ISSN: 0219 - 2152 April 2024 Vol.26 No.1

ADVERSE DRUG REACTION NEWS

HSA Health Sciences Authority

Health Product Safety Information Summary

Scan / click the QR code to read the full issue online

This is a case of a male patient in his 70s with underlying diabetes mellitus (DM) and hypertension who presented with pruritic rashes with blisters over his body, arms (Figure 1), legs and a blister in his mouth. He did not have any fever or eye symptoms. His medications included metformin, glipizide, linagliptin and amlodipine, all of which were started more than a year ago. He had urticarial plaques, blisters and multiple erosions over his trunk and limbs, with one intact bulla over the buccal mucosa. The affected body surface area was about 10%. His skin biopsy showed subepidermal blister with eosinophils.

What could have caused the blistering rash in this patient?

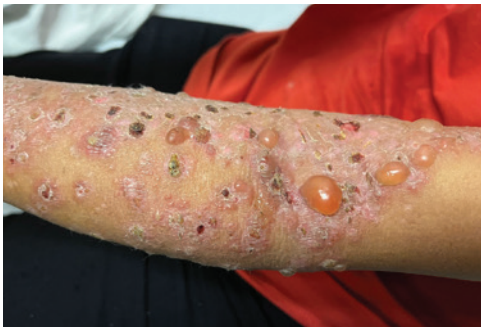


Figure 1. Tense bullae and erosions over the upper limb.

AE Case in Focus 2: Test Yourself

Pg 6

This is a case of an eight-year-old girl who was admitted for acute symptoms of shortness of breath, fever, maculopapular rash and vomiting. Five weeks prior, she had left hip osteomyelitis and Group D Salmonella bacteraemia. She was treated with intravenous (IV) ceftriaxone and underwent ultrasound-guided drainage of the abscess. Upon improvement, she was discharged home on oral trimethoprim-sulfamethoxazole (TMP-SMX) for treatment of osteomyelitis. After 19 days of taking TMP-SMX, she had a recurrence of fever with no other symptoms or hip pain. She was given doxycycline 70mg twice daily for possible rickettsial infection. Despite this, she continued to be febrile, with vomiting. She then developed a maculopapular rash over her hands, which spread to her body and face. On Day 25 of TMP-SMX and Day 6 of doxycycline, she developed acute breathlessness, leading to her current presentation. She had reduced air entry over her lower chest with scattered crepitations bilaterally, and a diffuse pruritic reticular maculopapular rash with no mucosal involvement. Chest X-ray and computed tomography (CT) of the neck and thorax showed diffuse ground glass changes involving the entire lung with an apical-basal gradient, as well as extensive pneumomediastinum, bilateral pneumothorax and subcutaneous emphysema (Figures 1 and 2). Microlaryngoscopy and bronchoscopy (MLB) and oesophagoscopy revealed normal trachea, mild oesophagitis, and no tracheal or oesophageal perforation. She required mechanical ventilation for severe oxygenation failure consistent with severe paediatric acute respiratory distress syndrome (PARDS).

What could have caused the respiratory failure in this patient?

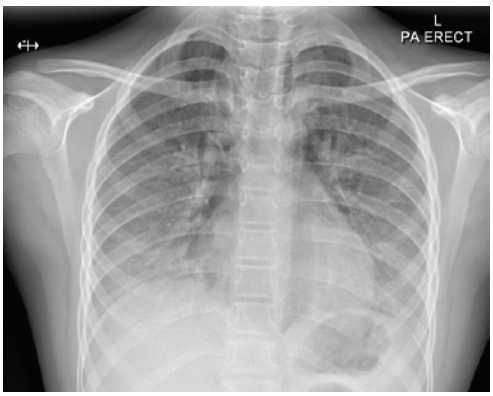


Figure 1. Initial chest X-ray showing extensive pneumomediastinum, subcutaneous emphysema extending up to the neck, small left pneumothorax and bilateral diffuse hazy lung opacification.

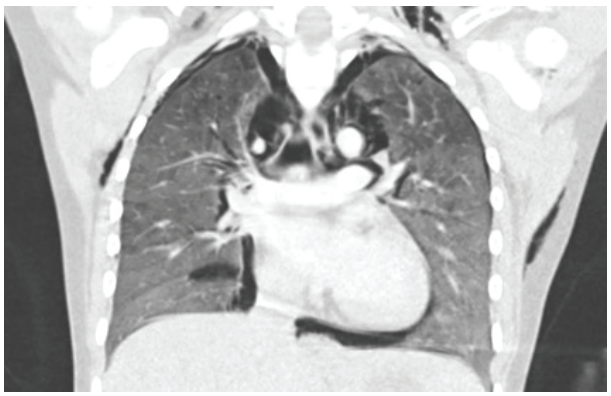
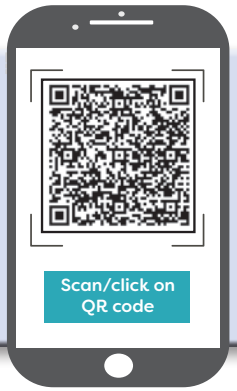


Figure 2. CT scan of the neck and thorax demonstrating extensive pneumomediastinum, bilateral pneumothorax, and lower cervical and thoracic subcutaneous emphysema. There were diffuse pulmonary ground glass changes, involving the entire lung with an apical-basal gradient. There were no fibrotic changes, honeycombing, interstitial thickening or bronchiectasis.

Dear Healthcare Professional Letters on safety concerns



Useful Information

Doctors, dentists and pharmacists can claim continuing education points for reading each issue of the HSA ADR News Bulletin. Doctors can apply for one non-core Continuing Medical Education (CME) point under category 3A, dentists can apply for one Continuing Professional Education (CPE) point under category 3A and pharmacists can apply for one patient-care Continuing Professional Education (CPE) point under category 3A per issue of the bulletin.

How to report suspected AEs to HSA?

For any suspected AEs, please report to us via the following:

HSA_productsafety@hsa.gov.sg

https://www.hsa.gov.sg/adverse-events

For any enquiries or assistance on AE reporting, please call us at 6866 1111

All website references were last accessed on 1 April 2024.

Pseudoephedrine and the rare risk of posterior reversible encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome (RCVS)

Key Points

- A very small number of overseas cases of posterior reversible encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome (RCVS) have been reported with pseudoephedrine. PRES and RCVS are rare and reversible conditions, and most patients fully recover with early recognition and appropriate treatment.
- Pseudoephedrine has been marketed in Singapore since the late 1980s with no significant safety issues reported. To date, HSA has not received any local adverse event reports of PRES or RCVS associated with pseudoephedrine.
- The local package inserts of pseudoephedrine-containing products will be strengthened to highlight the rare risk of PRES and RCVS and their symptoms.
- To facilitate the prompt detection of PRES and RCVS symptoms and the necessary medical intervention, healthcare professionals may consider counselling their patients on symptoms that require immediate medical attention, such as sudden onset of severe headache, nausea, vomiting, visual disturbances, seizures and altered mental status.

Pseudoephedrine is a sympathomimetic agent widely used to relieve nasal congestion by vasoconstricting the blood vessels in the nasal passages. It is often combined with other active ingredients such as antihistamines and antipyretics to treat common cold or allergic symptoms. Pseudoephedrine-containing products have been registered in Singapore since 1989 and there are 31 products currently registered. Of these, one is a Prescription Only Medicine while the others are Pharmacy Only Medicines. A few overseas cases of posterior reversible encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome (RCVS) have been reported with the use of pseudoephedrine.

Postulated role of pseudoephedrine in causing PRES and RCVS[1-3]

The use of vasoactive agents such as pseudoephedrine has been postulated to play a contributory role in the development of PRES or RCVS, which are rare neurological conditions involving cerebral ischaemia. Although the pathogenesis of PRES and RCVS remains unclear, potential mechanisms include acute blood pressure changes and cerebral vascular autoregulation dysfunction, which could be induced by vasoconstriction.

PRES typically presents with headaches, visual deficits, mental changes, seizures and brain oedema. Several risk factors have been identified, including immunosuppression, sepsis, pre-eclampsia, renal failure, autoimmune disorders and hypertension. Prognosis is generally favourable because clinical symptoms and imaging lesions are reversible in most patients.

RCVS is characterised by cerebral vasoconstriction, which typically follows a self-limiting course in disease progression, although RCVS-like vasoconstriction may also be observed in PRES. Its symptoms include thunderclap headaches accompanied by other clinical manifestations such as seizures, encephalopathy, and focal neurological deficits. The majority of patients with RCVS have a favourable prognosis, whereby headaches and angiographic abnormalities resolve within days or weeks upon the identification and elimination of any precipitating factors.

International regulatory actions

The European Medicines Agency (EMA) and UK Medicines and Healthcare products Regulatory Agency (MHRA) have completed their safety assessments on the risk of PRES and RCVS associated with pseudoephedrine.[4,5] Their reviews considered information from post-marketing safety data and advice sought from their pharmacovigilance expert groups. The EMA acknowledged that while PRES and RCVS could lead to serious and life-threatening complications, these are rare conditions that generally resolve with prompt diagnosis and treatment. The UK MHRA's review noted four reports of suspected PRES or RCVS with pseudoephedrine in the context of over 4 million packets sold in the UK in 2022 alone. Both agencies have contraindicated the use of pseudoephedrine in patients with severe or uncontrolled hypertension or severe renal disease, which are risk factors for PRES and RCVS, and recommended for the addition of warnings on these adverse events to the package inserts (PIs) or patient information leaflets (PILs) of pseudoephedrine-containing products. They have also recommended for healthcare professionals to advise their patients to stop using these products immediately and seek treatment if they develop symptoms of PRES or RCVS.

Local situation

To date, HSA has not received any local adverse event report of PRES or RCVS associated with pseudoephedrine despite its long history and widespread use. In March 2024, one of the product registrants issued a Dear Healthcare Professional Letter (DHCPL) to notify healthcare professionals about the risks of PRES and RCVS associated with the use of pseudoephedrine.[6] HSA will work with the product registrants to strengthen the warnings on PRES and RCVS and their related symptoms in the PIs or PILs of pseudoephedrine-containing products registered locally.

HSA's advisory

PRES and RCVS are rare and reversible conditions, and most patients fully recover with early recognition and appropriate treatment. Healthcare professionals are advised to take note of the advisories by the EMA and UK MHRA. They may also consider counselling their patients on symptoms that require immediate medical attention to facilitate the prompt detection of PRES and RCVS symptoms and necessary medical intervention. These include sudden onset of severe headache, nausea, vomiting, visual disturbances, seizures and altered mental status.

References

1. *J. Stroke Cerebrovasc. Dis. 2022; 31: 106472*
2. *Front. Neurol. 2020; 11: 34*
3. *J. Neurol. 2023; 270: 673-88*
4. *https://www.ema.europa.eu/en/medicines/human/referrals/pseudoephedrine-containing-medicinal-products*
5. *https://www.gov.uk/drug-safety-update/pseudoephedrine-very-rare-risk-of-posterior-reversible-encephalopathy-syndrome-pres-and-reversible-cerebral-vasoconstriction-syndrome-rcvs*
6. *https://www.hsa.gov.sg/announcements/dear-healthcare-professional-letter/zyrtec-d---risks-of-posterior-reversible-encephalopathy-syndrome-and-reversible-cerebral-vasoconstriction-syndrome-associated-with-the-use-of-pseudoephedrine*

Analysis of adverse event reports for year 2023

Key Points

- In 2023, HSA received 25,637 valid+ adverse event (AE) reports.
- The top pharmacotherapeutic product groups suspected of causing AEs were antibiotics, nonsteroidal anti-inflammatory agents, analgesics, antithrombotic agents and anti-diabetic agents.
- There were 675 vaccine adverse event (VAE) reports, including COVID-19 VAE reports. The commonly reported AEs with childhood vaccines in children aged 12 years and below included lymphadenopathy (suppurative and non-suppurative) with the *Bacillus Calmette-Guérin* (BCG) vaccine and seizures (febrile and afebrile) with various other vaccines. The commonly reported AEs with adult vaccines and COVID-19 vaccines were allergic reactions.
- There were 88 AE reports associated with complementary health products (CHPs). Majority of the AEs were allergic reactions associated with glucosamine-containing products and melatonin.

This is a review of AE reports received by HSA in 2023. The scope of this review includes pharmaceuticals (i.e., chemical drugs, biologics, vaccines), cell, tissue, and gene therapy products (CTGTP), complementary health products (CHPs) and cosmetic products.

Report analysis for 2023

(a) Volume of reports

In 2023, HSA received a total of 25,637 valid+ reports. This figure is close to the average annual volume of 23,574 reports received for the past 10 years (i.e. 2013 to 2022) and an increase of 22% compared to 2022 where 21,047+ reports were received.

+Reports include COVID-19 vaccine AE reports. Reports lacking important details such as names of suspected drugs and AE descriptions were regarded as invalid reports and not captured in the national AE database as these reports could not be assessed for causality.

(b) Types and sources of reports

Majority of the reports were associated with pharmaceuticals (99.6%), which included chemical drugs (95.8%), vaccines (2.6%), biologics (1.2%). This was followed by CHPs (0.4%), which included Chinese Proprietary Medicines, health supplements and traditional medicines. The remaining reports were associated with CTGTP (0.05%) and cosmetic products (0.01%).

Most of the AE reports were from public hospitals (40.4%), followed by General Practitioner (GP) clinics (35.0%) and polyclinics (18.5%). Other reporting sources included specialist clinics (2.6%), product registrants (2.2%), private hospitals (0.4%) and government agencies (0.4%). The increase in the number of reports (35.0% versus 13.5% in 2022) contributed by GP clinics may be due to their data contribution to the National Electronic Health Records in 2023 which included AEs from their patients. Doctors (91.4%) contributed the highest number of reports, followed by pharmacists (3.7%). Reports from dentists, nurses and research coordinators have also been received.

(c) Demographics

Where patient demographics were reported, more AE reports were received for females (61.7%) than males. Chinese patients constituted the highest proportion (70.6%) of AE reports, followed by Malays (14.1%) and Indians (7.9%).

The age range of patients with the highest reported frequency was 60 - 69 years of age (17.4%), followed by those in the age group of 50 - 59 years (16.9%), 40 - 49 years (14.7%), and 30 - 39 years (14.7%).

AE reports associated with chemical drugs, biologics and CTGTP

The top five drug classes suspected of causing AEs were from the following pharmacotherapeutic groups: antibiotics (32.8%), nonsteroidal anti-inflammatory drugs (NSAIDs) (22.7%), analgesics (9.9%), antithrombotic agents (3.5%) and anti-diabetic agents (3.2%). Refer to Figure 1 for the breakdown of the top three drugs within each drug class.

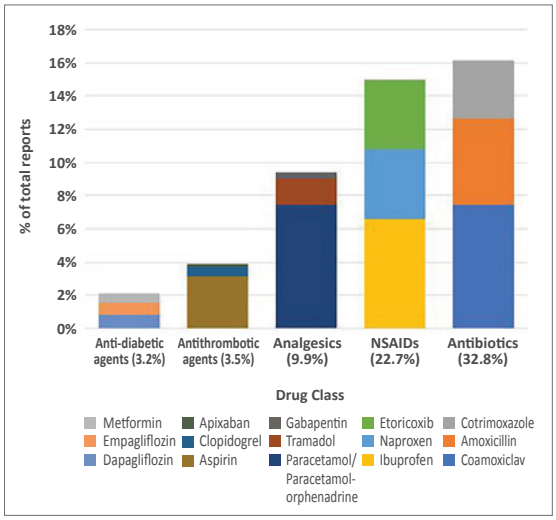


Figure 1. Top 5 drug classes and the top 3 drugs within each drug class (by active ingredients) suspected of causing AEs

A large proportion of AEs reported were skin reactions (60.1%), followed by those affecting the body as a whole (e.g. fever, anaphylaxis) (18.3%) and respiratory system disorders (coughing, dyspnoea) (5.8%). Most of the AE reports described non-serious reactions which included rash, pruritus, and angioedema. The top five drugs suspected to cause serious AEs of interest are summarised in Table 1.

It is worth noting that these figures do not take into consideration the drugs' utilisation rates and therefore do not inform on their relative safety profiles. More than one drug may be implicated in a single AE report. The increase in the number of reports in 2023 was also contributed by the increase in the retrospective AE reports from GP clinics and are not indicative of any new safety signals. Overall, the AEs associated with the implicated drugs are generally consistent with the known safety profile of these drugs.

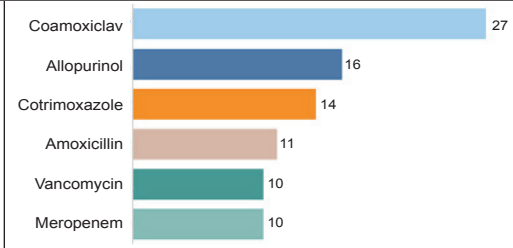
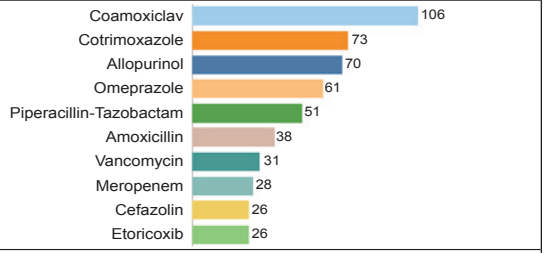
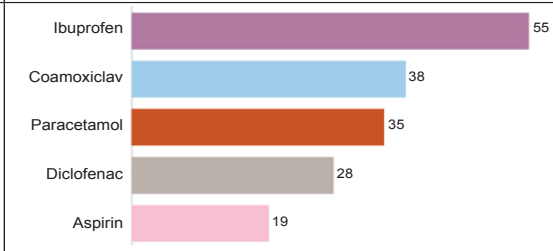
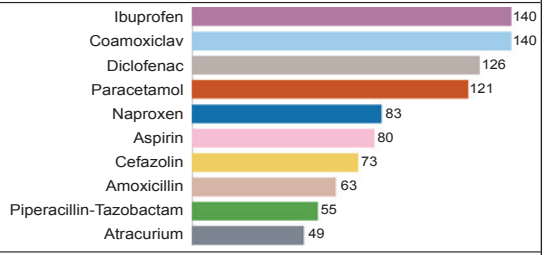
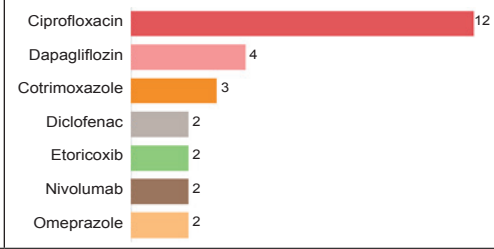
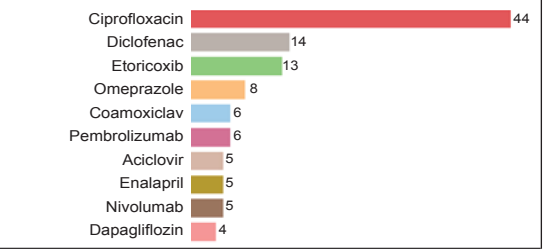
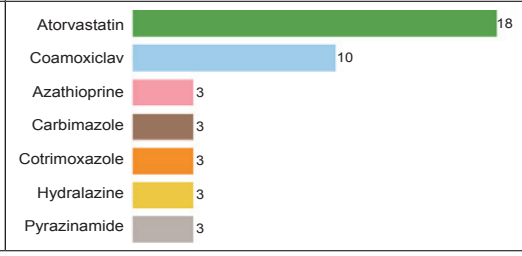
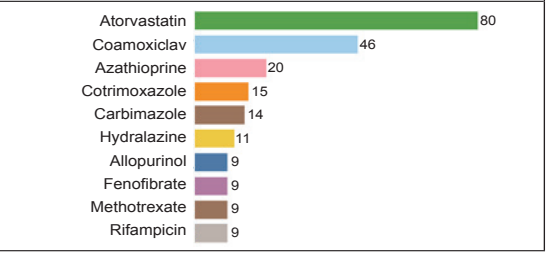
Vaccine AE reports

HSA received 675 vaccine adverse event (VAE) reports in 2023, including 243 (36.0%) reports associated with COVID-19 vaccines. Of these, 292 (43.3%) reports involved adults and 356 (52.7%) reports involved children and adolescents aged 18 and below. Age was not reported in the remaining 27 (4.0%) reports. Most of the reports in children and adolescents were received from the active surveillance site at KK Women's and Children's Hospital (n=321, 90.2%), which HSA partners to screen paediatric hospital admissions for AEs post-vaccination.

(a) VAEs with childhood and adult vaccines

The commonly reported VAEs in children aged 12 years and below were lymphadenopathy (suppurative and non-suppurative) with the *Bacillus Calmette-Guérin* (BCG) vaccine and seizures (febrile and afebrile) with various other vaccines. Seizures were most frequently reported with pneumococcal conjugate vaccine, measles, mumps, and rubella (MMR) vaccine, 5-in-1* vaccine, and varicella vaccine. Other VAEs reported for this age group included injection site reactions, allergic reactions such as rash and urticaria, Kawasaki disease, meningitis and thrombocytopenia. VAEs in adolescents aged 13 - 18 years old included isolated reports of syncope and menorrhagia with

Table 1. Top active ingredients suspected of causing serious adverse events

Description	Top 5 suspected active ingredients in 2023. (More than 5 active ingredients may be displayed if the number of reports of these active ingredients is the same)	Top 10 suspected active ingredients from 2019-2023. (Based on cumulative number of times the active ingredients were implicated from 2019-2023)
Severe cutaneous adverse reactions (SCAR) (Acute generalised exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN))		
Body as a whole (Anaphylactic Reaction)		
Renal disorders (Renal Tubular Disorder/ Necrosis, Renal Failure Acute/Chronic, Glomerulonephritis, Nephritis Interstitial, Toxic Nephropathy, Nephrosis)		
Hepatic disorders (Jaundice, Hepatic Coma, Hepatic cirrhosis, Hepatitis, Hepatitis Cholestatic, Hepatic Failure, Hepatocellular Damage, Liver Injury)		

Human Papillomavirus vaccine, and convulsion with varicella vaccine.

The commonly reported VAEs in adults were allergic reactions such as rash, urticaria, angioedema and injection site reactions with various vaccines. Serious VAEs included anaphylaxis with seasonal influenza and pneumococcal vaccines.

**5-in-1 refers to Diphtheria, Pertussis, Tetanus, Inactivated Polio and Haemophilus Influenza Type B*

(b) VAES with COVID-19 vaccines#

The commonly reported VAEs in children aged 12 years and below were allergic reactions such as rash and urticaria with the mRNA COVID-19 vaccines, Comirnaty and Spikevax. There were also reports of chest pain/discomfort with Comirnaty. Serious VAE reports included appendicitis, seizures and *Henoch-Schönlein* purpura with the mRNA COVID-19 vaccines. VAEs in adolescents aged 13 - 18 years included allergic reactions (such as rash), chest pain, appendicitis and myopericarditis with Comirnaty. The commonly reported VAEs in adults were allergic reactions such as rash, urticaria and angioedema with various COVID-19 vaccines, including Nuvaxovid. There were also reports of chest pain/discomfort with mRNA COVID-19 vaccines. Serious and rare VAE reports included Grave's disease/thyroid diseases, myocarditis, thrombosis and hepatitis with mRNA COVID-19 vaccines. There were isolated reports of Drug reaction with eosinophilia and systemic symptoms (DRESS) and bullous eruption with Comirnaty, as well as Stevens-Johnson Syndrome (SJS) and erythema multiforme with Spikevax.

#COVID-19 vaccines used in Singapore are mRNA vaccines (Comirnaty and Spikevax), protein subunit vaccine (Nuvaxovid) and inactivated vaccines (Sinovac-CoronaVac, Sinopharm). mRNA vaccines accounted for the majority of COVID-19 vaccines administered in Singapore.

HSA's review of the VAE reports in 2023 did not identify new safety concerns with the vaccines. Overall, the VAEs received in 2023 were within the expected AE frequencies listed in the product package inserts or reported in literature.

Complementary health products AE reports

There were 88 AEs involving complementary health products (CHPs), with 54 (61.4%) cases implicating products classified as health supplements. Majority of the CHP reports were associated with glucosamine-containing products (n=30, 34.1%) and melatonin (n=12, 13.6%), primarily describing allergic reactions, such as angioedema, rash and pruritus.

Serious AEs were rare, mainly describing skin reactions (n=5) which included fixed drug or bullous eruption and an isolated case of SJS. Reports of hepatic AEs, rhabdomyolysis accompanied with acute kidney injury and anaphylaxis associated with a variety of CHPs were also received. There were no safety concerns identified for these CHPs as the AE with each product occurred in isolation and some were confounded by patients' underlying medical conditions or concomitant use of other products.

Five reports described AEs of endocrine disorders such as Cushing's syndrome and adrenal insufficiency, which led to the detection of five adulterated products by HSA. There were individual case reports of headache associated with a product adulterated with tadalafil, and purpura with the use of a cream adulterated with arsenic, betamethasone and salicylic acid. Press releases[1] were issued to warn the public not to purchase and use these products.

References

1. https://go.gov.sg/hsa-press-releases

AE Case in Focus 1: Test Yourself

A male patient in his 70s with underlying diabetes mellitus (DM) and hypertension presented with pruritic rashes with blisters over his body (Figure 1), arms (Figure 2) and legs of two weeks' duration. He also reported one blister in the mouth that started two days ago. He did not have any fever or eye symptoms. He denied taking any new medication prior to the onset of rashes. His long-term medications included metformin, glipizide, linagliptin and amlodipine, all of which were started more than a year ago.

Upon review at the dermatology clinic, he was noted to have urticarial plaques, blisters and multiple erosions over his trunk and limbs, with one intact bulla over the buccal mucosa. The affected body surface area was about 10%. His skin biopsy showed subepidermal blister with eosinophils.

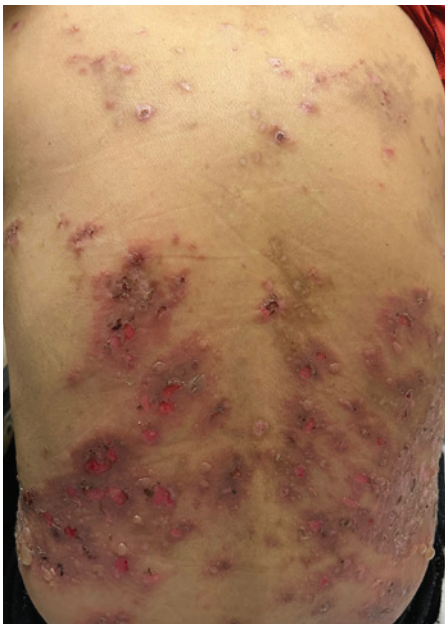


Figure 1. Tense bullae, plaques and erosions over the back

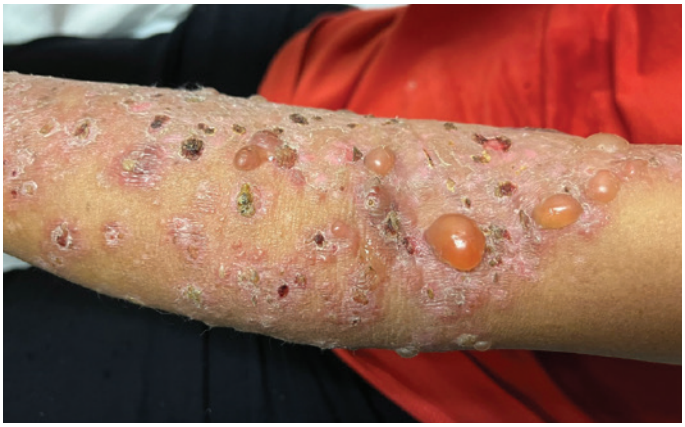


Figure 2. Tense bullae and erosions over the upper limb

What could have caused the blistering rash in this patient?

HSA would like to thank Dr Chai Zi Teng, Associate Consultant, and Assoc Prof Lee Haur Yueh, Head and Senior Consultant, Department of Dermatology, Singapore General Hospital for contributing this article.

Answers can be found on page 8.

AE Case in Focus 2: Test Yourself

An eight-year-old girl was admitted with acute symptoms of shortness of breath, fever, maculopapular rash and vomiting. Five weeks prior, she had left hip osteomyelitis and Group D Salmonella bacteraemia. She was started on intravenous (IV) ceftriaxone. She underwent ultrasound-guided drainage of a left acetabular extra-osseous abscess which improved and was discharged from the hospital with oral trimethoprim-sulfamethoxazole (TMP-SMX) (160mg TMP component twice daily (10mg/kg/day)) for the treatment of osteomyelitis. On Day 19 of taking TMP-SMX, she had a recurrence of fever with no other symptoms or hip pain. She was given doxycycline 70mg twice daily (4.4mg/kg/day) for possible rickettsial infection as her rickettsia serology test was positive (titres 1:512) for spotted fever group rickettsiae (SFGR). Despite this, she continued to be febrile with vomiting. She developed a maculopapular rash over her hands, which spread to her body and face. On Day 25 of TMP-SMX and Day 6 of doxycycline, she developed acute breathlessness, leading to her current presentation.

On examination, she appeared tired and unwell. She was febrile, tachycardic and tachypnoeic. She had reduced air entry over her lower chest with scattered crepitations bilaterally, and a diffuse pruritic reticular maculopapular rash with no mucosal involvement. She was started on supplemental oxygen via face mask at 5 L/minute. Chest X-ray and computed tomography (CT) of the neck and thorax showed diffuse ground glass changes involving the entire lung with an apical-basal gradient, as well as extensive pneumomediastinum, bilateral pneumothorax and subcutaneous emphysema (Figures 1 and 2). She required emergency intubation for acute deterioration, associated with increasing neck and upper chest swelling. Microlaryngoscopy and bronchoscopy (MLB) and oesophagoscopy revealed normal trachea, mild oesophagitis, and no tracheal or oesophageal perforation. She required mechanical ventilation for severe oxygenation failure consistent with severe paediatric acute respiratory distress syndrome (PARDS). She was started on IV ceftriaxone and metronidazole for presumed mediastinitis.

What could have caused the respiratory failure in this patient?

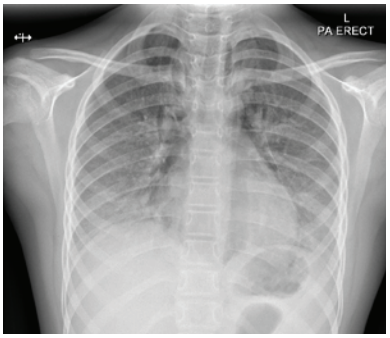


Figure 1. Initial chest X-ray showing extensive pneumomediastinum, subcutaneous emphysema extending up to the neck, small left pneumothorax and bilateral diffuse hazy lung opacification.

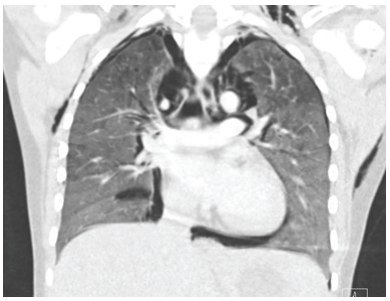


Figure 2. CT scan of the neck and thorax demonstrating extensive pneumomediastinum, bilateral pneumothorax, and lower cervical and thoracic subcutaneous emphysema. There were diffuse pulmonary ground glass changes, involving the entire lung with an apical-basal gradient. There were no fibrotic changes, honeycombing, interstitial thickening or bronchiectasis.

HSA would like to thank Dr Huang Peiqi, Associate Consultant, Department of Neonatology; Dr Kam Kai-Qian, Consultant; Dr Tan Yi Hua, Consultant; Dr Lee May Ping, Consultant, Department of Paediatrics; Dr Chan Su-Wan Bianca, Consultant, Department of Paediatric Subspecialties and Assoc Prof Lee Jan Hau, Senior Consultant, KK Women's & Children's Hospital for contributing this article.

Answers can be found on page 7.

Answers to AE Case in Focus 2: Test Yourself

The patient was diagnosed with severe paediatric acute respiratory distress syndrome (PARDS) with pneumonitis that was attributed to possible TMP-SMX-associated drug-induced lung injury (DLI).

Diagnostic investigations and treatment of PARDS

Several diagnostic categories were considered as potential aetiologies for the patient's respiratory failure. These included infectious causes, particularly spotted fever group rickettsiae (SFGR) in light of her positive serology and underlying immunodeficiency or autoimmunity. Drug reaction with eosinophilia and systemic symptoms (DRESS) was also considered based on her symptoms, which led to TMP-SMX being withheld on admission.

Extensive investigations for infectious causes of her pneumonitis and ground-glass changes were performed. The absence of a 4-fold increase in her repeated Rickettsia antibody titre implied that SFGR was not the culprit for her presentation. *Candida orthopsilosis* and *blastoconidia* isolated in her endotracheal tube (ETT) aspirate and stool fungal smears were attributed to fungal colonisation from prolonged antibiotic exposure as no improvement was observed despite IV antifungal therapy. Hence, these were unlikely culprits too. The remaining workup for viral, atypical and opportunistic infections was unremarkable. Her immunodeficiency and autoimmunity workup was also negative. Her clinical and laboratory parameters, alongside a low Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) score, made DRESS also less likely.[1]

The final working diagnosis for this patient was PARDS with pneumonitis that was attributed to possible TMP-SMX-associated drug-induced lung injury (DLI). TMP-SMX had originally been prescribed for presumed Group D *Salmonella* osteomyelitis. Our patient had no history of drug allergies or prior TMP-SMX exposure.

The patient was treated with IV methylprednisolone on Day 6 of admission for PARDS. With steroids, her fever and rash rapidly resolved, and her ventilatory requirements improved. She completed 32 days of tapering steroids without relapse. She was extubated after 22 days and discharged on Day 43 with home oxygen therapy of 1 L/min. Oxygen was discontinued six weeks post discharge. Nine months later, her chest x-ray (CXR) demonstrated fine reticular opacities in bilateral lower zones, with normal spirometry.

After excluding infective, autoimmune, and immunologic diagnoses, a diagnosis of possible TMP-SMX associated lung injury was made. The patient scored "probable" on the Naranjo causality assessment tool for adverse drug reactions.[2]

Literature findings

TMP-SMX induced lung toxicity encompasses hypersensitivity pneumonitis, acute fibrinous organising pneumonia, and interstitial lung disease. There have been cases similar to the above case of TMP-SMX-induced acute respiratory distress syndrome (ARDS) with extensive pneumomediastinum and pneumothorax reported.[3-9]

In the largest case series of TMP-SMX-associated severe ARDS involving 19 children and young adults, nearly all patients required tracheostomy, 84% required extracorporeal membrane oxygenation (ECMO), one third required lung or heart/lung transplant, one third had mild restrictive lung disease on follow-up pulmonary function tests, and 37% died. Notably, as with our patient, majority had early air leaks prior to intubation.[9]

Following these findings, in 2021, the United States Food and Drug Administration added new information to TMP-SMX products' labels to warn of the risk of acute respiratory failure and the potential need for ECMO.[10] The incidence rate of acute respiratory failure related to TMP-SMX, however, could not be reliably established due to the small number of cases and data limitation.

Discussion and conclusion

Diagnosing TMP-SMX associated ARDS is challenging due to the lack of a diagnostic test and diverse clinical features overlapping with other conditions. Drug provocation testing (DPT) was deferred given the severity of the patient's index reaction. A recently proposed novel disease definition characterises TMP-SMX-associated ARDS as unexplained severe respiratory failure after receiving six days or greater of TMP-SMX at treatment dose, upon excluding other explanations.[9]

Additional tests such as human leukocyte antigen (HLA) allele analysis and surgical lung biopsy have also been proposed to complement clinical evaluation.[9] Both HLA-B*07:02 and HLA-C*07:02 alleles were identified in a small multiracial cohort to be associated with TMP-SMX-induced severe respiratory failure.[11] Further studies are needed to better understand the association between HLA alleles and the pathogenesis of lung injury. In the case above, HLA testing was offered but declined.

A unique pathological pattern termed diffuse alveolar injury with delayed epithelialisation (DAIDE) has been described in TMP-SMX-associated ARDS. This is characterised by early organising diffuse alveolar damage, lack of hyaline membranes, diffuse alveolar denudation, and macrophages lining denuded alveolar walls with bronchiole sparing.[5,9,12] Surgical lung biopsy was considered for the patient but was not performed given her clinical instability, high ventilatory requirements, and the limited impact on clinical management as corticosteroids had already been instituted and TMP-SMX withdrawn by the time she was stabilised.

In DLI, early identification and discontinuation of the culprit drug is key, along with supportive care. Adjunct corticosteroid therapy may be considered, although efficacy is variable. The role of steroids remains controversial for both drug-induced and non-drug-induced ARDS.[13,14] For the case above, there was a positive dechallenge. TMP-SMX was discontinued on admission and her condition improved with steroids, with no relapse after completing her treatment.

To date, this is the only report of ARDS associated with TMP-SMX received by HSA. Healthcare professionals are encouraged to remain vigilant and obtain a history of TMP-SMX exposure in previously healthy individuals presenting with severe respiratory failure of unclear aetiology and report these to the Vigilance and Compliance Branch of HSA.

References

1. *Br J Dermatol 2007;156:609-11.*
2. *Clin Pharmacol Ther 1981;30:239-45.*
3. *Transl Pediatr. 2023 Nov 28;12(11):2062-2073.*
4. *Pediatrics 2019;143:e20183242.*
5. *Am J Respir Crit Care Med 2021;203:918-21.*
6. *J Pediatr Intensive Care 2022;11:67-71.*
7. *Chest 2022;161:e111-6.*
8. *Respir Med Case Rep 2021;34:101496.*
9. *Crit Care Med 2023;51:e264-8.*
10. *https://publications.aap.org/aapnews/news/16572*
11. *Pharmacogenomics J 2022;22:124-9.*
12. *Am J Pathol. 2018 May;188(5):1149-1160.*
13. *J Clin Med 2018;7:356.*
14. *Respir Investig 2013;51:260-77.*

Answers to AE Case in Focus 1: Test Yourself

The patient was diagnosed with bullous pemphigoid secondary to linagliptin, based on a skin biopsy showing subepidermal blister with eosinophils, positive serum BP180 autoantibody and positive serum indirect immunofluorescence (roof pattern).

Bullous pemphigoid

Bullous pemphigoid is the most common subepidermal blistering disorder, commonly affecting older adults. Clinically, it presents as tense bullae/blisters and erosions, sometimes with urticarial plaques, often accompanied by pruritus. Mucous membranes may be affected. Diagnosis is confirmed by skin biopsy for histology, direct immunofluorescence (DIF), along with serum indirect immunofluorescence (IIF), BP180 and BP230 serologies.

BP180 (type XVII collagen) and BP230 are hemi-desmosomes that promote dermal epidermal cohesion. Bullous pemphigoid occurs due to autoantibody formation against BP180 and/or BP230, as a result of loss of immune tolerance. These autoantibodies lead to an inflammatory response involving eosinophils and sometimes neutrophils migrating to the dermis, and release cytokines, chemokines, reactive oxygen species and hydrolytic degrading enzymes. These then lead to tissue damage and subepidermal blister formation.

Treatment is decided based on the severity of disease and the extent of body involvement. This varies from potent to super-potent topical steroid, doxycycline, systemic immunosuppressants (e.g., corticosteroid, mycophenolate mofetil), biologics, and in refractory cases, rituximab (anti CD-20) and intravenous immunoglobulin (IVIg) treatment. In the event that systemic corticosteroid is started as part of treatment regime, healthcare professionals should monitor patients for hyperglycaemic complications. Systemic corticosteroid may result in post-prandial hyperglycaemia, and therefore pre-prandial glucose monitoring is advised, as opposed to fasting blood glucose which may be falsely normal.

Dipeptidyl Peptidase-4 Inhibitors and bullous pemphigoid

Dipeptidyl Peptidase-4 Inhibitors (DPP4is) are increasingly known to be associated with bullous pemphigoid development.[1,2] Examples of DPP4is include linagliptin, sitagliptin and vildagliptin. DPP4 is expressed on the surface of keratinocytes, epithelial cells and T cells. The use of DPP4is lead to inappropriate cleavage of type XVII collagen (COL17, or also known as BP180) and breakdown of immune tolerance in the skin, resulting in induction of autoantibodies to COL17.[2,3]

Patients who developed bullous pemphigoid due to DPP4is were found to be younger on average, and had fewer cardiovascular and neurological comorbidities.[4] The estimated incidence of DPP4i-associated bullous pemphigoid was 0.9-1.4 cases per 1,000 DPP4i-treated patients.[5,6] A meta-analysis in 2018 showed that exposure to DPP4i was associated with more than a threefold increased risk of developing bullous pemphigoid,[7] and another recent systematic review and meta-analysis showed that use of DPP4i was significantly associated with bullous pemphigoid (pooled OR 1.92; 95% CI 1.55-2.38).[1] Some studies also suggest that there are risk differences among DPP4is. For example, a recent Japanese cohort study looking at the risk of bullous pemphigoid among DPP4is in the elderly showed hazard ratio (HR) of 2.411 with vildagliptin (95% CI 1.325-4.387) and HR of 2.550 (95% CI 1.266-5.136) with linagliptin.[8] In the same study, a statistically significant risk elevation was not observed with sitagliptin. Further studies are needed to confirm these observations. The latency period between initiation of DPP4is and bullous pemphigoid varies, ranging between six months to 26 months.[9]

In cases suspected of DPP4i-related bullous pemphigoid, withdrawal of the DPP4i and switching to another class of oral glucose-lowering agent is suggested if required for diabetes mellitus (DM) control. In such cases, frequent initial monitoring of glucose is essential, particularly for those who are on systemic corticosteroids for the treatment of bullous pemphigoid. Recent studies have found more common relapse or worsening of disease among patients who continued DPP4i treatment (37% vs 11%),[4] and DPP4i withdrawal may show favourable impact and a milder course of bullous pemphigoid.[10]

Local situation

From January 2019 to February 2024, HSA received 136 reports of bullous pemphigoid associated with DPP4is. Majority of the patients were male (82, 60.3%) and aged 60 years and above (123, 90.4%). The latency of the adverse event ranged from 2 months to about 4 years. The most commonly reported DDP4i was linagliptin followed by sitagliptin and vildagliptin. From available information, 77 (56.6%) of the reports were assessed as serious by the reporters while 9 (6.6%) were assessed as not serious. Twenty-two (16.2%) patients were hospitalised.

Other drugs associated with bullous pemphigoid

Other drugs that have been reported to be associated with bullous pemphigoid includes aldosterone antagonists, anticholinergics and dopaminergic medications.[1] With the emergence of immune checkpoint inhibitors for the treatment of malignancies, immune-related cutaneous adverse event, including bullous pemphigoid, have been reported at a higher incidence than the general population.[3]

Role of healthcare professionals

Healthcare professionals are advised to initiate early referral to dermatologists for suspected drug-induced bullous pemphigoid. In the interim period, the attending physician may consider temporarily discontinuing DPP4i treatment and use an alternative oral glucose lowering agent for DM control.

References

1. *JAMA Dermatology. 2020;156(8):891-900.*
2. *Am J Clin Dermatol. 2021;(0123456789).*
3. *J Dermatol. 2023 Feb;50(2):140-149.*
4. *Clin Exp Dermatol. 2023;48(8):873-880.*
5. *Case Rep Endocrinol. 2020;2020:8832643.*
6. *J Diabetes Investig. 2019;10(2):392-398.*
7. *J Dermatol. 2018;45(9):1094-1100.*
8. *J Diabetes Investig, 2023 Jun; 14 (6):756-766*
9. *Arch Dermatol Res. 2023;315(1):33-39.*
10. *Kaohsiung J Med Sci. 2023;39(10):1038-1044.*

Please send your enquiries, comments and suggestions to:

Vigilance and Compliance Branch
Health Products Regulation Group
Health Sciences Authority
11 Biopolis Way, #11-01,
Helios, Singapore 138667

Tel : (65) 6866 1111

Website: http://www.hsa.gov.sg
Email : HSA_productsafety@hsa.gov.sg