The role of in vitro testing in pharmacovigilance for β-lactam-induced serum sickness-like reaction: A pilot study

Abdelbaset A. Elzagallaai1,2, Awatif M. Abuzgaia1, Blanca R. Del Pozzo-Magaña2, Eman Loubani1 and Michael J. Rieder1,2*

1Departments of Paediatrics, Schulich School of Medicine and Dentistry, University of Western Ontario, London, ON, Canada, 2Physiology and Pharmacology, Schulich School of Medicine and Dentistry, University of Western Ontario, London, ON, Canada

Background: Current pharmacovigilance (PV) methods for detection of adverse drug reactions (ADRs) fail to capture rare immune-mediated drug hypersensitivity reactions (DHRs) due to their scarcity and the lack of clear diagnostic criteria. Drug-induced serum sickness-like reactions (SSLRs) are rare type of DHRs that occur in susceptible patients 1–3 weeks after exposure to the culprit drug with β-lactam antibiotics being the most associated drugs. The diagnosis of drug induced SSLR is difficult due to the lack of safe and reliable diagnostic tests for identifying the culprit drug. The lymphocyte toxicity assay (LTA) is an in vitro test used as a diagnostic tool for drug hypersensitivity reactions (DHRs).

Objective: To evaluate the role of the LTA test for diagnosing and capturing SSLR due to β-lactam antibiotics in a cohort of patients.

Methods: Patients were recruited from patients referred to the Drug Hypersensitivity Clinic at Clinic at London Health Science Centre with suspicion of drug allergy. Twenty patients (10 males and 10 females) were selected to be tested to confirm diagnosis. Demographic data was collected from the patients and blood samples were withdrawn from all patients and from 20 healthy controls. The LTA test was performed on all subjects and data is expressed as percentage increase in cell death compared to control (vehicle without the drug).

Results: In the result of LTA tests performed on samples from the selected 20 patients. There was a significant (p < 0.05) concentration-dependent increase in cell death in cells isolated from patients as compared to cells

Abbreviations: AH, antihistamine; Amox, amoxicillin; Ceph, cephalexin; EM, Erythema multiforme; JP, Joint pain; JP&S, Joint pain and swelling; MP, Maculopapular; NA, not available; St, steroids; UM, Urticaria multiforme.
from healthy controls when incubated with the drug in the presence of phenobarbitone-induced rat liver microsomes.

Conclusion: Giving its safety and good predictive value the LTA test has very strong potential to be a useful diagnostic tool for β-lactam-induced SSLR. The test procedure is relatively simple and not overly costly. Further studies including other drug classes are needed to evaluate the utility of the LTA test for SSLR due to other drugs.

KEYWORDS
drug hypersensitivity, pharmacovigilance, beta-lactam agents, serum sickness-like reaction, adverse drug reaction

Introduction

Pharmacovigilance (PV) is defined by the World Health Organization (WHO) as the science and activities relating to detection, assessment, understanding and prevention of adverse effect or any other medicine-related problem (WHO, 2014). The importance of the discipline of PV is generally considered to have been established by the release of the Kefauver-Harris Amendment (Drug Efficacy Amendment) to the Federal Food and Cosmetic Act in the United States in 1962. The law required drug manufacturer to provide proof of effectiveness and safety of their drugs before approval (Peltzman, 1973). The terms “pharmacovigilance” and “drug safety” are commonly used in the field to describe the systematic collection and review of post-marketing drug safety data to guide drug use (Beninger, 2018). However, PV activities also include reviewing reports submitted by clinical investigators early during the drug development process and during selection of first safe human dose.

Adverse drug reactions (ADRs) are one of the leading causes of death in the developed world and represent a heavy cost burden on the healthcare system causing many hospital admissions and extended hospitalizations (Bates et al., 1997). ADRs cause one death every 5 min and cost over $136 billion annually in the United States (Johnson and Bootman, 1995). In the European Union, ADRs are estimated to be responsible for 5% of hospital admissions and cases 197,000 deaths annually (Bouvy et al., 2015). ADRs can either be type A, which are predictable from the drug pharmacology and dose dependent and type B, which are unpredictable, unrelated to the drug’s known pharmacology and do not have clear dose dependency. Type B ADRs include immune-mediated drug hypersensitivity reactions (DH Rs; drug allergy) and non-immune mediated DHRs (also called pseudoallergy). They represent smaller fraction of total ADRs (~15%–20%) with some types of reactions lie under the rare and very rare categories (i.e., incidence between ≥1/10,000 to 1,000 and <1/10,000 of drug exposure, respectively). Rare and very rare ADRs cannot be captured during the pre-marketing stages of drug development due to the underpowered sample size (Chan et al., 2015). In addition, it is always not feasible nor practical to study unpredictable (type B) ADRs in prospective, interventional, and clinical trial studies due to their unpredictability and rare occurrence. Another inherited problem associated with these reactions is the difficulty in defining cases based on clinical presentation and associated signs and symptoms (Uetrecht and Naisbitt, 2013). Many of these rare ADRs are underreported due to poor case definition and lack of diagnostic methods (Lopez-Gonzalez et al., 2009). In fact, it is estimated that over 95% of ADRs go unreported (Bailey et al., 2016). This is a major problem as the only way to fully evaluate drug safety in real world is though robust pharmacovigilance studies and data collection. Many drugs have met all the regulatory efficacy and safety requirements only to be later withdrawn from the market due to efficacy or safety concerns jeopardizing patient safety and costing the drug developers and the healthcare systems billions of dollars (Qureshi et al., 2011). It is therefore extremely important to develop sensitive and specific methods to detect and report ADRs in the early stages of clinical use. The current PV systems, which largely depends on spontaneous voluntarily reporting lack such robustness and fundamentally inefficient to detect signal from noise due to lack of reliable diagnostic test to identify cases (Salvador et al., 2022). We propose that a reliable in vitro diagnostic test for rare and very rare idiosyncratic ADRs would help capture and report them enhancing PV and ADR surveillance. Efficiency of surveillance is particularly essential for rare and very rare ADRs; for instance, missing one case of an ADRs with 5% prevalence may not have a significant effect on the overall surveillance process but missing one case 1 in 10,000 exposures may result in failure to detect the ADR leading to unsafe exposure of a large number of patients to the drug.

DHRs are divided, according to the immune mechanism and type of immune cells involved, into type I (IgE-mediated), type II (cytotoxic reactions mediated by drug-specific IgG), type III (immune complex-mediated), and type IV reactions (delayed reactions, T-cell-mediated) (Elzagallaai and Rieder, 2015). Serum sickness (SS), which belongs to type III immune-complex mediated reaction, was first described by von Pirquet and Schick in 1915 (von Pirquet and Schick, 1951). It was later found that circulating immune complexes and complement activation is important in the pathophysiology of these immune-mediated reactions (Vaughan et al., 1967). Serum sickness-like reaction (SSLR) is clinically similar reaction that mostly triggered by drugs. They are most associated with β-lactam antibiotics (especially cefadroxil and amoxicillin), sulfonamides, fluoroquinolones, aromatic
anticonvulsants, tetracyclines, minocycline, metronidazole, bupropion, and other drugs including biologicals (Lawley et al., 1984; Platt et al., 1988; Heckbert et al., 1990; Weiss and Smith, 2020). This type of reactions can also develop as a result of vaccine administration including recent cases of SSLR to inactivated COVID-19 vaccine (Chung et al., 2021; Chajaras et al., 2022). The condition is defined by sudden appearance of skin rash (usually urticaria-like) and arthritis usually manifested 1–3 weeks after drug exposure, which can be accompanied by fever, lymphadenopathy, eosinophilia, and rarely renal involvement (Del Pozzo-Magana et al., 2021). It is uncommonly seen in clinical practice, but its incidence appears to be on the rise since the introduction of biologic drugs (Finger and Scheinberg, 2007; Khan, 2016). It has been estimated that the incidence of SSLR associated with cefaclor is between 0.024% and 0.2% per course (Knowles et al., 2000). The diagnosis of SSLR is challenging due to other possible causes (Schryver, 2015). The exact prevalence of SSLR due to ß-lactam antibiotics is not known, however, studies have estimated it to complicate 0.4%–0.5% of antibiotic courses (Reynolds, 1996; Isaacs, 2001). In a 10-year retrospective cohort study we found that SSLR represent 15.4% of all patients with ADRs also include pseudallergy Related to the administration of a ß-lactam antibiotics (penicillins or cephalosporins); 2) symptoms developed are highly suggestive of ß-lactam-induced SSLRs for the purpose of optimizing and improving pharmacovigilance to these rare types of DHRS.

Materials and methods

Materials

Penicillin, cephalaxin, tetrazolium salt 3-(4, 5-dimethylthiazol-2-yl) 2, 5 diphenyl-tetrazolium bromide (MTT), hydrogen peroxide (H₂O₂), 2′, 7′-dichlorofluorescin diacetate (DCFH-DA), Histopaque® -1077 (Ficoll), Hank’s balanced salt solution (HBSS) and dimethyl sulfoxide (DMSO) were purchased from Sigma-Aldrich (St, Louis, MO, United States). RPMI 1640 and trypan blue were purchased from Invitrogen™, Life Technologies Inc. (Burlington, ON, Canada). Phenobarbitone-induced pooled male Sprague-Dawley rat liver microsomes were purchased from BioIVT (Westbury, NY, United States). All other chemicals used in this study were the highest purity commercially available.

Subjects

Informed consent was obtained from all participants and the study protocol was approved by the Western University Research Ethics Board for Human Subjects (REB No. 11883E). Two groups of individuals were included in our study. The first group consisted of patients who had experienced a ß-lactam antibiotic-induced SSLR. The diagnosis of SSLR was established by revising patients’ files by two clinicians (AMA and BD-M), who have experience in managing patients with DHRs. Any ambiguity in the diagnosis was confirmed by a third clinician (MJR). The general criteria for diagnosis include development of skin rash and joint inflammation with or without fever after exposure to the culprit drug (De Schryver and Ben-Shoshan, 2015; Del Pozzo-Magana et al., 2021). The inclusion criteria of this group include: 1) Having a history of SSLR related to the administration of a ß-lactam antibiotics (penicillins or cephalosporins); 2) symptoms developed are highly suggestive of SSLR and should include skin rash and joints involvements; 3) the patient consents to participate in the study and provides a sufficient blood sample. We excluded patients with any underlying rheumatological conditions (e.g., lupus, rheumatoid arthritis,
dermatomyositis, spondyloarthropathies, Sjogren’s disease. Juvenile idiopathic arthritis, and polymyalgia rheumatica). The second group is composed of 20 healthy individuals, who denied any history of DHRs to β-lactam antibiotics. Overall, 20 patients between the age of 11 months and 67 years were recruited. The patients’ characteristics are summarized in Table 1.

### Blood collection and isolation of cells

Thirty milliliters of peripheral venous blood samples were collected from each participant by venipuncture into heparinized syringes and processed immediately. To isolate peripheral blood monocytes (PBMCs), blood was diluted 1:1 with phosphate-buffered saline (PBS, 10 mM NaH2PO4, 2 mM KH2PO4, 137 mM NaCl, 2.7 mM KCl; pH 7.2) and 30 ml were layered over 15 ml of Ficoll-Paque density gradient and centrifuged at 500 g for 20 min. The interface layer (buffy coat) was then collected. Cells were washed twice with PBS and adjusted to 1×10^6 cell/mL in HEPES [4-(2-hydroxyethyl)-1-piperazine] ethanesulfonic acid buffered saline containing 15 mM HEPES, 125 mM NaCl, 6 mM KCl, 1.2 mM MgSO4, 1.0 mM NaHCO3, 1.0 mM CaCl2, 10 mM glucose; pH 7.4).

### In vitro toxicity testing

The LTA was performed as described previously (Elzagallaai et al., 2010; Elzagallaai et al., 2011). Briefly, PBMCs were plated in flat-bottom 96-multi-well plates at a density of 1×10^5 cells per well in quadruplicate and treated with a final concentration of 6.25–125 μg/ml of either amoxicillin or cephalaxin depending on the suspected drug. Drug solutions were freshly prepared in dimethyl sulfoxide (DMSO) and diluted in culture media to give the desired final concentration (DMSO final concentration is always kept at ≤1%). Microsomal protein was added at a concentration of 0.25 mg/ml, followed by addition of the NADPH-generating system (nicotinamide adenosine dinucleotide phosphate [NADP] 0.6 mM, glucose-6-phosphate 2.4 mM, glucose-6-phosphate dehydrogenase 2 U/ml). Preparations were incubated for 2 h at 37°C in a 5% CO2 humidified atmosphere. A standard curve for measuring cell death was generated by seeding cells at 25%, 50%, 75% or 100% of cell populations in culture media in quadruplicate. After incubation, drugs in solution were removed by centrifugation at 500 g for 10 min. Then, cells were suspended in 100 μl fresh RPMI-1640 media supplemented with 10% FBS, 100U/ml penicillin G sodium and 100 μg/ml streptomycin sulfate, and left to recover for 18 h in an atmosphere of 5% CO2 at 37°C. Cell

### Table 1 Characteristics of patients included in the study.

| Patient # | Sex | Age (Y, M) | Drug involved | Onset of reaction (Days) | Type of skin rash | Presence of fever | Other symptoms | Time to resolution | Treatment |
|-----------|-----|------------|---------------|-------------------------|-------------------|------------------|----------------|-------------------|-----------|
| 1         | F   | 18M        | Amox          | 7                       | MP                | Y                | JP&S          | 4                 | St        |
| 2         | M   | 3Y         | Amox          | 10                      | MP                | N                | JP&S          | 6                 | St        |
| 3         | F   | 2Y         | Amox          | 7                       | MP                | Y                | JP&S          | 5                 | St        |
| 4         | M   | 32Y        | Amox          | 10                      | MP                | NA               | JP&S          | 6                 | St        |
| 5         | F   | 30M        | Amox          | 5                       | UM                | Y                | JP            | 5                 | St        |
| 6         | M   | 2Y         | Amox          | 6                       | MP                | N                | JP&S          | 5                 | NA        |
| 7         | M   | 29M        | Amox          | 7                       | MP                | N                | JP            | 5                 | St        |
| 8         | F   | 5.5Y       | Amox          | 7                       | MP                | Y                | JP            | 5                 | St        |
| 9         | F   | 19M        | Amox          | 7                       | UM                | NA               | JP            | 5                 | AH        |
| 10        | M   | 67Y        | NA            | 7                       | EM                | NA               | JP            | 15                | St        |
| 11        | F   | 3Y         | Amox          | 7                       | EM                | NA               | JP            | 14                | St        |
| 12        | M   | 50Y        | Amox          | 10                      | EM                | Y                | JP            | 6                 | St        |
| 13        | F   | 2Y         | Amox          | 10                      | MP                | N                | JP&S          | 14                | St        |
| 14        | M   | 6Y         | Amox          | 10                      | MP                | y                | JP            | 5                 | St        |
| 15        | M   | 8Y         | Ceph          | 7                       | EM                | NA               | JP&S          | 5                 | AH        |
| 16        | M   | 2Y         | Amox          | 5                       | MP                | NA               | JP&S          | 8                 | AH        |
| 17        | F   | 2Y         | Amox          | 7                       | EM                | NA               | JP&S          | 5                 | AH        |
| 18        | M   | 11M        | Amox          | 7                       | MP                | NA               | JP&S          | 5                 | AH        |
| 19        | F   | 3Y         | Amox          | 7                       | MP                | Y                | JP&S          | 3                 | AH        |
| 20        | F   | 2Y         | Ceph          | 8                       | MP                | Y                | JP&S          | 4                 | St        |

TABLE 1 Characteristics of patients included in the study.
viability was quantified using MTT staining as described previously. (Elzagallaai et al., 2010).

Statistical analysis

Statistical analysis was performed using Prism GraphPad software. The numbers of dead cells were expressed as a percentage of control (vehicle without drug) and blotted as mean ± standard error (SEM). Significant differences were determined by two-tailed Student’s t-test. A probability of more than 95% (p ≤ 0.05) was considered significant. Correlations were made using Pearson correlation analyses. Unless otherwise indicated, values are presented as mean ± standard error (SEM).

Results

Twenty patients (10 males and 10 females) presented with symptoms that meet our inclusion criteria for SSLR to beta-lactam antibiotics (penicillins and cephalosporins). Clinical symptoms included cutaneous lesions (maculopapular, EM, urticaria) and joint inflammation (arthritis) that included hands, feet, or both. Eight of the 20 patients also developed fever as part of the hypersensitivity syndrome. The mean age of the patients was 9.9 years and ranged from 11 months to 67 years. The characteristics of the patient population is summarized in Table 1. All patients had positive LTA test results using a cut-off value of 20% increase in cell death (Figure 1). At 125 μM of the drug and in the presence of MICs, degree of cell death was significantly higher (p < 0.0001) in cells isolated from ß-lactam-induced SSLR patients (Mean: 60.37%) than cells from healthy controls (Mean: 27.61%). Difference between means (controls and patients) ± SEM = 32.76 ± 7.117 (95% confidence interval: 47.17 to 18.35) (Figure 2).

Discussion

Case definition in PV studies require applying rigorous criteria, which in cases of idiosyncratic reactions are almost always lacking. In addition, use of PV algorithms in the
diagnosis of DHRs in general is not accurate because of the often lack of sufficient information for scoring (Benahmed et al., 2005). An alternative would be a reliable and safe in vitro test with adequate sensitivity and specificity to detect true cases among the suspected cohort of patients. It is understandable that these criteria can only be applied in prospective PV studies but can be used for PV surveillances.

Drug-induced SSLR represent a major problem to healthcare—along with other idiosyncratic hypersensitivity reactions—due to the difficulty in diagnosis and accurate identification of the culprit drug. Approximately 10% of the general population report an allergy to β-lactam antibiotics; however, 90% of reported allergies to β-lactam antibiotic cannot be ruled out immunologically (Surtees et al., 1991). Such false labeling of patients puts them at greater risk of adverse reaction due to the use of less safe alternative drugs with inferior effectiveness to treat their infection which increases length of hospital stay and worsen the outcome. Furthermore, false labeling result in the use to non-beta-lactam antibiotics leading to cost increases and contributes to worsening the bacterial resistance problem. Capturing true cases of β-lactam-induced SSLR using available clinical criteria is difficult due to lack of reliable diagnostic tests. On the other hand, for newly marketed drugs, especially biologicals, capturing IDRAs for safety evaluation is utmost important for proper PV monitoring. All the available diagnostic aids including skin testing and oral re-challenge have their risks and shortcomings and are not always feasible to perform either due to lack of expertise or fear of inducing a severe reaction in the patient. The LTA has the advantage of being safe as an in vitro test and can be used both as a diagnostic test and an investigative tool for the pathophysiology of SSLRs. Kearns et al. (Kearns et al., 1994) tested 19 patients (10 male and 9 females) suspected of developing SSLR to cefaclor and found that subjects with SSLR exhibited an increase in cell death of 50%–167% above baseline. The effect was specific to cefaclor and was not produced by incubation of isolated cells with another cephalosporin (cephalexin) along with metabolic activation system (Kearns et al., 1994). In another study, the same group also tested 10 patients with SSLR to cefaclor using the LTA test. The degree of cell death in the patient pollution was highly positive and ranged from 40% to 140% increase above baseline (Kearns et al., 1998). In a validation study for the LTA test using systemic re-exposure as a gold standard to determine the predictive value of the test for diagnosis of hypersensitivity reactions (HSRs) to different groups of drugs, we tested 11 patients with HSRs to beta-lactam antibiotics (6 to amoxicillin and 5 to cefaclor) (Elzagallaai et al., 2010). When the results of the re-exposure were compared to the LTA results, all except one patient had complete agreement.

The main pitfall associated with evaluating the role of in vitro toxicity testing for pharmacovigilance monitoring of rare drug-induced reactions is the lack of large studies looking at the predictive value of these tests (Elzagallaai et al., 2009). We speculate that one of the main reasons for this is the technical skills and special equipment required to perform the test restricting it to highly sophisticated research centers. We have introduced a more simplified version of the LTA test—the in vitro platelet toxicity assay (iPTA)—using blood platelets as a surrogate cell model for toxicity testing (Elzagallaai et al., 2011). The iPTA test has been proven to be less technically demanding and less expensive than the LTA with potentially better predictive value (Elzagallaai et al., 2013).

Data from this pilot study points to the value of the LTA (and potentially the iPTA) both as a diagnostic tool for beta-lactam-induced SSLRs and as a PV monitoring tool. Further research with larger numbers of patients is needed to further explore the pathophysiology and biology of SSLR to β-lactam antibiotics.

### Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

### Ethics statement

The studies involving human participants were reviewed and approved by REB of the University of Western Ontario. Written informed consent to participate in this study was provided by the participants’ legal guardian/next of kin.

### Author contributions

AE designed the study, analyzed the data and wrote the manuscript. AA Collected data and blood samples and performed the in vitro testing. BD recruit patients and collected clinical data. EM recruited patients and healthy controls to the study and revised the manuscript. MR contributed to the original design of the study, recruitment of patients and writing of the manuscript.

### Funding

This research was funded by the GSK-CIHR Chair in Paediatric Clinical Pharmacology to MR.

### Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
Publisher’s note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

Bailey, C., Peddie, D., Wickham, M. E., Badke, K., Small, S. S., Doyle-Waters, M. M., et al. (2016). Adverse drug event reporting systems: A systematic review. Br. J. Clin. Pharmacol. 82 (1), 17-29. doi:10.1111/bcp.12944

Bates, D. W., SpellN Cullen, D. J., Burdick, E., LairdN Petersen, L. A., et al. (1997). The costs of adverse drug events in hospitalized patients. Adverse Drug Events Prevention Study Group. JAMA J. Am. Med. Assoc. 277 (4), 307–311. doi:10.1001/jama.277.4.307

Ben Ahmed, S., Picot, M. C., Dumas, F., and Demoly, P. (2005). Accuracy of a pharmacovigilance algorithm in diagnosing drug hypersensitivity reactions. Arch. Intern. Med. 165 (15), 1500-1505. doi:10.1001/archinte.165.15.1500

Beninger, P. (2018). Pharmacovigilance: An overview. Clin. Ther. 40 (12), 1991–2004. doi:10.1016/j.clinthera.2018.07.012

Boury, J. C., De Bruin, M. L., and Koopsman, M. S. (2015). Epidemiology of adverse drug reactions in europe: A review of recent observational studies. Drug Saf. 38 (5), 437–453. doi:10.1007/s40264-015-0281-0

Chajjaras, S., Serere-Apapin, C., Rutnin, S., Ngamjanyaporn, P., and Rattanakaemakorn, P. (2022). Serum sickness-like reaction following an administration of the first dose of inactivated COVID19 vaccine. J.AAD Case Rep. 19, 21–24. doi:10.1016/j.jaaddcr.2021.11.004

Chan, E. W., Liu, K. Q. L., Chui, C. S. L., Sing, C. W., Wong, L. Y. L., and Wong, I. C. K. (2015). Adverse drug reactions - examples of detection of rare events using databases Br J Clin Pharmacol. 80 (4), 855–861. doi:10.1111/bcp.12474

Chung, B. S., Liu, W. T., and Chen, P. W. (2021). Serum sickness-like reactions after pneumococcal vaccination. Careeu 13 (9), e17877. doi:10.7759/careeucase.17877

De Schryver, S. N., and Ben-Shoshan, M. (2015). Severe serum sickness-like reactions to cefaclor: Lack of in vitro cross-reactivity with loracarbef. Clin. Pharmacol. Ther. 63 (6), 686–693. doi:10.1002/cpt.9269(68)(9)0093-5

Khan, D. A. (2016). Hypersensitivity and immunologic reactions to biologics: Opportunities for the allergist. Ann. Allergy Asthma Immunol. 117 (2), 115–120. doi:10.1016/j.anai.2016.05.013

Knowles, S. R., Uetrecht, J. C., and Shear, N. H. (2000). Idiosyncratic drug reactions: The reactive metabolite syndromes. Lancet 356 (9241), 1587–1591. doi:10.1016/S0140-6736(00)03137-8

Lawley, T. J., BieLory, L., Gascon, P., Yancey, K. B., Young, N. S., and Frank, M. M. (1984). A prospective clinical and immunologic analysis of patients with serum sickness. N. Engl. J. Med. 312 (22), 1407–1413. doi:10.1056/NEJM198412311212204

Lopez-Gonzalez, E., Herderito, M. T., and Figueroa, A. (2009). Determinants of under-reporting of adverse drug reactions: A systematic review. Drug Saf. 32 (1), 19–31. doi:10.2165/00003495-20093201-000002

Matzinger, P. (1994). Tolerance, danger, and the extended family. Annu. Rev. Immunol. 12, 991–1045. doi:10.1146/annurev.immunol.12.1.991

Naranjo, C. A., Kwok, M. C., Lncot, K. L., Zhao, H. P., Spielberg, S. P., and Shear, N. H. (1994). Enhanced differential diagnosis of anticonvulsant hypersensitivity reactions by an integrated Bayesian and biochemical approach. Clin. Pharmacol. Ther. 56 (5), 564–575. doi:10.1002/cpt.1994.178

Neuman, M. G., Malikewicz, I. M., Phillips, E. J., Rahils, A. R., Ong, D., Yeung, E., et al. (2002). Monitoring adverse drug reactions to sulfonamide antibiotics in human immunodeficiency virus-infected individuals. Ther. Drug Monit. 24 (6), 728–732. doi:10.1093/thermobi/24.6.728

Neuman, M. G., Malikewicz, I. M., and Shear, N. H. (2000). A novel lymphocyte toxicity assay to assess drug hypersensitivity syndromes. Clin. Biochem. 33 (7), 517–524. doi:10.1016/S0009-9120(00)00146-6

Neuman, M. G., Shear, N. H., Malikewicz, I. M., Taeri, M., Shapiro, L. E., Kirnov, N., et al. (2007). Immunopathogenesis of hypersensitivity syndrome reactions to sulfonamides. Transl. Res. 149 (5), 243–253. doi:10.1016/j.trsl.2006.12.001

Petelts, S. (1973). An evaluation of consumer protection legislation: The 1962 drug amendments. J. Political Econ. 81 (5), 1049–1091. doi:10.1086/260107

Pichler, W. J., Adam, J., Daubner, B., Gentinetta, T., Keller, M., and Verly, D. (2010a). Drug hypersensitivity reactions: Pathomechanism and clinical symptoms. Med. Clin. North Am. 94 (4), 645–664. doi:10.1016/j.mcna.2010.04.003

Platt, R., Dreis, M. W., Kennedy, D. L., and Kuritsky, J. N. (1988). Serum sickness-like reactions to amoxicillin, cefaclor, cephalaxin, and trimethoprim-sulfamethoxazole. J. Infect. Dis. 158 (2), 474–477. doi:10.1093/infdis/158.2.474

Qureshi, Z. P., Sesane-Vazquez, E., Rodriguez-Monguio, R., Stevenson, K. B., and Sebechel, S. L. (2011). Market withdrawal of new molecular entities approved in the United States from 1980 to 2009. Pharmacoeconom. Drug Saf. 20 (7), 772–777. doi:10.1080/108281612000000074

Reynolds, R. D. (1996). Cefadrox and serum sickness-like reaction. JAMA 276 (12), 950–951. doi:10.1001/jama.1996.03551021280107

Salvador, M. R., Monteiro, C., Pereira, L., and Duarte, A. P. (2022). Quality of spontaneous reports of adverse drug reactions sent to a regional pharmacovigilance unit. Int. J. Environ. Res. Public Health 19 (7), 3754. doi:10.3390/ijerph19073754
Schryver, D. (2015). Severe serum sickness-like reaction: Challenges in diagnosis and management. *J. Clin. Exp. Dermatology Res.* 06. doi:10.4172/2155-9554.1000279

Surtees, S. J., Stockton, M. G., and Gietzen, T. W. (1991). Allergy to penicillin: Fable or fact? *BMJ* 302 (6784), 1051–1052. doi:10.1136/bmj.302.6784.1051

Szebeni, J. (2005). Complement activation-related pseudoallergy: A new class of drug-induced acute immune toxicity. *Toxicology* 216 (2-3), 106–121. doi:10.1016/j.tox.2005.07.023

Uetrecht, J., and Naisbitt, D. J. (2013). Idiosyncratic adverse drug reactions: Current concepts. *Pharmacol. Rev.* 65 (2), 779–808. doi:10.1124/pr.113.007450

Vaughan, J. H., Barnett, E. V., and Leadley, P. J. (1967). Serum sickness. Evidence in man of antigen-antibody complexes and free light chains in the circulation during the acute reaction. *Ann. Intern. Med.* 67 (3), 596–602. doi:10.7326/0003-4819-67-3-596

von Pirquet, C., and Schick, B. T. (1911). *Serum sickness*. Baltimore, MD: Williams & Wilkins.

Weiss, S. L., and Smith, D. M. (2020). A case of serum sickness-like reaction in an adult treated with omalizumab. *Mil. Med.* 185 (5-6), e912–e913. doi:10.1093/milmed/usz357

WHO (2014). *Pharmacovigilance: Ensuring the safe use of medicines*. Geneva, Switzerland: WHO.

Zhang, B., Li, Q., Shi, C., and Zhang, X. (2018). Drug-induced pseudoallergy: A review of the causes and mechanisms. *Pharmacology* 101 (1-2), 104–110. doi:10.1159/000479878