxic Epidermal Necrolysis Cases: A Systematic Review of Published Case Reports and Case Series

[1]Sharonjeet Kaur, [2]Sujit Rajagopalan, [3]Nusrat Shafiq, [4]Sunil Dogra, [5]Anand Srinivasan
[6]Promila Pandhi, [7]Samir Malhotra

ABSTRACT

Background: Toxic epidermal necrolysis (TEN) is a rare idiosyncratic mucocutaneous reaction associated with high mortality. Drugs are most commonly implicated in TEN. The treatment constitutes stopping the offending drug, along with symptomatic management. In this study, we searched for case reports/series of TEN and analyzed data to find the most commonly implicated drugs in TEN, effects of use of corticosteroids on mortality in TEN patients, changing trends in mortality over the past 3 decades and difference in mortality rates in both developing and developed countries.

Materials and methods: We searched for case reports/series of TEN to evaluate most commonly implicated drugs in TEN, effects of use of corticosteroids on mortality in TEN patients, changing trends in mortality over the past three decades and difference in mortality rates in both developing and developed countries.

Results: Antibiotics (28.6%) followed by antiepileptics (17.4%) and nonsteroidal anti-inflammatory drugs (9.6%) are most commonly implicated. There was nonsignificant decrease in mortality among steroids users as compared to nonusers (OR = 2.0, CI 0.96-4.24). During the period between 1980 and 1989 the reported mortality in TEN cases was approximately 33.4%, which decreased to 27% in the next two decades. There was a nonsignificant difference in mortality in developing countries as compared to developed countries (OR: 0.70, CI 0.32-1.53).

Conclusion: Corticosteroids have been associated with non significant reduction in the mortality. Apart from this, mortality did not differ over years together in both developing and developed countries.

Keywords: Toxic epidermal necrolysis, Corticosteroids, Mortality.

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[1,2,5]Senior Resident, [3]Assistant Professor, [4]Associate Professor
[6]Ex-Head, [7]Additional Professor

[1-3,5-7]Department of Pharmacology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

[4]Department of Dermatology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Corresponding Author: Nusrat Shafiq, Assistant Professor Department of Pharmacology, Postgraduate Institute of Medical Education and Research, Chandigarh, India, e-mail: nusrat_shafiq@hotmail.com

INTRODUCTION

Toxic epidermal necrolysis (TEN) is a rare life-threatening idiosyncratic mucocutaneous drug reaction characterized by widespread epidermal necrosis followed by epidermal detachment.[1] Drugs, infections and immunizations are the most common causes of TEN. Drug-induced TEN is the commonest cause and antiepileptics, antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), and allopurinol are the most commonly implicated agents.[2]

Prompt diagnosis and stoppage of suspected drugs is essential in the management of the TEN cases. This may be particularly challenging in some cases where multiple drugs are being used, especially when treatment discontinuation is not desirable. Although several review articles and textbooks have listed drugs causing TEN, they may not assist a clinician in deciding which drug, out of the several patients may be taking, has the highest probability of causing TEN.

Besides stopping the offending agent, treatment is mainly supportive, which includes, fluid replacement, correction of electrolyte imbalance, nutritional support, prevention of infection, and treatment with specific therapy. Cyclosporine, cyclophosphamide, plasmapheresis, intravenous immunoglobulin, and N-acetylcysteine have been used for management and have shown inconsistent results. Corticosteroids are routinely used however, the evidence for their benefit is still lacking.[3-10] The rationale behind conducting this study was to evaluate the changing trends in the TEN regarding drugs, mortality, and effectiveness of corticosteriods. The objective of this study was to identify drugs, more likely to cause TEN, the difference in mortality rates over the years and also between developed and developing nations and the effect of use of corticosteroids on mortality in TEN cases. The review was conducted by following the guidelines of preferred reporting items for systematic reviews and meta-analyses statement.

MATERIALS AND METHODS

We searched the Medline, PubMed and Embase for published case reports and case series from 1950 to 2011. The MeSH TEN was used to elicit the articles. The subheading 'drug-induced' was then added to short list only the relevant articles. Additionally, databases like Cochrane were also searched. References from identified articles were also scanned for additional relevant information. There was no publication limit in our literature search. Two independent authors evaluated the articles (SR, SK) and data was extracted and pooled and consensus was arrived. In case of discrepancy, it was resolved by third author (NS). All studies related to drug-induced TEN were searched and further screened. Eligible studies were included in systematic review. The exclusion criteria for systematic review were animal studies, *in vivo* experiments, case reports of SJS or SJS-TEN overlap and insufficient information provided regarding determination of causative relation between drug and TEN.

Mean time for onset of symptoms, time to recovery or death was evaluated. Besides causality assessment, other parameters evaluated were commonly implicated diseases changing trends in the mortality over previous years as compared to recent years, and mortality rates in developing and developed countries and incidence of TEN among newer (approved after 1980) *vs* older drugs (approved till 1980). Data regarding different treatment modalities provided to patients during admission was also evaluated. Developing countries were defined on the basis of economy (gross domestic product, the per capita income, level of industrialization, amount of widespread infrastructure, and general standard of living) as a nation with a low living standard, undeveloped industrial base, and low human development index relative to other countries. Developed countries are the one with highly developed economy and advanced technological infrastructure relative to other less developed nations.

Causality assessment was done using a method of 'Karch and Lasagna' if the authors had not carried out the causality assessment themselves.[11] The assessment in Karch and Lasagna method in relation to drugs implicated was based on temporal sequence, known response pattern to drug, improvement on dechallenge, reaction returns on rechallenge and alternative explanation. Further drugs implicated were classified either into definite, probable, possible and conditional.

Mortality was calculated based on the number of deaths from TEN as compared to number of cases that were analyzed in the review.

STATISTICAL ANALYSIS

Categorical data were expressed as n (%) and quantitative data were expressed as mean ± standard deviation. Comparisons between groups were made using chi-square or Fisher's exact test. $p < 0.05$ was considered statistically significant. Odds ratio (95% CI) was estimated to compare mortality between developing and developed countries. The primary analysis was done on published case reports/case series.

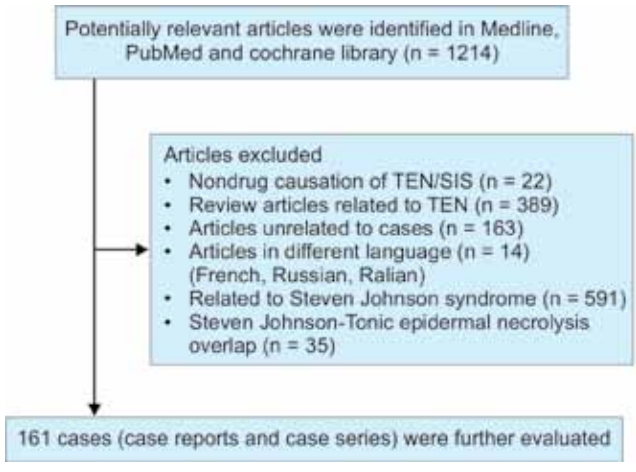
RESULTS

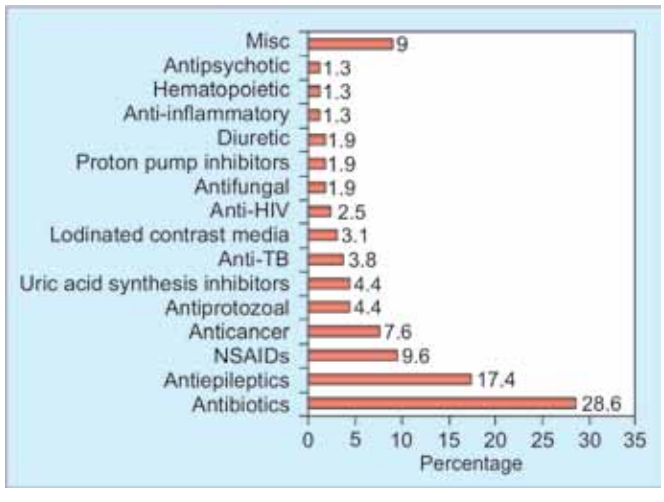
The 1214 hits were obtained when the search terms were combined. Out of these hits, we identified 161 cases which included both case reports and case series (Flow Chart 1).

The mean (standard deviation) time to onset of the prodromal symptoms, like fever and malaise, after the administration of the suspected drug was 12.3 (±17.4) days with median of 7 days (0.2 to 120 days). The mean age of presentation of TEN was 44 years with median of 45 years (0.2 to 93 years). Gender distribution was almost equal with a total of 83 males and 78 females presenting with TEN.

The most commonly implicated group of drugs were antibiotics, followed by antiepileptics, NSAIDs (Graph 1). Among the various antibiotics, beta-lactams, sulphonamides,

Flow Chart 1: Depicting the digible cases reports and series





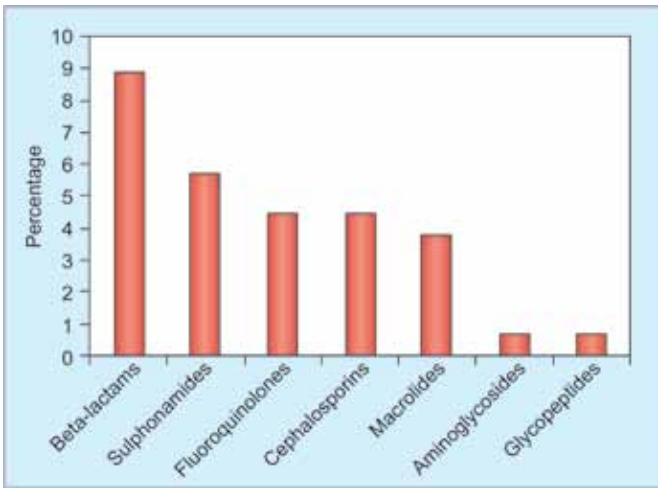
Graph 1: Commonly implicated drugs

fluoroquinolones, and cephalosporins were commonly implicated drugs in antibiotic class (Graph 2).

Out of 161 cases of TEN, 139 were due to single drug and the rest were due to multiple drugs (Table 1). In one case, there was no data regarding drugs implicated and in another case, syndrome of inappropriate secretion of antidiuretic hormone (SIADH) was an alternate diagnosis. SIADH has been implicated as one of the causative factors of TEN. Broadly, the division is as shown in Table 1.

The primary diagnosis for which the suspected drugs were prescribed in majority was central nervous system diseases followed by disorders of respiratory system, musculoskeletal system, gastrointestinal system and infectious disease.

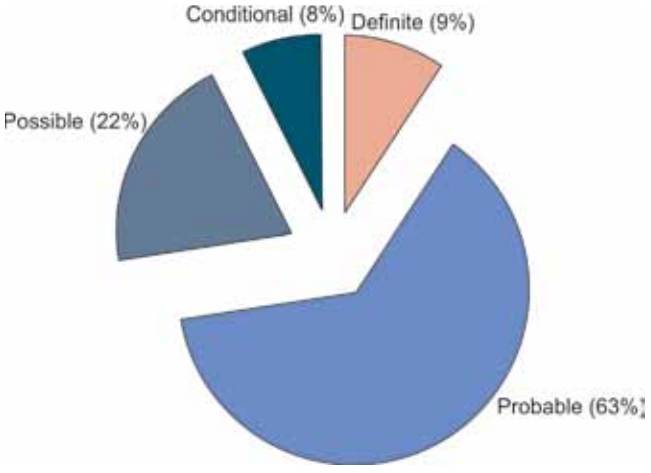
Causality assessment of drugs in cases of TEN revealed that in 9.3% of the cases causality was definite, in 63.3% of cases it was probable, in 20% of the cases it was possible and in 7.4% of the cases it was conditional (Graph 3).



Graph 2: Commonly implicated class of antibiotics

Table 1: Drug combinations associated with TEN

Drug combinations/others	*No. of cases*
Rifampicin + pyrizinamide + isoniazid + ethambutol	3
Aspirin + cephalosporins + statins	2
Thalidomide + dexamethasone	2
Clarithromycin + disulfiram	1
Trimethoprim + amoxycillin	1
Sulfasalazine + tobramycin + ticarcillin	1
Allopurinol + iodinated contrast media	1
Nelfinavir/lamivudine plus zidovudine	1
Oxacillin + ampicillin + moxalactum	1
Amlobarbitone + trichloroethylene	1
Minoxidil + allopurinol	1
Pemetrexed and carboplatin with vitamin B12 and folic acid	1
Phenobarbitone + phenolphthalein	1
Cetuximab plus minocycline	1
Indomethacin + acetylsalicylic acid	1
Carbamazepine + trimipramine	1



Graph 3: Causality assessment of drugs (%)

Causality assessments of drugs implicated in TEN are shown in Table 2.

Corticosteroids were used in the management in 90 cases. Out of which, 71 (79%) survived and 19 (21.1%) died. Among total of 57 steroid nonusers, 37 (65%) survived and 20 (35.1%) died. This difference in mortality among steroid users and nonusers just missed statistical significance. (OR = 2.0, CI = 0.96-4.24).

The mortality among TEN patients observed during the early decades (1980-1989) was approximately 33.4%, which decreased to 27% (1990-1999). In 2000 to 2010, the mortality remained 27.5% and in subsequent two years (2010-2011) it was 28% (p = 0.96) (Graph 4).

The overall mortality in the published studies was non-significant different in the developing countries as compared to developed countries (%) (OR: 0.70, CI: 0.32-1.53).

The overall mean time to recover was 23.4 ± 17.8 days and death occurred within a mean time 15.8 ± 18 days. Rechallenge was carried out in 15 cases and in four cases mortality was observed.

MANAGEMENT OF THE TEN CASES

The first line in the management of TEN was to stop the offending drug. Supportive treatment in the form of intravenous fluids was given to all the patients. Antihistaminics were used in 14.2% and antimicrobial in 61.4% of the cases. Antifungals were prescribed in 6% patients to prevent complications related to TEN. Newer treatment modalities like intravenous immunoglobulins were administered in 18.6% of the cases, 5% received immunosuppressant and 2.4% received granulocyte macrophage colony stimulating factor (GMCSF). Appropriate care of cutaneous and ocular lesions was done if needed.

DISCUSSION

In this study, mean age at which TEN was observed was 44 years (Median = 45 years) indicating that middle age

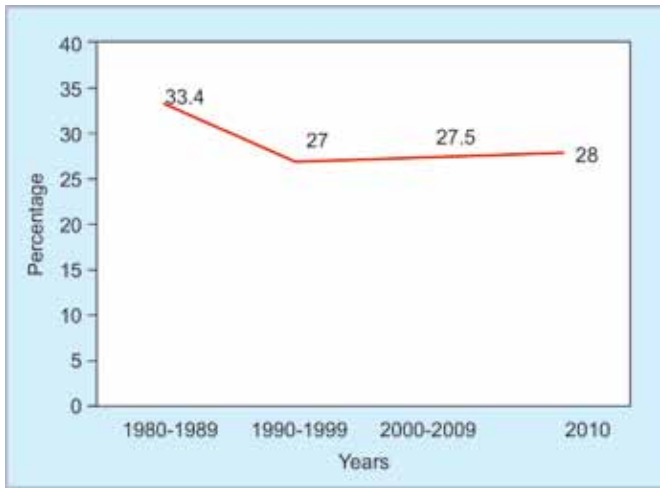
Table 2: Causality assessment of drugs

S.no.	*Drugs*	*Causality*
1.	Aminosalicylic acid	Definite
2.	Allupurinol	Probable
3.	Benozaparen	Conditional
4.	Mefloquine	Probable
5.	Cotrimoxazole	Probable
6.	Moxifloxacin	Possible
7.	Etritinate	Possibe
8.	Amifostine	Conditional
9.	Trimethoprim/sulphamethoxazole	Probable
10.	Ceftrixone	Conditional
11.	Acetylsalicylic acid	Possible
12.	Herbal powder	Possible
13.	Chloroquinine	Possible
14.	Chloroquinine	Possible
15.	Chlorpromazine	Probable
16.	Ciprofloxacin	Possible
17.	Erythromycin	Probable
18.	Tetramisole	Probable
19.	Diluted diatrizoate	Conditional
20.	Fluconazole	Probable
21.	Indapamide	Probable
22.	Tiecoplanin/amikacin	Conditional
23.	Lamotrigene	Probable
24.	Nimesulide	Probable
25.	Omeprazole	Probable
26.	Carbamazepine	Probable
27.	Sulphasalzine	Possible
28.	Methimazole	Probable
29.	Mesalamine	Probable
30.	Clarithromycin	Probable
31.	Trimethoprim	Probable
32.	Trimethoprim/amoxycillin	Possible
33.	Methotrexate	Conditional
34.	Voriconazole	Conditional
35.	Zonisamide	Probable
36.	Lamotigene	Probable
37.	Carbamate poisoning	Conditional
38.	Ceftizimidine/vancomycin	Possible
39.	Ceftizimidine/acyclovir	Possible
40.	Cefsulodin	Probable
41.	Clindamycin	Possible
42.	Clobazam	Conditional
43.	Carbamazepine	Probable
44.	Famotidine	Conditional
45.	Lamotrigine	Probable
46.	Methotrexate/trimethoprim sulphamethoxazole	Probable
47.	Trimethoprim	Possible
48.	Thalidomide	Probable
49.	Sidenafil	Conditional
50.	Sparfloxacin	Probable
51.	Ceftrixone	Definite
52.	Trimethoprim/sulphomethoxazole	Probable
53.	Contrast media	Definite
54.	Phenytoin	Probable
55.	Phenytoin	Probable
56.	Mefloquine	Possible
57.	Caspofungin	Probable
58.	Capecitabine	Probable
59.	Iohexol	Definite
60.	Oflaxacin	Probable
61.	Norflox	Probable
62.	Nevirapine	Probable
63.	Nevirapine	Probable
64.	Phenytoin	Probable
65.	Carbamazepine	Probable
66.	Sulphasalzine/tobramycin/ticracillin	Probable
67.	Amoxycillin	Probable
68.	Cotriamoxazole	Probable
69.	Allupurinol	Probable
70.	Darunavir/abacavir	Probable
71.	Iodinated contrast media	Definite
72.	Vancomycin/beta lactam	Probable
73.	Paracetamol	Probable
74.	Allopurinol	Probable
75.	Allopurinol	Probable
76.	Allopurinol	Probable
77.	Allopurinol	Probable
78.	Adefovir	Conditional
79.	Aspirin	Possible
80.	Nelfinavir/lamivudine plus zidovudine	Probable
81.	Phenobarbitone/whole brain radiotherapy	Probable
82.	Naproxen	Possible
83.	Clarithromycin	Probable
84.	Etoricoxib	Probable
85.	Amoxycillin	Possible
86.	Hydroxychloroquinine	Probable
87.	Isoniazid	Definite
88.	Lamotrigene	Probable
89.	Phenytoin	Probable
90.	Lamotrigene	Probable
91.	Lansoprazole	Possible
92.	Methotrexate	Possible
93.	Ampicillin-sulbactum	Probable
94.	Cytosine arabinoside	Possible
95.	Ferritin	Possible
96.	Phenytoin	Probable
97.	Phenytoin	Probable
98.	Penicillin derivatives	Possible
99.	Oral fluropyrimidine (5FU)	Possible
100.	Tetrazepam	Possible
101.	Ciprofloxacin	Probable
102.	Thiacetazone	Probable
103.	Thiacetazone	Probable
104.	Amlobarbitone	Probable
105.	Celecoxib	Possible
106.	Voriconazole	Probable
107.	Gabapentin	Possible
108.	Lamotrigene	Possible
109.	Cetuximab	Possible

Contd...

Contd...

110.	Celecoxib	Possible
111.	Carbamazepine	Probable
112.	Paracetamol	Possible
113.	Baclofen	Probable
114.	Trazodone	Probable
115.	Captopril	Probable
116.	Minoxidil	Probable
117.	Allopurinol	Probable
118.	Procaine penicillin	Probable
119.	Amoxycillin/cefalexin	Probable
120.	Ampicillin-sulbactum	Probable
121.	Cefuroxime, allopurinol and/or amoxicillin/clavulanic acid	Probable
122.	Augmentin	Probable
123.	Pemetrexed and carboplatin with Vit B12 and folic acid	Possible
124.	Hypericum	Probable
125.	Phenolphthalein and aloin	Definite
126.	Blood purifying pills	Probable
127.	Penicillic derivatives	Definite
128.	Imipenam/cilastatin/ meropenam	Definite
129.	Pentobarbitonum sodium	Probable
130.	Leflunomide	Probable
131.	Lamotrigene	Probable
132.	Lenalidomide	Probable
133.	Pseudoephidrine	Definite
134.	Thalidomide	Probable
135.	Clarithromycin	Definite
136.	Telithromycin	Definite
137.	Ampicillin	Definite
138.	Omeprazole	Probable
139.	Carvidilol	Probable
140.	Indomethacin	Probable
141.	Phenylbutazone	Probable
142.	Paroxitine	Probable
143.	Aerosolized pentamidine	Definite
144.	Rifampicin, isoniazid, pyrazinamide and ethambutol	Probable
145.	Rifampicin, isoniazid, pyrazinamide and ethambutol	Probable
146.	Rifampicin, isoniazid, pyrazinamide and ethambutol	Probable
147.	Aspirin/cefuroxime/pravastatin	Probable
148.	Trimethoprim-sulphamethoxazole	Probable
149.	Brinzolamide	Probable
150.	Dorzolamide	Probable
151.	Cetuximab plus minocycline	Definite
152.	Oxaprozin	Probable
153.	Cetuximab	Probable
154.	Lamotrigene	Probable
155.	Trovafloxacin	Probable
156.	Docetaxel	Probable
157.	Lmitinib	Probable
158.	Indomethacin	Possible
159.	Lamotrigene	Probable
160.	Carbamazepine	Probable
161.	Carbamazepine	Probable



Graph 4: Mortality trends over decades

group people are more susceptible to TEN. No significant difference in terms of gender was seen among the reported TEN cases. This systematic review of published case reports/series of TEN found that antibiotics followed by the anti-epileptics and NSAIDs were the most frequently implicated drugs necessitating vigilance on the part of prescribers regarding these drugs. This data is very much similar to the previous studies regarding drugs implicated in TEN.[1,12-15] In this study, among the antibiotics, beta-lactams were the foremost causative agent followed by sulphonamides and fluroquinolones. Previous studies have shown sulphonamides to be the foremost causative agents among antibiotics. Beta-lactams were found to be most common group of drugs causing TEN. This may be because of discovery of newer congeners like cephalosporins. Another reason could be that beta-lactams have been widely prescribed. In comparison to our study, EuroSCAR study reported strong association of TEN with nevirapine and lamotrigine among newer drugs and among older drugs sulphonamides followed by allopurinol, carbamazepine, phenobarbitone, phenytoin and oxicams.[16]

Single drugs were suspected in causing TEN as compared to multiple drugs. A physician should have adequate awareness regarding drugs indicated in TEN.

Our study found that in 63.3% of the reported cases, drugs implicated had a probable causation. A definite causality requires a rechallenge test to be performed. Since majority of the TEN cases are severe, it becomes difficult to perform rechallenge in most of the cases. Hence, a definite causality is difficult to arrive at.

Since TEN is an immunologically mediated reaction, it is but rational to use corticosteroids to suppress it. However, use of corticosteroids may increase the risk of infection, delay healing of lesions, mask early signs of sepsis and induce severe gastrointestinal bleeding. Hence, the use of corticosteroids in TEN cases is debatable. Previous studies reveal conflicting results regarding corticosteroid use in

the management of TEN cases. Some studies have reported corticosteroids as life saving if given early and especially in high doses (pulse therapy) for few days.[17-19] Other studies have reported that corticosteroid treatment does not affect the mortality in TEN.[20-22] Again, some other studies have reported an increase in mortality and morbidity in TEN cases treated with corticosteroids.[23,24] Infact, one study reports corticosteroids as being causative of TEN.[25] In our systematic review, treatment with steroid was found to be associated with a nonsignificant decrease in the mortality in the TEN cases. Since, this data is derived from case reports/series, a definite conclusion cannot be derived on the basis of this study. We require further well conducted, randomized clinical trials to determine the place of steroid therapy in the management of TEN cases.

Mortality in TEN cases during the period between 1980 and 1989 was 33.4%. This decreased to 27% in the next two decades although this decrease was not significant. This underlines a need for better diagnostic and treatment modalities for this condition and also more vigilance on the part of the prescribing physicians.

The difference in mortality indices in both developed and developing countries were nonsignificant, pointing toward good patient care in the developing nations which is at par with developed countries. On the contrary this might also be due to reporting bias in the developing nations due to a lack of good healthcare infrastructure. The main limitation of the study is that of publication bias from analysis of case reports and case series from Medline, PubMed, Cochrane and Embase leading to publication bias.

In less than 20% of the patients GMCSF, immunoglobulins and immunosuppressants were prescribed. These drugs are not approved for treating TEN and their efficacy in treating such cases need to be established by conducting randomized clinical trials. If proven efficacious they will add to the resources available to treat TEN successfully.

CONCLUSION

The best way to manage TEN is to detect it by constant vigilance, early diagnosis and prompt institution of therapy. Initial therapy should include maintenance of hydration, controlling pain, preventing secondary infection, and long term sequel. No specific treatment has shown to be effective. Role of corticosteroids in management of TEN has to be explored by conducting proper randomized controlled trials.

Questions which need to be addressed regarding the treatment of TEN:

1. How can we generate good quality evidence investigating the role of corticosteroids in TEN?
2. How can better understanding of pathophysiology of TEN lead to change in mortality?
3. What steps should be followed to prevent drug induced TEN?
4. What would be the effect of time to initiation of therapy on mortality in TEN?
5. What steps should be taken to stop to prevent long-term complication?
6. How can we bridge the gap between onset of TEN (prodromal symptoms) and full blown TEN?
7. What could be the reasons for differences in mortality trends in developing and developed countries though nonsignificant?
8. What steps should be taken to decrease the trend of mortality in both developing and developed countries?

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