Clinical, Cosmetic and Investigational Dermatology Dovepress

Open Access Full Text Article

CASE REPORT

D-Penicillamine-Induced Stevens–Johnson Syndrome in a Patient with Gold Cyanide Intoxication: A Case Report

Tanaporn Anuntrangsee, Kumutnart Chanprapaph, Wimolsiri Iamsumang

Division of Dermatology, Department of Medicine, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

Correspondence: Wimolsiri Iamsumang, Division of Dermatology, Department of Medicine, Faculty of Medicine Ramathibodi Hospital, Mahidol University, 270 Rama VI Road, Rajthevi, Bangkok, 10400, Thailand, Tel +662-201-1141, Fax +662-201-1211, Email i.wimolsiri@hotmail.com

Abstract: D-penicillamine is used as the mainstay of chelation therapy for Wilson's disease and for heavy metal intoxication. D-penicillamine itself has been noted to cause several systemic side effects as well as symptoms related to the skin. Common cutaneous side effects such as acute hypersensitivity reactions, elastic fiber abnormalities, and bullous diseases have been occasionally described. Herein, we report a case of a 23-year-old Thai female with gold intoxication who developed Stevens–Johnson syndrome (SJS) following the treatment of D-penicillamine. To our knowledge, D-penicillamine-induced SJS is exceptionally rare. To raise awareness of potentially fatal cutaneous adverse drug reaction triggered by D-penicillamine, published literature regarding SJS induced by this agent has also been reviewed. D-penicillamine should be regarded as a possible culprit in patients presenting with SJS following D-penicillamine administration and should be promptly discontinued.

Keywords: chelating agent, cutaneous adverse drug reaction, cyanide, epidermal necrolysis, gold salt, penicillamine

Introduction

D-penicillamine or penicillamine (D-β, β-dimethylcysteine), a derivative of penicillin, is an amino acid with a thiol side chain, a carboxyl group, and an a-amine group.[1] It has been approved by Food and Drug Administration (FDA) as the mainstay for chelation therapy in patients with Wilson's disease, as well as cystinuria, and is considered as a conventional disease-modifying antirheumatic drug (DMARD).[2,3] As a chelating agent, it is used to treat heavy metal intoxication eg, copper, iron, mercury, arsenic, and lead.[4,5] With its toxic metabolites, D-penicillamine may cause a wide range of clinical adverse effects, presenting with either extra-cutaneous and cutaneous manifestations or both. Cutaneous reactions could range from auto-immune or degenerative dermatoses to hypersensitivity reactions. The common adverse events can be categorized according to their mechanisms into four groups including (1) acute hypersensitivity reactions, (2) dermopathies, (3) autoimmune disorders, and (4) miscellaneous dermatoses.[1] However, the occurrence of D-penicillamine-induced SJS is extremely rare as there are only a few publications in the literature regarding toxic epidermal necrolysis (TEN) or SJS/TEN induced by this medication.[6,7] We hereby present a case of SJS that occurred after taking D-penicillamine for the treatment of gold cyanide intoxication with confirmed enzyme-linked immunosorbent spot (ELISpot) test.

Case Presentation

A 23-year-old Thai female with an underlying disease of major depressive disorder presented to the emergency department with a complaint of acute onset of high-grade fever, painful oral ulcers, and generalized rash. Thirty-three days prior to the admission, she was diagnosed as having gold cyanide intoxication due to suicidal attempt. Then, she received intramuscular dimercaprol as the first anti-dote treatment for a total of 14 days. After clinical improvement, D-penicillamine was prescribed as the second treatment for detoxication with the initial dosage at 250 mg twice daily for one week followed by 500 mg twice daily for a couple of weeks. However, on day 12 after receiving D-penicillamine or

Received: 2 August 2024
Accepted: 7 October 2024
Published: 28 October 2024

5 days prior to this visit, the patient developed fever and erythematous rash which started on the trunk and extended to the extremities. She also reported rash progression, sore mouth, and eye pain of 3 day-duration. She denied a history of previous herpetic infection. On examination, vital signs showed body temperature of 40 degree Celsius, blood pressure of 119/75 mmHg, pulse rate of 112 beats per minute, and respiratory rate of 24 breaths per minute. Dermatologic examination revealed generalized ill-defined non-blanchable erythematous to dusky red macules coalescing into patches with some central erosions on the face, trunk, and extremities including palms and soles (Figures 1A, 2 and 3A). Nikolsky's sign was positive on the truncal lesions (Figure 1B [inset]). The area of epidermal detachment was 8% of body surface area. She also had bilateral conjunctival injections (Figure 3A) and multiple oral erosions with some lesions on the lips having hemorrhagic crusts (Figure 3B). Other examinations were unremarkable. Further ophthalmic evaluation including slit-lamp examination was also within normal limits except for 1-millimeter corneal infiltration with minimal epithelial defects without punctate epithelial erosions on the right eye which was compatible with an ocular involvement of SJS.

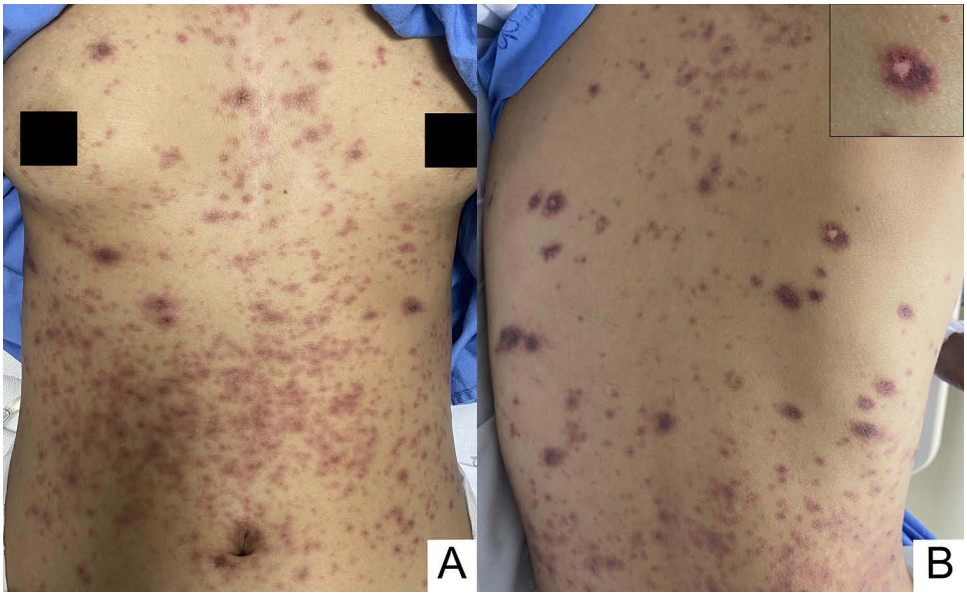

Figure 1 Cutaneous manifestation of D-penicillamine-induced Stevens-Johnson syndrome. Clinical features show multiple erythematous to dusky red macules coalescing into patches on the chest, abdomen (**A**), and back (**B**) with positive Nikolsky's sign (**B**, inset).

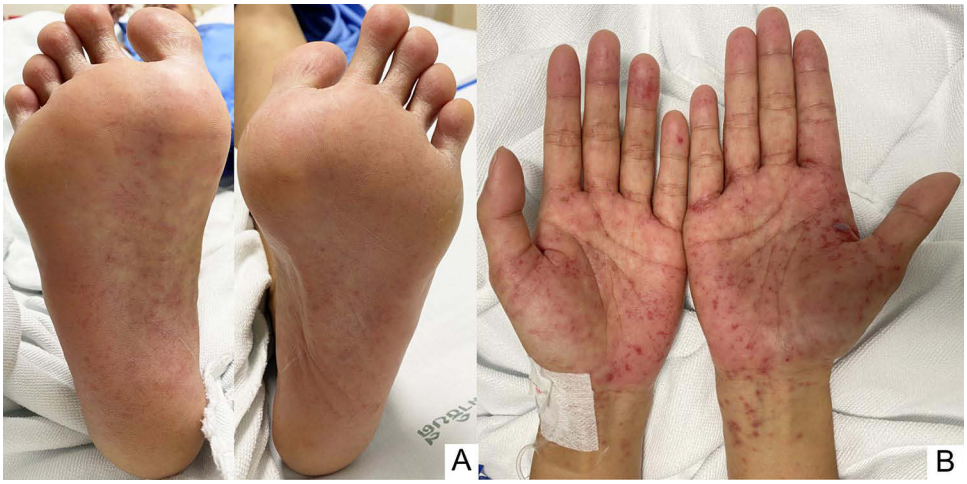

Figure 2 Multiple erythematous to dusky red macules coalescing into patches on the palms (**A**) and soles (**B**).

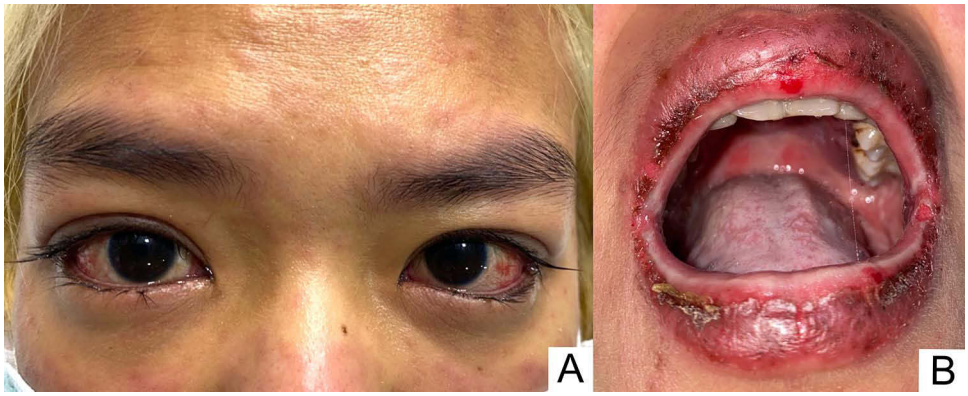

Figure 3 Facial involvement together with bilateral conjunctival injections (**A**). Multiple erosions in the oral cavity and lips, some with overlying hemorrhagic crust (**B**).

Regarding relatively typical clinical presentations including the rash morphology and distribution with positive Nikolsky's sign as well as the involvement of two mucosal membranes and systemic symptoms following a history of administration of the new medication, a provisional diagnosis of SJS was established. Since D-penicillamine was the only medication that had been continued through the latency period of SJS, it was considered as the most likely culprit and therefore immediately withheld. As for fever, infectious evaluations including blood, sputum, urine samples, and chest radiography were performed but later indicated no sources of infection. Complete blood count (CBC) was normal with no eosinophilia or atypical lymphocytosis. Her liver and renal function test were also unremarkable. The autoimmune panel revealed fine speckled and nucleolar antinuclear antibodies (ANA) with a titer of 1:80. Infectious workup revealed negative result for Mycoplasma IgM. Regarding prognosis, the calculated Severity-of-Illness Score for Toxic Epidermal Necrolysis (SCORTEN) in this patient was 0 on both day 1 and 5 which predicted the mortality rate of 3.2%, whereas the newer prognostic tool, Age, Bicarbonate, Cancer, Dialysis, 10% Body Surface Area (ABCD-10) score was 0 which predicted a mortality rate of 2.3%.[8] Intravenous dexamethasone 5 mg every 6 hours was prescribed for a period of 3 days and then was switched to 5 mg every 8 hours for 2 days. Symptomatic and supportive treatment including local wound care, and water/electrolyte, as well as nutritional support were provided. Wet dressings with normal saline and sodium fusidate ointment were applied on the eroded skin, whereas petroleum jelly and xylocaine viscous were used on the lips and in the oral cavity, respectively. Ophthalmic medications included 0.1% dexamethasone in balanced salt solution, 0.5% levofloxacin eye drops, and lubricant eye drops. Significant clinical improvement was observed after 3 days of therapy and the patient was discharged after 1 week of hospitalization when the cutaneous eruption and the mucosal lesions began to subside. Long-term follow-up did not show any sequelae and the eye examination showed complete resolution. ELISpot test was positive for D-Penicillamine at a dose of 12.5 microgram/milliliter (μg/mL), and D-penicillamine plus anti-programmed death ligand 1 antibody (anti-PD-L1) at a dose of 2.5 μg/mL and 12.5 μg/mL, whereas negative for dimercaprol. The results helped confirm that D-penicillamine was the causative agent for her condition.

Discussion

SJS is a rare life-threatening mucocutaneous reaction, which is considered as a variant of epidermal necrolysis spectrum including SJS, TEN, and SJS/TEN overlap syndrome. The overall incidence was estimated at 1–6 cases per million person-years, whereas the overall mortality rate for SJS ranged from 4.8 to 9%.[9] Epidermal necrolysis is characterized by acute extensive necrosis and detachment of epidermis and mucosa, where erythematous lesions could appear alongside epidermal necrosis. The initial presentation are nonspecific flu-like symptoms including fever, malaise, myalgia, cough, rhinitis, and sore eyes, which usually begin 1–3 weeks after exposure to the drug. Soon after these symptoms, the cutaneous manifestations occur. In most cases, the mucous membrane is involved, presenting with erythema and painful erosions of the genital, buccal, and ocular mucosa.[10] In this report, our patient first complained of fever, eye discomfort, and erythematous rash. Her rash progressively worsened and the oral lesions appeared shortly after. All of these features

are consistent with the manifestations of SJS. Nevertheless, since D-penicillamine is not a common triggering agent for epidermal necrolysis, other investigations were done in the initial steps to exclude other cutaneous conditions. Erythema multiforme major could be considered in this patient due to the palmoplantar and oral involvement but was less likely since there were no typical target lesions. Negative blood tests for Mycoplasma together with an absence of previous herpes infection also helped exclude erythema multiforme. Additionally, SJS-like acute cutaneous lupus erythematosus could be another differential diagnosis in this patient as it commonly affects young females and can present with similar clinical pictures to SJS.[11,12] D-penicillamine-induced systemic and cutaneous lupus erythematosus have also been reported.[1] However, the acute onset with rapidly progressive course and extensive mucosal involvement, lack of photo distributed predilection, and low titer ANA test made this autoimmune condition unlikely.

Drug is the most common identified cause in 80% of patients with SJS/TEN.[13] Common offending agents are aromatic antiepileptic drugs, antibiotics, allopurinol, and nonsteroidal anti-inflammatory drugs (NSAIDs), among others.[13,14] Newer medications such as immune checkpoint inhibitors or commonly prescribed antimicrobial/antiviral agents including terbinafine, itraconazole, and acyclovir were also reported.[15–18] However, infectious causes such as *Mycoplasma pneumoniae* and herpes simplex virus infections have also been documented as a cause of SJS/TEN.[19] Recently, the new revised classification of SJS in pediatric patients was established. These blistering cutaneous reactions were divided into 2 groups based on etiologies and pathogeneses, including drug-induced epidermal necrolysis and reactive infectious mucocutaneous eruption and have different treatment strategies.[20] In our patient, apart from D-penicillamine, the recent medications also included dimercaprol and gold cyanide, which were prescribed at 32 and 33 days prior to her symptoms, respectively. There are no previous reports regarding dimercaprol induced SJS/TEN; nevertheless, dimercaptopropane-1-sulfonate (DMPS), which is a water-soluble chemical analog of dimercaprol, has been reported to cause SJS in children suffering from chronic mercury exposure.[21] Gold itself can induce cutaneous reactions, eg, pruritus, macules, papules, urticarial rashes, lichen planus-like or pityriasis rosea-like eruptions.[22,23] However, to our knowledge, gold has never been reported as a cause of SJS or TEN in the literature. Moreover, both dimercaprol and gold were ceased at 16 and 32 days prior to the beginning of symptoms, respectively, making both medications unlikely causes of SJS in this patient. ELISpot also confirmed that D-penicillamine was the causative agent in the present case. According to the literature, the sensitivity of interferon-gamma (IFN-γ) ELISpot for drug confirmation in SJS/TEN was 50% from a study in Thais,[24] and 71% in one systematic review with specificity as high as 96%.[25]

D-penicillamine is d-isomer of dimethylcysteine, a degradation product of penicillin.[5] Since it has chelating properties by binding to the heavy metals and increasing the excretion of these metals in the urine, it has been used as a chelating agent for several decades.[3–5] Multiple adverse events, including cutaneous and extra-cutaneous manifestations, are associated with D-penicillamine and could result in drug discontinuation in at least 30% of patients.[26] Most adverse events are dose dependent except for autoimmune and immediate-hypersensitivity reactions.[1] Extracutaneous adverse reactions include fever, lymphadenopathy, arthralgia, leukopenia/or thrombocytopenia, proteinuria, and neurological symptoms.[26] For cutaneous manifestation, various reactions from D-penicillamine have been occasionally reported and could be divided into 4 groups based on the underlying mechanisms as follows: (1) hypersensitivity reaction, (2) elastic fiber abnormalities (eg, elastosis perforans serpiginosa, acquired cutis laxa, anetoderma, and pseudo-pseudoxanthoma elasticum), (3) autoimmune diseases (eg, bullous disease, D-penicillamine-induced lupus-erythematosus-like syndrome),[27] and (4) undefined mechanisms (eg, lichen planus, psoriasiform dermatitis, alopecia). In terms of autoimmune skin disorders caused by D-penicillamine, the exact mechanism remains uncertain. The hypotheses involve genetic predisposition and some inflammatory processes modulated by this drug including decreasing the number of T-lymphocytes, triggering the synthesis of autoantibodies, and activating macrophage functions. Additionally, D-penicillamine can be associated with decreasing serum levels of cytokines, eg interleukin (IL)-1 and rheumatoid factor, and increasing levels of IL-6, 13, 15, and 23, tumor necrosis factor-alpha, and interferon-gamma. These could lead to autoimmunity and autoimmune complications of D-penicillamine treatment.[28]

The majority of D-penicillamine hypersensitivity responses are known to manifest as urticarial and morbilliform eruptions, occurring in approximately 15% of patients within the first few weeks of treatment.[1] Although severe cutaneous adverse drug reactions related to D-penicillamine are exclusively rare, there are two published cases with epidermal necrolysis spectrum. First, in 2014, a 20-year-old Korean patient with Wilson's disease suffered from TEN

with hepatic involvement after one week of D-penicillamine administration.[6] He was successfully treated with drug cessation, intravenous immunoglobulin, systemic corticosteroid, and supportive care. Recently, a 30-year-old man with hepatitis B, human immunodeficiency virus infection, and Wilson's disease who developed D-penicillamine-induced SJS/TEN overlap has been published.[7] The patient was effectively treated with intravenous immunoglobulin. However, he had a neurotrophic ulcer in the right cornea as a delayed sequela. Cross-reactivity to penicillin was reported up to one-third of patients taking D-penicillamine and can present with some episodes of urticarial and maculopapular rash with edema, itching, and fever due to penicillin cross-reactivity. Nonetheless, this risk has been eliminated nowadays since D-penicillamine is now synthetically produced without penicillin traces.[1]

After diagnosis of SJS/TEN, in-hospital prediction of mortality rate is important. The widely used scoring system prediction in patients hospitalized with SJS/TEN is SCORTEN.[29] Another recently proposed mortality prognostication tool is ABCD-10, which is calculated by using age, bicarbonate, cancer, dialysis, and 10% body surface area.[30] In our patient, the calculated scores using both tools were 0, indicating the low mortality rate (3.2% for SCORTEN and 2.3% for ABCD-10). According to the management for SJS/TEN, the mainstay is early diagnosis and immediate cessation of offending drug(s). All the baseline laboratory tests including CBC, liver function test, urinalysis, and blood culture should be carried out. General supportive management also includes fluid and nutritional care, pain control, appropriate skin care in order to prevent secondary bacterial infection and to promote wound healing.[31] Due to the pathogenesis of SJS/TEN, which is primarily triggered by CD8+ T cells and mediated by granulysin,[32–34] immunomodulatory medications including systemic corticosteroid, cyclosporin A,[35] intravenous immunoglobulin (IVIG),[36] plasmapheresis,[37] and tumor necrosis factor-α inhibitors[38] have been reported with variable success. Due to the lack of randomized controlled trials, the use of systemic corticosteroid for SJS/TEN remains controversial. Although it is suggested that systemic corticosteroid treatment did not significantly decrease mortality rate compared to supportive care,[39] a meta-analysis in 2017 demonstrated the effectiveness of systemic glucocorticoid therapy in patients with SJS/TEN.[40] The study conducted in the Asian population noted that early glucocorticoid administration in the course of treatment may be a viable therapeutic option to improve the prognosis of SJS/TEN.[41,42] A multidisciplinary approach is also recommended if multiple organ involvement is anticipated. In the present case, when a diagnosis of D-penicillamine induced SJS was made, management including drug withdrawal, supportive care, and a short course of systemic corticosteroid resulted in favorable clinical improvement without long-term sequalae. The severity of adverse reactions determines whether D-penicillamine can be reintroduced. If the reaction is mild and D-penicillamine is necessary, it can be started with low dosages, followed by gradual titration, and careful monitoring for the occurrence of the adverse effect or new events.[26] Nevertheless, since the reaction in this case was SJS, which is classified as severe cutaneous adverse reaction, therefore drug rechallenge is contraindicated.[43]

Conclusion

Although exclusively rare, life-threatening severe cutaneous adverse drug reaction such as SJS should be recognized as a possible cutaneous adverse response following D-penicillamine administration. When clinically suspected, D-penicillamine should be immediately discontinued in order to minimize mortality and morbidity. In vitro-testing such as ELISpot proved to be helpful in making diagnosis and identifying the offending medication.

Abbreviations

ABCD-10, Age, Bicarbonate, Cancer, Dialysis, 10% Body Surface Area; ANA, antinuclear antibody; anti-PD-L1, anti-programmed death ligand 1 antibody; CBC, complete blood count; DMARD, disease-modifying antirheumatic drug; DMPS, 2,3-dimercaptopropane-1-sulfonate; ELISpot, enzyme-linked immunosorbent spot; FDA, Food and Drug Administration; IFN-γ, interferon-gamma; IL, interleukin; IVIG, intravenous immunoglobulin; mL, milliliter; NSAIDs, nonsteroidal anti-inflammatory drugs; SCORTEN, Severity-of-Illness Score for Toxic Epidermal Necrolysis; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis; μg, microgram.

Ethics Approval and Informed Consent

The patient's parent has given written informed consent for the publication of her clinical details and accompanying images, as the patient was not fully conscious and lacked the capacity to provide informed consent during the course of the disease (major depressive disorder and Stevens–Johnson Syndrome). Institutional approval is not required for this case study.

Funding

The author received no financial support for this research.

Disclosure

The authors declare that this manuscript was prepared in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Ishak R, Abbas O. Penicillamine revisited: historic overview and review of the clinical uses and cutaneous adverse effects. *Am J Clin Dermatol*. 2013;14(3):223–233. doi:10.1007/s40257-013-0022-z
2. Hedera P. Update on the clinical management of Wilson's disease. *Appl Clin Genet*. 2017;10:9–19. doi:10.2147/TACG.S79121
3. Mejias SG, Ramphul K. Penicillamine. In: *StatPearls*. Treasure Island (FL): ineligible companies. Disclosure: Kamleshun Ramphul declares no relevant financial relationships with ineligible companies; 2024.
4. Friedman M. Chemical basis for pharmacological and therapeutic actions of penicillamine. *Adv Exp Med Biol*. 1977;86B:649–673. doi:10.1007/978-1-4757-9113-6_36
5. Gerhardsson L, Aaseth J. Chapter 7 - guidance for clinical treatment of metal poisonings—use and misuse of chelating agents. In: Aaseth J, Crisponi G, Andersen O, editors. *Chelation Therapy in the Treatment of Metal Intoxication*. Boston: Academic Press; 2016:313–341.
6. Lee YI, Lee MY, Park YT, et al. Penicillamine-induced toxic epidermal necrolysis in a patient with Wilson disease. *Allergy Asthma Respir Dis*. 2014;2(4):302–305. doi:10.4168/aard.2014.2.4.302
7. Chhabra N, Reddy PSM, Bhatnagar A, Ganguly S. Penicillamine-induced Stevens Johnson Syndrome-toxic Epidermal Necrolysis (SJS-TEN) overlap in an HIV-infected patient with Wilson's disease and Hepatitis B. *Curr Drug Saf*. 2024;19(2):295–298. doi:10.2174/1574886318666230525102008
8. Dobry AS, Himed S, Waters M, Kaffenberger BH. Scoring assessments in Stevens-Johnson Syndrome and toxic epidermal necrolysis. *Front Med*. 2022;9. doi:10.3389/fmed.2022.883121.
9. Frantz R, Huang S, Are A, Motaparthi K. Stevens-Johnson Syndrome and toxic epidermal necrolysis: a review of diagnosis and management. *Medicina*. 2021;57(9):895. doi:10.3390/medicina57090895
10. Klimas N, Quintanilla-Dieck J, Vandergriff T. Stevens–Johnson Syndrome and toxic epidermal necrolysis. *Cutaneous Drug Eruptions*. 2015;15:259–269. doi:10.1007/978-1-4471-6729-7_24
11. Tankunakorn J, Sawatwarakul S, Vachiramon V, Chanprapaph K. Stevens-Johnson Syndrome and toxic epidermal necrolysis-like lupus erythematosus. *J Clin Rheumatol*. 2019;25(5):224–231. doi:10.1097/RHU.0000000000000830
12. Chanprapaph K, Tankunakorn J, Suchonwanit P, Rutnin S. Dermatologic manifestations, histologic features and disease progression among cutaneous lupus erythematosus subtypes: a prospective observational study in asians. *Dermatol Ther*. 2021;11(1):131–147. doi:10.1007/s13555-020-00471-y
13. Houschyar KS, Tapking C, Borrelli MR, et al. Stevens-Johnson syndrome and toxic epidermal necrolysis: a 10-year experience in a burns unit. *J Wound Care*. 2021;30(6):492–496. doi:10.12968/jowc.2021.30.6.492
14. Carrasquillo OY, Santiago-Vazquez M, Cardona R, Cruz-Manzano M, Figueroa LD. Stevens-Johnson syndrome and toxic epidermal necrolysis: a retrospective descriptive study. *Int J Dermatol*. 2019;58(11):1293–1299. doi:10.1111/ijd.14493
15. Das A, Sil A, Mohanty S. Itraconazole-induced Stevens-Johnson syndrome and toxic epidermal necrolysis overlap: report of a rare incident. *Dermatol Ther*. 2020;33(6):e14311. doi:10.1111/dth.14311
16. Banik B, Bhar D, Sil A. Terbinafine-induced Steven-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) overlap. *Postgrad Med J*. 2021;97(1152):630–631. doi:10.1136/postgradmedj-2020-138326
17. Sen SS, Sil A, Chakraborty U, Chandra A. Stevens-Johnson syndrome-toxic epidermal necrolysis: a fatal cutaneous adverse reaction to oral Acyclovir. *BMJ Case Rep*. 2020;13(8):e238555. doi:10.1136/bcr-2020-238555
18. Geisler AN, Phillips GS, Barrios DM, et al. Immune checkpoint inhibitor-related dermatologic adverse events. *J Am Acad Dermatol*. 2020;83(5):1255–1268. doi:10.1016/j.jaad.2020.03.132
19. Harr T, French LE. Toxic epidermal necrolysis and Stevens-Johnson syndrome. *Orphanet J Rare Dis*. 2010;5(39). doi:10.1186/1750-1172-5-39
20. Ramien M, Goldman JL. Pediatric SJS-TEN: where are we now? *F1000Res*. 2020;9:982. doi:10.12688/f1000research.20419.1
21. Van der Linde AA, Pillen S, Gerrits GP, Bouwes Bavinck JN. Stevens-Johnson syndrome in a child with chronic mercury exposure and 2,3-dimercaptopropane-1-sulfonate (DMPS) therapy. *Clin Toxicol (Phila)*. 2008;46(5):479–481. doi:10.1080/15563650701779687
22. Thomas I. Gold therapy and its indications in dermatology. A review. *J Am Acad Dermatol*. 1987;16(4):845–854. doi:10.1016/s0190-9622(87)70111-x
23. Lizeaux-Parneix V, Bedane C, Lavignac C, Bernard P, Bonnetblanc JM. Cutaneous reactions to gold salts. *Ann Dermatol Venereol*. 1994;121(11):793–797.
24. Suthumchai N, Srinoulprasert Y, Thantiworasit P, et al. The measurement of drug-induced interferon gamma-releasing cells and lymphocyte proliferation in severe cutaneous adverse reactions. *J Eur Acad Dermatol Venereol*. 2018;32(6):992–998. doi:10.1111/jdv.14890

25. Porebski G. In vitro assays in severe cutaneous adverse drug reactions: are they still research tools or diagnostic tests already? *Int J Mol Sci*. 2017;18(8):1737. doi:10.3390/ijms18081737
26. Litwin T, Członkowska A, Socha P. Chapter 34 - oral chelator treatment of Wilson disease: d-Penicillamine. In: Kerkar N, Roberts EA, editors. *Clinical and Translational Perspectives on WILSON DISEASE*. Academic Press; 2019:357–364.
27. Antos AJ, Litwin T, Przybylkowski A, Skowronska M, Kurkowska-Jastrzebska I, Czlonkowska A. D-penicillamine-induced lupus erythematosus as an adverse reaction of treatment of Wilson's Disease. *Neurol Neurochir Pol*. 2021;55(6):595–597. doi:10.5603/PJNNS.a2021.0080
28. Antos A, Czlonkowska A, Bembenek J, Kurkowska-Jastrzebska I, Litwin T. D-Penicillamine-induced myasthenia gravis-a probable complication of Wilson's Disease treatment-A case report and systematic review of the literature. *Life*. 2023;13(8):1715. doi:10.3390/life13081715
29. Torres-Navarro I, Briz-Redon A, Botella-Estrada R. Accuracy of SCORTEN to predict the prognosis of Stevens-Johnson syndrome/toxic epidermal necrolysis: a systematic review and meta-analysis. *J Eur Acad Dermatol Venereol*. 2020;34(9):2066–2077. doi:10.1111/jdv.16137
30. Noe MH, Rosenbach M, Hubbard RA, et al. Development and validation of a risk prediction model for in-hospital mortality among patients with Stevens-Johnson syndrome/toxic epidermal necrolysis-ABCD-10. *JAMA Dermatol*. 2019;155(4):448–454. doi:10.1001/jamadermatol.2018.5605
31. Schneider JA, Cohen PR. Stevens-Johnson Syndrome and toxic epidermal necrolysis: a concise review with a comprehensive summary of therapeutic interventions emphasizing supportive measures. *Adv Ther*. 2017;34(6):1235–1244. doi:10.1007/s12325-017-0530-y
32. Chung WH, Hung SI, Yang JY, et al. Granulysin is a key mediator for disseminated keratinocyte death in Stevens-Johnson syndrome and toxic epidermal necrolysis. *Nat Med*. 2008;14(12):1343–1350. doi:10.1038/nm.1884
33. Le Cleach L, Delaire S, Boumsell L, et al. Blister fluid T lymphocytes during toxic epidermal necrolysis are functional cytotoxic cells which express human natural killer (NK) inhibitory receptors. *Clin Exp Immunol*. 2000;119(1):225–230. doi:10.1046/j.1365-2249.2000.01119.x
34. Nassif A, Bensussan A, Dorothee G, et al. Drug specific cytotoxic T-cells in the skin lesions of a patient with toxic epidermal necrolysis. *J Invest Dermatol*. 2002;118(4):728–733. doi:10.1046/j.1523-1747.2002.01622.x
35. Senda A, Fushimi K, Morishita K. Effect of early cyclosporine treatment on survival in Stevens-Johnson syndrome and toxic epidermal necrolysis. *Cureus*. 2024;16(4):e57862. doi:10.7759/cureus.57862
36. Barron SJ, Del Vecchio MT, Aronoff SC. Intravenous immunoglobulin in the treatment of Stevens-Johnson syndrome and toxic epidermal necrolysis: a meta-analysis with meta-regression of observational studies. *Int J Dermatol*. 2015;54(1):108–115. doi:10.1111/ijd.12423
37. Han F, Zhang J, Guo Q, et al. Successful treatment of toxic epidermal necrolysis using plasmapheresis: a prospective observational study. *J Crit Care*. 2017;42:65–68. doi:10.1016/j.jcrc.2017.07.002
38. Nikitina EA, Fomina DS, Markina UA, et al. Positive experience with TNF-alpha inhibitor in toxic epidermal necrolysis resistant to high-dose systemic corticosteroids. *Front Med*. 2023;10(1210026). doi:10.3389/fmed.2023.1210026
39. Roujeau JC, Bastuji-Garin S. Systematic review of treatments for Stevens-Johnson syndrome and toxic epidermal necrolysis using the SCORTEN score as a tool for evaluating mortality. *Ther Adv Drug Saf*. 2011;2(3):87–94. doi:10.1177/2042098611404094
40. Zimmermann S, Sekula P, Venhoff M, et al. Systemic immunomodulating therapies for Stevens-Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. *JAMA Dermatol*. 2017;153(6):514–522. doi:10.1001/jamadermatol.2016.5668
41. Choonhakarn C, Limpawattana P, Chaowattanapanit S. Clinical profiles and treatment outcomes of systemic corticosteroids for toxic epidermal necrolysis: a retrospective study. *J Dermatol*. 2016;43(2):156–161. doi:10.1111/1346-8138.13040
42. Hsieh MH, Watanabe T, Aihara M. Recent dermatological treatments for Stevens-Johnson syndrome and toxic epidermal necrolysis in Japan. *Front Med Lausanne*. 2021;8(636924). doi:10.3389/fmed.2021.636924
43. Po AL, Kendall MJ. Causality assessment of adverse effects: when is re-challenge ethically acceptable? *Drug Saf*. 2001;24(11):793–799. doi:10.2165/00002018-200124110-00001