MADRAC Bulletin

For healthcare professionals only
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The MADRAC Bulletin is a bi-monthly publication that provides a selection of local safety signals and articles discussing local individual case safety reports (ICSRs) meant to raise awareness among healthcare professionals. Information contained in this publication is not comprehensive but rather represents a selection of clinically relevant items warranting enhanced dissemination.

The MADRAC Bulletin also features pharmacovigilance-related activities conducted by the National Pharmaceutical Regulatory Agency (NPRA) and contains a list of directives based on safety issues advised by the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) and endorsed by the Drug Control Authority (DCA) as well as safety alerts that have been published on the NPRA website.

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Highlights

NPRA has recently incorporated quantitative signal detection into routine drug safety monitoring activities, marking a new milestone in the Malaysian pharmacovigilance landscape.

Signals

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What's New

Highlights

Venturing into Quantitative Signal Detection

Written by Lee Sing Chet and Nora Ashikin Mohd Ali

At the national pharmacovigilance centre located within National Pharmaceutical Regulatory Agency (NPRA), we have recently incorporated **quantitative signal detection** into our routine drug safety monitoring activities, marking a new milestone in the national pharmacovigilance landscape. Over the years, we have been detecting signals from various sources, including safety updates from reference regulatory agencies and pharmacovigilance documents submitted by product registration holders (Figure 1). After years of incremental efforts, **we have now developed the procedures and workflow to identify safety signals based on the local adverse drug reaction (ADR) / adverse event following immunisation (AEFI) reports recorded in the Malaysian Pharmacovigilance Database (QUEST).**

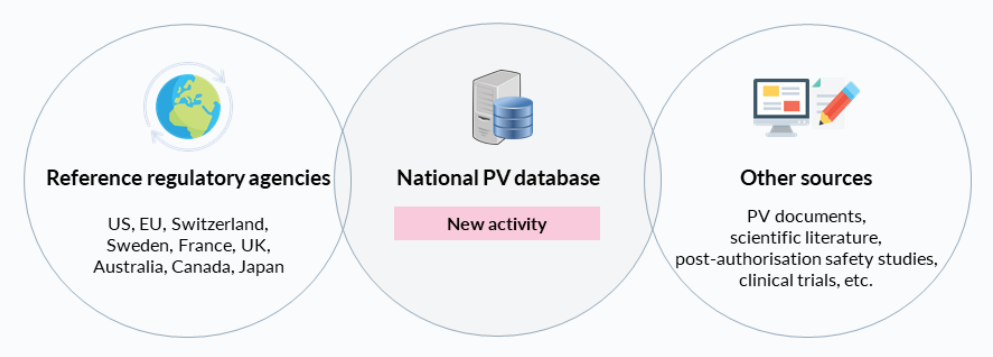


Figure 1. Sources of safety signals

PV: pharmacovigilance; PRH: product registration holders

This new activity had been planned since the year 2020, but has faced enormous challenges when the pandemic hit when we were inundated with AEFI reports for COVID-19 vaccines. Nonetheless, the pandemic opens up numerous learning opportunities with other regulatory agencies, one of which is the **Australian Therapeutic Goods Administration (TGA)**, who graciously shared their expertise and experience with us. By actively engaging in joint discussions with international regulators pertaining to safety monitoring for COVID-19 vaccines, we have not only accelerated our understandings and competencies in signal detection, but also gained new insights and perspectives on the overall process.

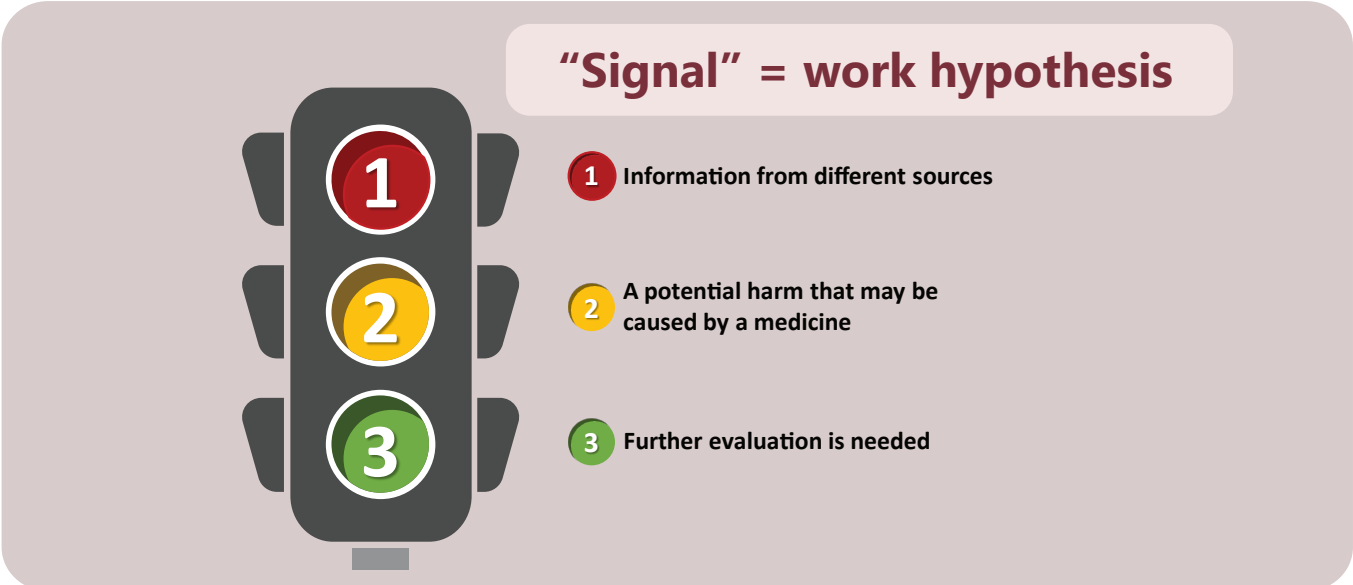


Figure 2. What is a signal?

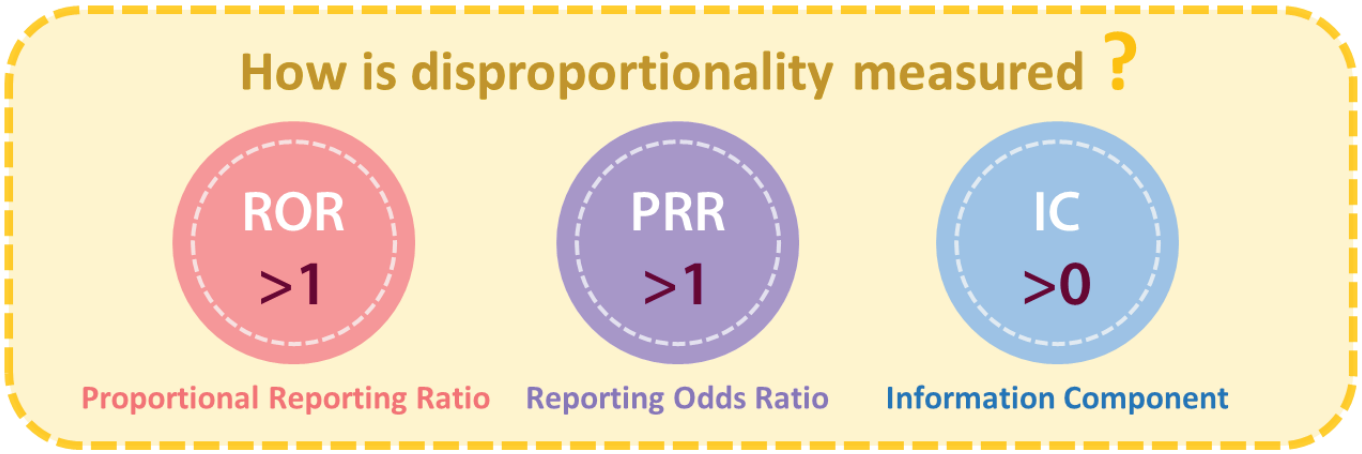
What is signal detection?

Signal detection is an essential aspect of pharmacovigilance that *aims to identify new safety signals from the large data pool on adverse events in a timely manner.*

- A **safety signal** (**Figure 2**) refers to *information on a new or known side effect that may be caused by a medicine and is typically generated from more than a single report of a suspected side effect,* according to the World Health Organisation-Uppsala Monitoring Centre (WHO-UMC) definition.[1]
- It is important to note that *a signal does not indicate a direct causal relationship between a side effect and a medicine, but is essentially only a hypothesis that, together with data and arguments, justifies the need for further assessment.*

Signal detection can be **qualitative** (*case-by-case clinical review of individual adverse event reports*) or **quantitative** (*disproportionality analysis based on statistical measures*).

While qualitative methods help detect rare signals, quantitative methods help in handling large amounts of data and transforming it into useful safety information. **Disproportionality analysis (DPA)** identifies drug-reaction pairs that are reported more often than expected (**Figure 3**). Subsequently, a **clinical assessment** is performed to determine whether the available evidence is sufficient to validate the signal and whether regulatory actions are justified.



	Event y	Not Event y
Drug x	a	b
Not Drug x	c	d

Report count in the database

$$\text{ROR} = \frac{a/b}{c/d}$$

$$\text{PRR} = \frac{a/(a+b)}{c/(c+d)}$$

$$\text{IC} \approx \log_2 \frac{O_{xy} + 1/2}{E_{xy} + 1/2}$$

Observed count, $O_{xy} = a$

Expected count, $E_{xy} = \frac{(a+c)}{(a+b+c+d)} \cdot (a+b)$

Figure 3. Measures of disproportionality analysis (DPA)

What steps are involved in signal detection?

This year, we have identified our first several signals, some of which will be discussed at a later part of this article. Let's first look at the four (4) main steps in quantitative signal detection in Malaysia (**Figure 4**).

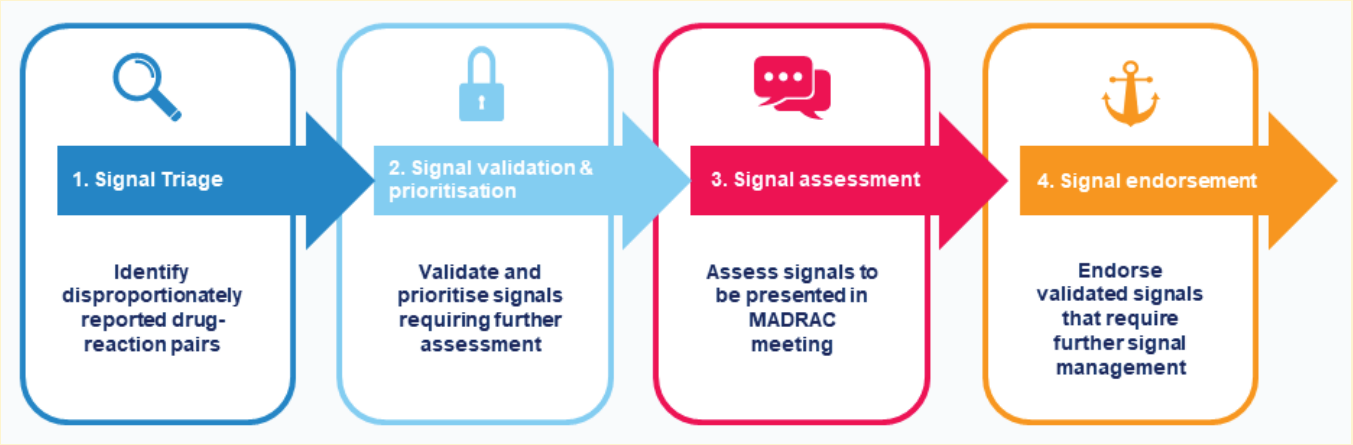


Figure 4. Workflow of Quantitative Signal Detection in Malaysia

Step 1 is "***Signal triage***" that aims to identify disproportionately reported drug-reaction pairs (potential signals), that have been reported in at least three (3) local reports and within the past three years.

All the pairs in VigiLyze are periodically screened before listing them in the "Potential Signal List (PSL)".

Step 2 is "***Signal validation and prioritisation***".

Signal validation is an initial assessment that aims to evaluate and verify that the available documentation contains sufficient evidence to suggest a new potential causal association, or a new aspect of a known association, and therefore justifies further assessment.

Based on pre-determined criteria and a priority matrix, we prioritise validated signals that require urgent attention and need to be managed immediately.

Step 3 is "***Signal assessment***" where further in-depth assessment is performed by considering the strength of association, clinical relevance, causality of reports, confounding factors, previous awareness of the same safety concern, biological plausibility, external evidence and potential class effect.

Signal Assessment Report (SAR) is prepared for each validated signal (**Figure 5**)

Step 4 is "***Signal endorsement***" that involves the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) members before subsequent regulatory actions are taken, if necessary.

Signal Assessment Report (SAR)

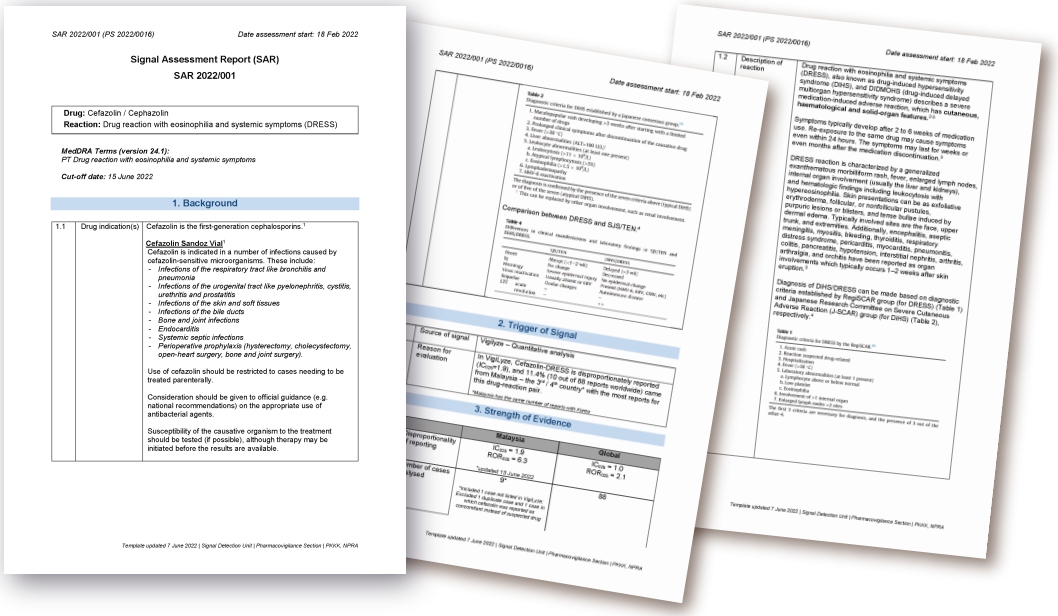


Figure 5. A Signal Assessment Report (SAR) is prepared for each validated signal

"There is no one giant step that does it. It's a lot of little steps."

With over 260,000 reports in our database[2], and the support from the WHO-UMC via its signal detection and management tool called VigiLyze[3], quantitative signal detection is now an integral part of our routine safety monitoring activities.

While signal detection remains a highly skilled and challenging process, we have begun familiarising ourselves with a constant curiosity for uncovering every potential signal from our national pharmacovigilance database. In pursuit of our mission to keep patients safe from drug-induced harms, we are passionate and committed to continuously expanding our knowledge, skills, and competence in detecting local safety signals.

Hence, each and every ADR/AEFI report counts towards enriching the national pharmacovigilance database and consequently in detecting important local safety signals. MADRAC encourages all healthcare professionals to report all suspected ADR/AEFI through the various channels provided.

References

1. Uppsala Monitoring Centre (UMC). What is signal? [Internet]. 2022 [cited 2022 Sep 19]. Available from: https://who-umc.org/signal-work/what-is-a-signal/
2. National Pharmaceutical Regulatory Agency (NPRA). The Malaysian National ADR Database (QUEST) [Internet]. 2022 [cited 2022 Sep 15]. Available from: https://www.npra.gov.my (access restricted)
3. Uppsala Monitoring Centre (UMC). Your window to a world of global safety insights. [Internet]. 2022 Oct 11 [cited 2022 Oct 18]. Available from: https://who-umc.org/pv-products/vigilyze/

Signals

The signals in this Newsletter are based on information derived from reports of suspected adverse events available in the Malaysian Pharmacovigilance Database (QUEST)[1] and the WHO global database of individual case safety reports (VigiBase)[2].

A safety signal, according to the WHO-Uppsala Monitoring Centre (UMC) definition[3], refers to information on a new or known side effect that may be caused by a medicine and is typically generated from more than a single report of a suspected side effect. It is important to note that a signal does not indicate a direct causal relationship between a side effect and a medicine, but is essentially only a hypothesis that, together with data and arguments, justifies the need for further assessment.

The signals presented below are intended to raise awareness of reported averse events and stimulate additional reporting from healthcare professionals.

Cephalosporins – Severe Cutaneous Adverse Reactions (SCARs)

Written by Lee Sing Chet; Reviewed by Nora Ashikin Mohd Ali

Introduction

NPRA previously communicated about the risk of severe cutaneous adverse reactions (SCARs) associated with beta-lactam antibiotics on 31st January 2019.[4] NPRA reminded healthcare professionals that before initiating therapy with any beta-lactam antibiotics, careful inquiry should be made regarding previous hypersensitivity reactions to penicillins, cephalosporins, carbapenems or other beta-lactam agents. If an allergic reaction occurs, the beta-lactam antibiotic must be discontinued immediately and appropriate alternative therapy instituted.

Due to ongoing concerns about this issue, NPRA closely monitors the reporting of SCARs associated with the use of beta-lactam antibiotics. Our recent analysis found two disproportionately reported drug-reaction pairs that are related to this safety concern, which are discussed below. Of note, a signal does not imply a direct causal relationship, but rather that further assessment is necessary to confirm the association.[3]

Signal #1 Cefazolin – Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

The review was triggered following quantitative analysis that showed a disproportionality in reporting (IC_{025}=1.9; ROR_{025}=6.3).[2] Worldwide, Malaysia was also among the top three countries with the most reports for this drug-reaction pair. Besides, DRESS is not listed in the local package insert (PI) of products containing cefazolin[5], and therefore requires further assessment.

Reports in QUEST[1]

As of September 2022, NPRA has received ten (10) cefazolin-associated DRESS reports. The mean age of these patients was 48 years, ranging from 25 to 70 years. Males made up the vast majority (70%). The median time-to-onset was 21 days, with a range of three (3) to 28 days. Most cases (90%) reported the incident as serious. Of it, there was one (1) fatal case, of which the cause of death was deemed not related to DRESS by the initial reporter. Positive de-challenge was observed in seven (7) cases (70%), and more than half (60%) were recovered or recovering at the time of reporting. In five (5) cases (50%), co-suspected or concomitant drugs, including antibiotics, were reported. All reports were assigned causality *C3 possible*.

Reports in VigiBase[2]

Globally, there have been 92 cases of cefazolin-associated DRESS recorded, to date. The characteristics of these cases were similar to those that in Malaysia, with the majority being male (65%), the mean age being 52 years, and the majority being reported as serious (80%). The median time-to-onset, however, was much shorter, with a median of 11 days (ranging from within the same day to 30 days). Co-suspected or concomitant drugs were reported in 75% of the cases.

Background

Cefazolin is a first-generation cephalosporin indicated for infections of the respiratory tract, urogenital tract, skin and soft tissue, bile duct, bones and joints, endocarditis, systemic septic infection, and peri-operative/surgical prophylaxis.[5] Cefazolin exhibits its bactericidal effect by inhibiting cell wall synthesis through blocking the penicillin-binding proteins like transpeptidases. In Malaysia, there are three (3) registered products containing cefazolin, all in injection form.[6]

DRESS reaction is characterised by a generalised exanthematous morbilliform rash, fever, enlarged lymph nodes, internal organ involvement (typically the liver, kidneys, and lungs), and haematologic findings including leukocytosis with hypereosinophilia.[7-8] Symptoms usually appear two (2) to six (6) weeks after exposure to the causative drug. Re-exposure to the same drug may trigger symptoms even within 24 hours. After stopping the drug, the symptoms may persist for weeks or even months.

DRESS is a delayed type IVb hypersensitivity reaction thought to be mediated by antiviral T cells. It is likely that the Th2 cytokines IL-4, IL-5, and IL-13 induce eosinophilic inflammation and IgE production from B cells, which results in the manifestation of DRESS.[7,9] On the other hand, induction of CD8+ T cell responses may contribute to disease progression that involves internal organ damage.

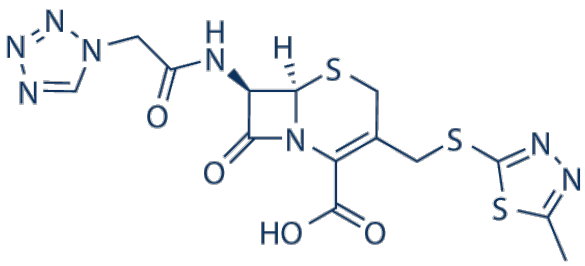


Figure 1: Cefazolin

The most common culprit drugs causing DRESS include anticonvulsants, allopurinol, anti-tuberculosis drugs, and antibiotics like vancomycin and cephalosporins.[7-8,10] Besides, the occurrence of DRESS might also be linked to viral reactivation (mostly human herpesvirus (HHV-6) and a genetic preposition.[10] Emerging evidence revealed that polymorphisms of HLA alleles are associated with the development of DRESS.

Conclusion & Advice

Although the current available evidence could not confirm the association between cefazolin and DRESS due to confounding factors such as co-suspected/concomitant drugs, this signal could not be refuted given the plausible mechanism and time-to-onset. DRESS is potentially fatal, but early management can reduce the risk of fatal complications and the subsequent development of autoimmune diseases.

Therefore, healthcare professionals are reminded to advise patients to stop the antibiotic and seek medical assistance immediately if they experience any of the following symptoms: skin reddening, blisters, rash, fever, sore throat or eye irritation.

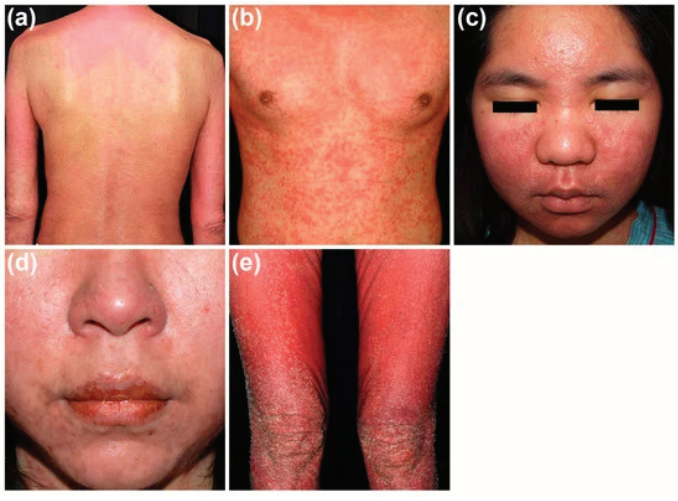


Figure 2: Cutaneous presentations of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome[10]

Signal #2 Cefepime – Acute Generalised Exanthematous Pustulosis (AGEP)

Similarly, the trigger was disproportionality reporting (IC_{025}=1.6; ROR_{025}=5.6) of this drug-reaction pair, and that Malaysia being the top three reporting countries worldwide.[2] AGEP is not listed in the local PI for products containing cefepime.[11] Therefore, further assessment was deemed necessary.

Reports in QUEST [1]

To date, NPRA has received a total of eight (8) reports involving adults ranging in age from 34 to 86 years (mean: 62 years), with a male predominance (63%). The median time-to-onset was two (2) days, with a range from one (1) to seven (7) days. The majority (75%) were reported as serious, and most of them (75%) were recovered or recovering at the time of of reporting. Positive de-challenge was reported in the majority of cases (75%). Co-suspected and concomitant drugs, including anti-infectives and anticonvulsants, were reported in 63% of cases. All cases were given causality *C3 possible*.

Reports in VigiBase[2]

There are 107 cefepime-associated AGEP cases reported worldwide, to date.[4] These patients had a mean age of 70 years (range: 11 to 96 years), with a similar proportion of males (45%) and females (49%). The median time-to-onset was seven (7) days (range: within the same day to 30 days). The vast majority were reported as serious (89%), with no fatalities. Co-suspected or concomitant drugs were reported in 77% of all cases.

Background

Cefepime is a fourth-generation cephalosporins indicated for febrile neutropenia, septicaemia, lower respiratory infection, urinary tract infection, skin and skin structure infections, gynaecologic and intra-abdominal infections.[11] It has a broad spectrum activity against a wide range of gram-positive and gram-negative bacteria, including most strains resistant to aminoglycosides or third-generation cephalosporins. There are 10 registered products containing cefepime in Malaysia, all of which are in injection form.[6]

AGEP is characterised by the rapid appearance of sterile, non-follicular, pin-head sized pustules, oedema, erythema, that generally begin on the face and skin flexures before becoming more widespread.[12] The rash often develops rapidly within two (2) days after initiating the causative drug, although it can occasionally take up to two (2) weeks. Patients may have fever and leukocytosis during the acute phase. In up to 20% of cases, internal organ involvement (usually the liver and kidney) has been documented.[13]

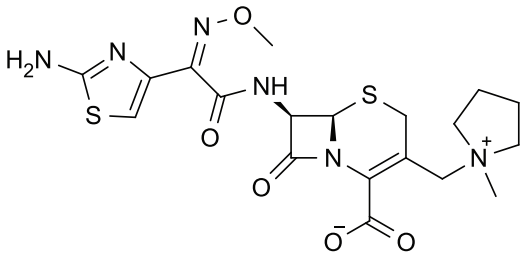


Figure 3: Cefepime

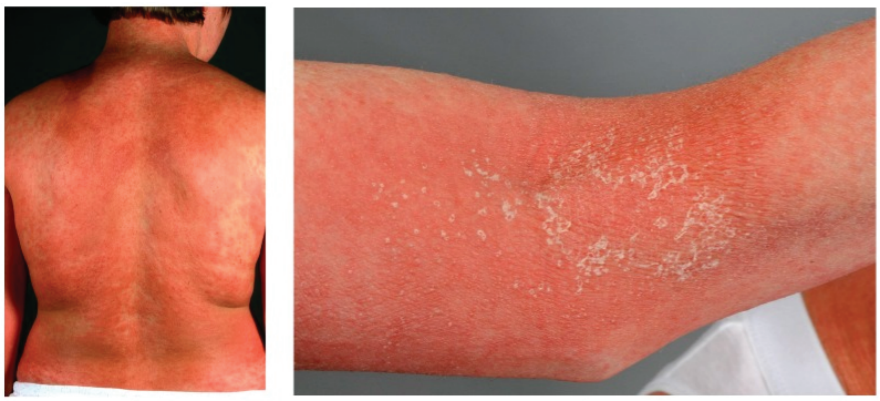


Figure 4: Cutaneous presentations of acute generalized exanthematous pustulosis (AGEP)[14]

AGEP is a T-cell mediated type IVd hypersensitivity reaction that results in neutrophilic inflammation.[12] Compared to Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN), which are characterised by epidermal detachment and histological full-thickness epidermal necrosis, AGEP is less severe with less mucosal involvement, a shorter latency, and a quicker resolution after discontinuation of the causative drug.[12-14] However, it may be challenging to distinguish between these other SCARs and severe cases of AGEP, especially when mucosal involvement is present. In addition, although it occurs rarely, the clinical manifestations may/ overlap between AGEP and SJS/TEN or DRESS.

Over 90% of AGEP cases are provoked by drugs, most commonly beta-lactam antibiotics, oral antifungals, anticonvulsants, antimalarials, and calcium channel blockers.[12-15] While cephalosporins are commonly reported to cause AGEP, literature search found limited studies that specifically linked AGEP to cefepime.[16] With regards to genetic relevance, the correlation between mutations in the interleukin-36RN (IL-36RN) gene and AGEP is still unclear.[14,17]

Conclusion & Advice

Because most cases were confounded by co-suspected/concomitant drugs, and the available literature is limited, we could not confirm the causal relationship between cefepime and AGEP. At the same time, we could not totally rule out its association as it is biologically plausible and supported by the reasonable time-to-onset being reported.

Considering that AGEP is typically mild and resolves quickly after withdrawal of the causative drug, NPRA is alerting healthcare professionals to be aware of this signal so that early treatment can be provided, when necessary, to prevent further complications and fatality.

References

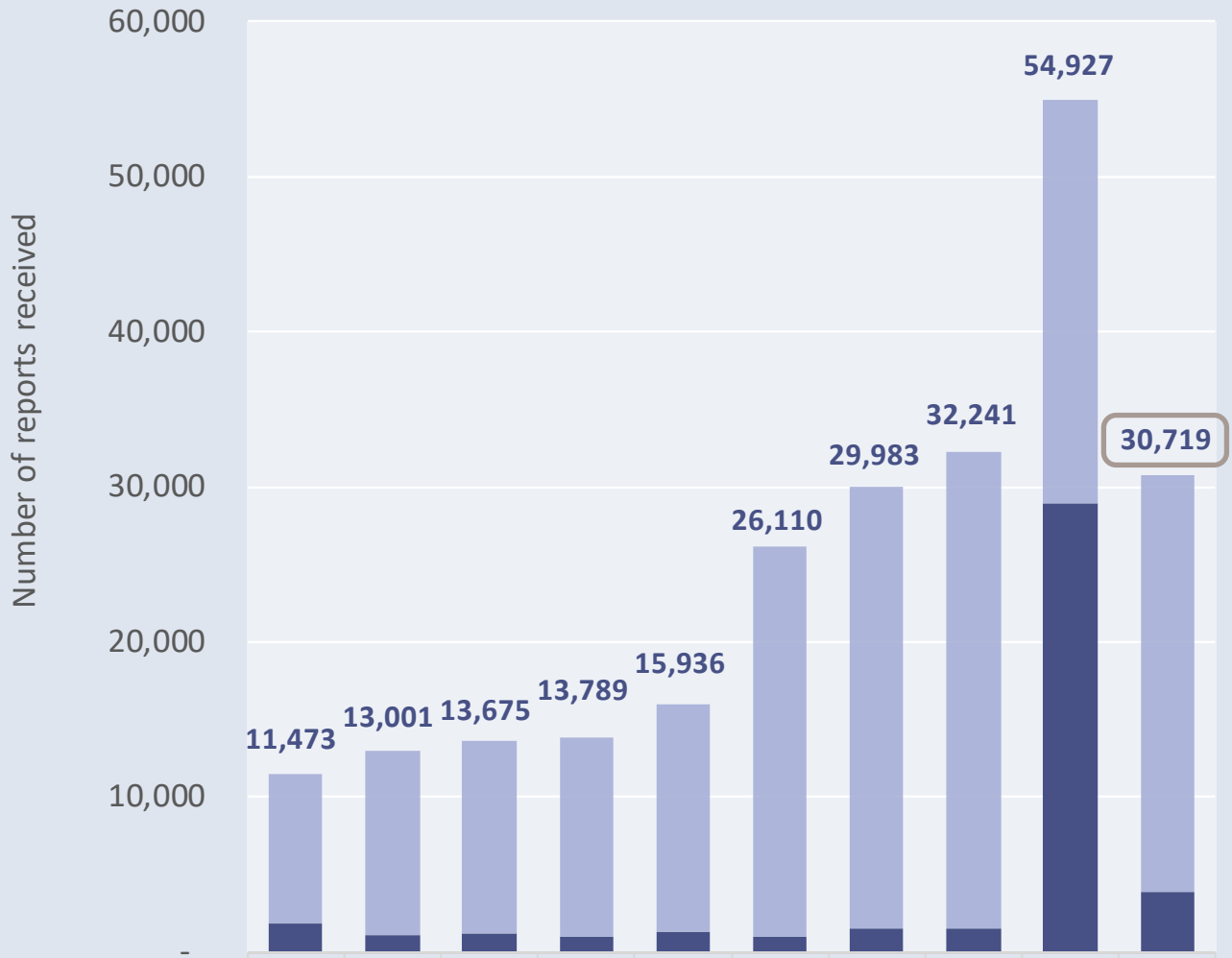
1. National Pharmaceutical Regulatory Agency (NPRA). The Malaysian National ADR Database (QUEST) [Internet]. 2022 [cited 2022 Sep 15]. Available from: https://www.npra.gov.my (access restricted)
2. Uppsala Monitoring Centre (UMC). The WHO Global ICSR Database (VigiLyze) [Internet]. 2022 [cited 2022 Jul 12]. Available from: https://www.vigilyze.who-umc.org (access restricted)
3. Uppsala Monitoring Centre (UMC). What is signal? [Internet]. 2022 [cited 2022 Sep 19]. Available from: https://who-umc.org/signal-work/what-is-a-signal/
4. National Pharmaceutical Regulatory Agency (NPRA). Beta-Lactam antibiotics: Severe Cutaneous Adverse Reactions (SCARs) [Internet]. 2019 [cited 2022 Sep 19]. Available from: https://www.npra.gov.my/index.php/en/component/content/article/414-english/safety-alerts-main/safety-alerts-2019/2050-beta-lactam-antibiotics-severe-cutaneous-adverse-reactions-scars.html?Itemid=1391
5. National Pharmaceutical Regulatory Agency (NPRA). CEFAZOLIN SANDOZ VIAL (cefazolin) [Package Insert]. QUEST3+ Product Search. 2020 Nov [cited 2022 Sep 15]. Available from: http://www.npra.gov.my.
6. National Pharmaceutical Regulatory Agency (NPRA). QUEST3+ Product Search [Internet]. 2022 [cited 2022 Sep 15]. Available from: https://www.npra.gov.my
7. Sharifzadeh S, Mohammadpour AH, Tavanaee A, Elyasi S. Antibacterial antibiotic-induced drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome: a literature review. European journal of clinical pharmacology. 2021 Mar;77(3):275-89.
8. Sim DW, Yu JE, Jeong J, Jung JW, Kang HR, Kang DY, Ye YM, Jee YK, Kim S, Park JW, Kang MG. Variation of clinical manifestations according to culprit drugs in DRESS syndrome. Pharmacoepidemiology and Drug Safety. 2019 Jun;28(6):840-8.
9. Schrijvers R, Gilissen L, Chiriac AM, Demoly P. Pathogenesis and diagnosis of delayed-type drug hypersensitivity reactions, from bedside to bench and back. Clinical and translational allergy. 2015 Dec;5(1):1-0.
10. Cho YT, Yang CW, Chu CY. Drug reaction with eosinophilia and systemic symptoms (DRESS): an interplay among drugs, viruses, and immune system. International Journal of Molecular Sciences. 2017 Jun;18(6):1243.
11. National Pharmaceutical Regulatory Agency (NPRA). Vaxcel Cefepime 1g Injection (cefepime) [Package Insert]. QUEST3+ Product Search. 2021 Oct 25 [cited 2022 Sep 15]. Available from: http://www.npra.gov.my.
12. Medsafe. Acute generalised exanthematous pustulosis (AGEP) [Internet]. 2020 Dec [cited 2022 Sep 15]. Available from: https://www.medsafe.govt.nz/profs/PUArticles/December2020/Acute-generalised-exanthematous-pustulosis-AGEP.html
13. Oh DA, Yeo YW, Choo KJ, Pang SM, Oh CC, Lee HY. Acute generalized exanthematous pustulosis: Epidemiology, clinical course, and treatment outcomes of patients treated in an Asian academic medical center. JAAD international. 2021 Jun 1;3:1-6.
14. Feldmeyer L, Heidemeyer K, Yawalkar N. Acute generalized exanthematous pustulosis: pathogenesis, genetic background, clinical variants and therapy. International journal of molecular sciences. 2016 Aug;17(8):1214.
15. Alniemi DT, Wetter DA, Bridges AG, el-Azhary RA, Davis MD, Camilleri MJ, McEvoy MT. Acute generalized exanthematous pustulosis: clinical characteristics, etiologic associations, treatments, and outcomes in a series of 28 patients at Mayo Clinic, 1996–2013. International journal of dermatology. 2017 Apr;56(4):405-14.
16. Haraszti S, Sendil S, Jensen N. Delayed presentation of acute generalized exanthematous pustulosis following treatment with cefepime in a patient with COVID-19 without the use of hydroxychloroquine. The American journal of case reports. 2020;21:e926901-1.
17. De A, Das S, Sarda A, Pal D, Biswas P. Acute generalised exanthematous pustulosis: an update. Indian journal of dermatology. 2018 Jan;63(1):22.

Features

Adverse Event Reports Received 2013-2022

Between 1st January 2022 and 31st December 2022, the Centre for Adverse Drug Reaction Monitoring, NPRA received a total of 30,719 adverse drug reaction (ADR) and adverse event following immunisation (AEFI) reports, with a decrease of 44.1% from 2021*. Specifically, the number of AEFI reports decreased by 86.6% from 28,976 in 2021 to 3,890 in 2022.

Total Adverse Drug Reaction (ADR) and Adverse Event Following Immunisation (AEFI) Reports Received Annually (2013-2022)



	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
ADR Reports	9,678	11,921	12,489	12,834	14,590	25,127	28,505	30,746	25,951	26,829
AEFI Reports	1,795	1,080	1,186	955	1,346	983	1,478	1,495	28,976	3,890

**The apparent surge in 2021 was attributable to the massive influx of AEFI reports following the mass vaccination roll-out under the National Immunisation Program for COVID-19 (PICK) in Malaysia since 24th February 2021. For more information, read the Summary Report on Adverse Events Following Immunisation of COVID-19 Vaccines in Malaysia available on the NPRA Website.*

What's New

List of Safety Alerts/Directives Related to Drug Safety Issues

NPRA reviews and presents drug safety issues at meetings of the Malaysian Adverse Drug Reactions AdvisoryCommittee (MADRAC) to determine the appropriate risk minimisation measures. Regulatory actions are proposed to the Drug Control Authority (DCA), resulting in DCA directives issued to ensure local package inserts and consumer medication information leaflets (RiMUP) for all products containing the affected active ingredients are updated with the required safety information. The table below shows the safety alerts/DCA directives that were recently issued, which are available on the NPRA website.

	Active Ingredients	Safety Alerts (SA)	SA Date	Directive Ref. No. [Date]
1	Donepezil	Risk of QT Prolongation and Torsade de Pointes	16-Jan-2023	NPRA.600-1/9/13 (18) Jld.1 [19-Dec-2022]

How to report adverse events?

NPRA encourages all healthcare professionals to report all suspected adverse drug reactions (ADR) to medicines, including pharmaceutical products, over-the-counter medicines, traditional medicines, and health supplements, as well as adverse events following immunisation (AEFI) with vaccines.

To report ADR/AEFI:

1. Visit **www.npra.gov.my**
2. Report ADR **as healthcare professional**
   a) Choose **Online Reporting** or
   b) Download the **ADR manual form** and submit the completed form via email or post:

fv@npra.gov.my

Pharmacovigilance Section,
National Pharmaceutical Regulatory Agency (NPRA),
Ministry of Health, Malaysia.
Lot 36, Jalan Prof Diraja Ungku Aziz (Jalan Universiti),
46200 Petaling Jaya, Selangor, Malaysia.

NPRA Safety Information Mailing List

To join the mailing list, complete the **subscription form** available on NPRA website, or send an email with your details to **fv@npra.gov.my**