International Journal of Community Medicine and Public Health
Baik MA et al. Int J Community Med Public Health. 2022 Dec;9(12):4731-4736
http://www.ijcmph.com
pISSN 2394-6032 | eISSN 2394-6040

DOI: https://dx.doi.org/10.18203/2394-6040.ijcmph20222971

Review Article

Classification and management of hypersensitivity reactions

Maryam Abdullah Baik[1]*, Ali Naji Al Nihab[2], Abdulmanem Mohammed Al Aman[3], Ameen Ridha Al Ghareeb[4], Mohammed Hashim Alaish[5], Ashraf Hassan Al Awani[6], Ahmed Mansour Al-Jadher[7], Faisal Mohammed Al Muaddi[8], Ali Hussain Al-Shehab[9], Tayseer Ali Al Tufaif[10], Hussain Ahmad Alsheef[10]

[1]Department of Emergency Medicine, East Jeddah Hospital, Jeddah, Saudi Arabia
[2]Department of Emergency Medicine, Anak General Hospital, Dammam, Saudi Arabia
[3]Primary Health Care, Qatif Central Hospital, Qatif, Saudi Arabia
[4]Directorate of Health Affairs, Saihat, Saudi Arabia
[5]College of Medicine, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia
[6]Comprehensive Screening Center, Dammam, Saudi Arabia
[7]Dammam Medical Complex, Dammam, Saudi Arabia
[8]Department of Emergency Medicine, Hera General Hospital, Mecca, Saudi Arabia
[9]Department of Emergency Medicine, Anak General Hospital, Qatif, Saudi Arabia
[10]Department of Family Medicine, Ministry of Health, Dammam, Saudi Arabi

Received: 28 October 2022
Accepted: 01 November 2022

***Correspondence:**
Dr. Maryam Abdullah Baik,
E-mail: Maryam.Abdullah.baik@gmail.com

ABSTRACT

An inappropriate or excessive immune response to an antigen that has unfavourable effects is referred as a hypersensitivity reaction. People who have experienced at least one prior exposure to the antigen are more likely to have the symptoms. Nearly 60 years ago, Gell and Coombs first classified hypersensitivity reactions into four broad categories. Many forms of hypersensitivity reactions frequently occur at the same time, especially in allergic disorders. The purpose of this research is to review the available information about the classification and management of hypersensitivity reactions. Allergen-specific immunoglobulin E, which is associated with the high-affinity receptors of basophils and mast cells mediates type 1 hypersensitivity reactions. These receptors are cross-linked by allergens, which release mediators that elicit urticaria, angioedema, and anaphylaxis. Immunoglobulin G and immunoglobulin M attach to self-antigens on cell surfaces in type II reactions, which can lead to phagocytosis, and cytotoxicity that is complement-directed and antibody-dependent all of which can lead to tissue damage. Immune complexes of immunoglobulin G and immunoglobulin M with antigens, which deposit in tissues and directly harm organs, mediate type III reactions. T cells mediate type IV reactions which are delayed responses. In every case of allergic hypersensitivity, the trigger must be stopped right away. Antihistamines, glucocorticoids, and epinephrine are used to treat acute responses Some potential management techniques include drug allergy testing, graded challenges, desensitization, and/or choosing an alternative, non-cross-reactive substance. Further clinical research is however needed for the elaborated study of hypersensitive reactions and development of preventive strategies.

Keywords: Hypersensitive, Reaction, Allergen, Immunoglobulin

INTRODUCTION

Illness or disease can be caused by abnormalities or malfunctions in the innate or adaptive immune response. Such illnesses are typically brought on by either an inefficient immune response, an improper immune response to oneself, or an overactive immunological response. Adverse responses generated by immune system to an allergen are termed as hypersensitivity reactions.[1] Gell and Coombs established the basis for categorizing hypersensitivity reactions in 1963 by grouping them into four different categories based on the mechanisms causing tissue injury: type I; immediate or immunoglobulin (Ig)E mediated, type II; cytotoxic or mediated by IgG/IgM, type III; immune complex mediated, and type IV; delayed type or T-cell mediated. Sub-classes of type II and IV have recently been incorporated to this classification system in an effort to reflect the immunopathology of diseases more precisely. Despite fact that in clinical practice, symptoms of several forms of hypersensitivity reactions can coexist in a single patient and cause overlapping hypersensitivity reactions.[2]

All types and sizes of antigens might result in hypersensitivity reactions. T-cell receptors or Ig can process and recognize large-molecular-weight protein antigens directly, whether they are native to an individual or foreign. Many biologic medications are recombinant antibodies that can connect to leukocyte Fc receptors or form immune complexes.[3] Small, low-molecular-weight compounds, on the other hand, cannot be directly ingested or exhibited by antigen-presenting cells and therefore as a result does not initiate an immune response on their own. Although they might activate immunological responses in other ways. In the Hapten model, smaller compounds, such as penicillin, which has a molecular weight of 300 Daltons, covalently bond to cellular or serum proteins, such as albumin, to produce new epitopes that can become antigenic. As with sulfamethoxazole, several medications have property of prohaptens, which means that while they are inactive in their natural state, metabolites can cause haptenization.[4]

Immune responses to small-molecule substances, such as medications, can result in a number of illnesses, primarily affecting the skin but also affecting other organs including liver, kidney, lungs among certain others. Many drug-induced hypersensitivity reactions seem delayed in addition to the well-known rapid, IgE-mediated reactions to medicines.[5] Also, unfavourable reactions to food are frequently observed, which is a source of worry and anxiety as it might result in an extremely restrictive diet. The type of food and the mechanism can affect how severe the reaction is, and it can be challenging to distinguish between the several hypersensitivity diagnoses that can occasionally coexist. Food hypersensitivity is frequently ruled out or suspected following a thorough medical history. IgE-mediated food allergy is the most prevalent form of allergic reaction accounting for approximately 5%-10% of cases. From slight itching, stomach ache, and rash to severe anaphylaxis, symptoms might range.[6]

Epinephrine, antihistamines, oxygen support, intravenous fluids administration, and surgical treatments such as tracheotomies in case of significant laryngeal edema all contribute to the management of anaphylaxis or acute hypersensitivity reactions. Leukotriene antagonists, disodium cromoglycate, short- and long-acting bronchodilators, inhaled corticosteroids, and environmental changes are among the treatment options for allergic bronchial asthma. Also, Omalizumab, methotrexate, or cyclosporin have all been tested experimentally in modest doses. Treatments for autoimmune diseases including systemic lupus erythematosus include nonsteroidal anti-inflammatory medicines, hydroxychloroquine, azathioprine, methotrexate, mycophenolate, cyclophosphamide, intravenous Ig, and belimumab.[7] Purpose of this research is to review the available information about classification and management of hypersensitivity reactions.

LITERATURE SEARCH

This study is based on a comprehensive literature search conducted on October 6, 2022, in the Medline and Cochrane databases, utilizing the medical topic headings (MeSH) and a combination of all available related terms, according to the database. To prevent missing any possible research, a manual search for publications was conducted through Google Scholar, using the reference lists of the previously listed papers as a starting point. We looked for valuable information in papers that discussed the information about classification and management of hypersensitivity reactions. There were no restrictions on date, language, participant age, or type of publication.

DISCUSSION

The immune system or one of its effector pathways, such as inflammation, are activated in both traditional immunological or allergic reactions and non-allergic hypersensitivity reactions. Clinically stated, hypersensitivity reactions can either be immediate that is arising within an hour of exposure or late, arising more than an hour later. It was once believed that hypersensitivity reactions were unpredictable, but owing to advances in immune system research, data from cohort studies, and pharmacovigilance, it is now possible to pinpoint the medications and underlying mechanisms that cause these reactions, as well as to identify specific clinical syndromes. Variable indications of immediate reactions include pruritus, edema, urticaria, and anaphylactic shock. About 77% of all hypersensitivity reactions are non-allergic reactions, which can be induced by a variety of medications, such as nonsteroidal anti-inflammatory medicines and penicillin.[8] Effector processes serve as the foundation for Gell and Coombs' classification of hypersensitive reactions. Although this approach is still frequently utilized, subsequent research

showed that several groups of hypersensitivity reactions frequently have striking similarities. In fact, all of these reactions include the activation of adhesion mechanisms designed to promote the generation of cytokines and the local recruitment of blood leukocytes. Although it is simply an approximation, the idea of two distinct immune response modes caused by two distinct T lymphocyte subpopulations including TH1 and TH2 has been helpful in understanding hypersensitive reactions. Recent findings provided motivation for the creation of novel diagnostic and therapeutic approaches, the efficacy of which needs to be determined further.[9]

Classification of hypersensitivity reactions

Conventionally hypersensitivity reactions are classified into four following types.

Type 1

Involvement of IgE is linked to type 1 of hypersensitivity reactions. Genetics, T cell responsiveness, antigenic burden, and other factors all have an impact on a person's predisposition to generate IgE. IgE antibodies are released in response to an antigen or allergen. Mast cells and basophils have high-affinity receptors on their surfaces, which IgE attaches to, priming them to respond when they come into contact with the allergen again. IgE cross-linking on cell surfaces results in rapid cellular degranulation and the activation of many chemical mediators. Histamine, protease enzymes, proteoglycans, and chemotactic factors are among the mediators released during mast cell degranulation. Interaction of antigen with IgE on mast cells further leads to the stimulation of leukotrienes, prostaglandins, and platelet activating factor. Histamine's effects vary depending on where it is released. It elicits smooth muscle contraction in the airways and the recognizable wheal and flare reaction in the skin. Anaphylactic shock, which can entail circulatory shock, hypotension, collapse, chest tightness, and, in the worst scenarios, respiratory arrest and death, is spurred on by widespread mast cell activation. Type I hypersensitivity reactions, also known as acute hypersensitivity reactions, occur right away almost within 20 min of injury.[10] Symptoms of anaphylaxis, a type I systemic allergic reaction that can be fatal, include urticaria, angioedema, bronchospasm, nausea, vomiting, diarrhoea, hypotension, in rare cases, shock. Foods, medications/ venom of stinging insects can all be allergens. It is important to note that many diseases can be caused by non-specific, IgE-independent mast cell activation, which might be considered as subtype of type I hypersensitivity reaction. Include iodinated contrast media, biologic medicines, opiates, and other medications that cause systemic responses.[11]

Type 2

Since the damage is caused by hapten-specific antibodies that are capable of inducing cytotoxicity in the target cell, type II hypersensitivity reactions are also referred as cytolytic reactions. Both IgM and IgG antibodies can cause a type II reaction, with IgG being more common. Complement system and phagocytic cells both are the specific effectors that cause cell damage. Numerous blood cell types that are in circulation are among the organs that targeted by type II reactions.[12] Medications interact with blood components and change their cellular antigens; this phenomenon is observed in clinical settings. Some medications can produce type II hypersensitivity reactions, such as haemolytic anaemia developed as a result of the immune system's destruction of erythrocytes and thrombocytopenia which is caused by the immune system's destruction of platelets. Chemically reactive drug molecules attach covalently to red blood cells or platelets surfaces, forming new epitopes that the immune system recognizes as foreign antigens and triggers the production of IgM and IgG antibodies that are reactive with the drug and protein conjugate on the cell surface.[13]

Type 3

Immune complex reactions are another name for type III hypersensitivity reactions. Antigen and antibody complexes can either develop immediately in the tissue or in the circulation before being deposited in vulnerable tissues. The appearance of a red, swelling lesion after numerous insect stings is indicative of the latter process, which is referred as the Arthus reaction. Type II and III hypersensitivity reactions manifest approximately 3-6 hours following exposure to the antigen, which is longer than type I reactions. In autoimmune reactions, where the antigen remains, the reaction can potentially turn chronic. Clinical signs and symptoms of type III hypersensitivity reactions include extrinsic allergic alveolitis, tissue deposition, vasculitis illness, serum sickness, and nephritis.[10] Most of the pathophysiology underlying chronic autoimmune disease, systemic lupus erythematosus, is anchored by type III hypersensitivity. Some inflammatory reactions may involve a combination of types II and III hypersensitivities with the development of in situ immunocomplexes.[14]

Type 4

Type IV hypersensitivity often manifests at least 48 hours after an antigen exposure. It involves the production of cytokines and chemokines by activated T cells, as well as the targeting of such molecules by macrophages and cytotoxic CD8+ T cells. Tissue damage is associated with infections with slowly growing intracellular organisms, such as in the case of tuberculosis and leprosy, and is mostly due to delayed-type hypersensitivity and granuloma. Many of the chlamydial disease's clinical symptoms, most notably trachoma, appear to be caused by a delayed-type hypersensitivity sparked by the disease's heat shock proteins.[15] The type IV reaction that Gell and Coombs first identified as the classic reaction is now termed as type IVa, and it is mediated by Th1 cells, which cause macrophages to release cytokines including

interferon gamma and tumour necrosis factor alpha. A typical example to explain this type is contact dermatitis, which can be induced by a number of substances including poison ivy, oak, and sumac. In type IVb reactions, interleukins 4, 5, and 13 are secreted by Th2 cells, which encourage eosinophilic inflammatory response and IgE synthesis. For instance, drug sensitized Th2 cells encourage eosinophilic survival, activation, and tissue migration to harm several organs in individuals with drug reactions with eosinophilia and systemic symptoms. Type IVb reactions may also be involved in the inflammation that occurs in the late stages of atopic illnesses like allergic rhinitis or asthma. Cytotoxic CD8 T lymphocytes, which selectively target certain cells using a variety of mediators including perforin, granulysin, and granzyme B, are the primary cause of type IVc. The primary contributor to tissue damage in Stevens-Johnson syndrome and toxic epidermal necrolysis is what appears to type IVc responses, in which activated CD8 T cells induce keratinocyte apoptosis and/or necrosis. When T cell-derived interleukin 8 attracts neutrophils to tissues to induce neutrophilic inflammation, as is the situation in acute widespread exanthematous pustulosis, type IVd reactions result in tissue degradation.[2]

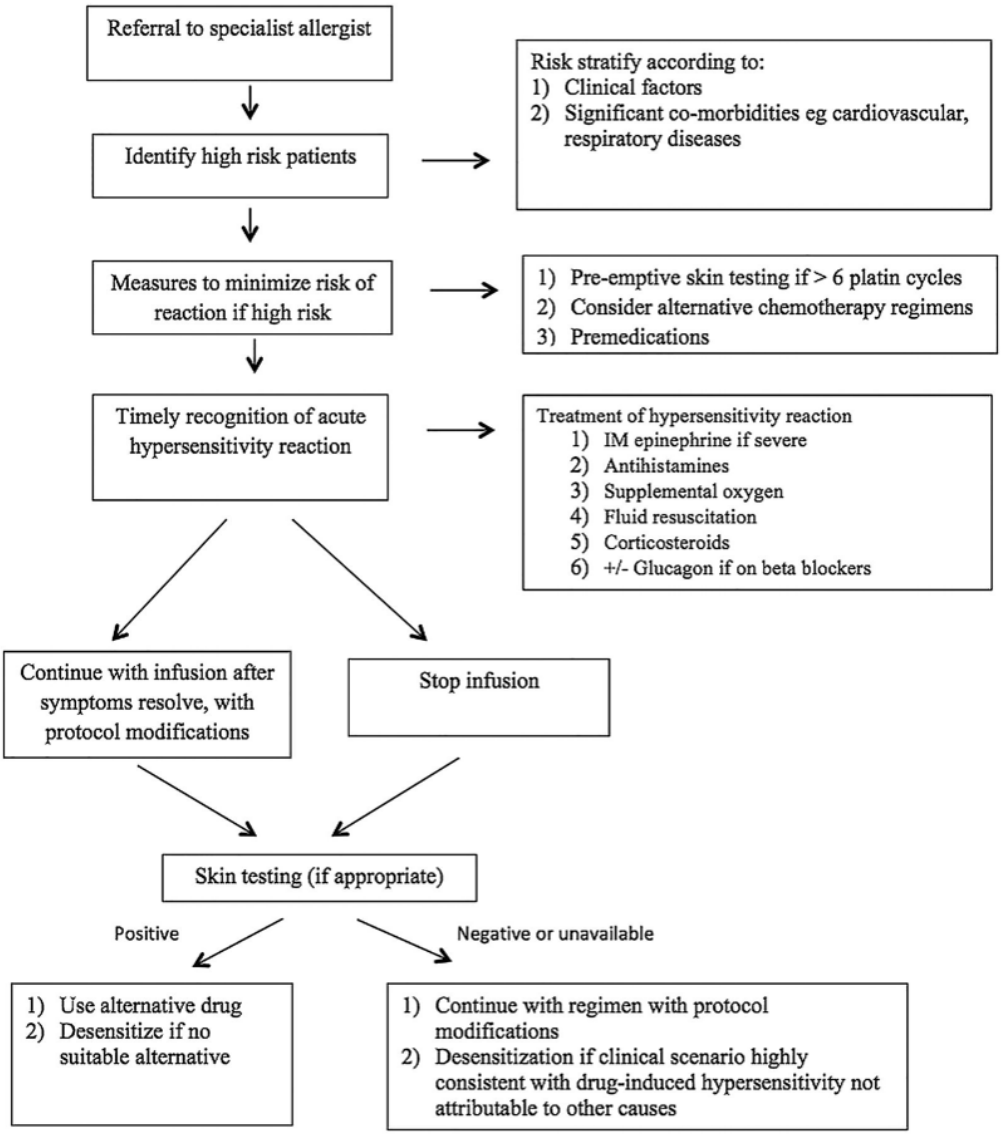

Figure 1: Evaluation and management of hypersensitive reactions to chemotherapeutic agents.[22]

Management of hypersensitivity reactions

Drug allergy testing, graded challenges, desensitization, and/or alternate, non-cross reactive agent selection are some possible management strategies. Immediate skin testing is valid only for identification of potential for immediate-type allergic drug hypersensitivity reactions and has a small number of medicines with a low negative predictive value including penicillin. Desensitization causes a transient level of tolerance that is only sustained

while substance is being used.[16] Desensitization enables patients to receive chemotherapy treatments that would otherwise be impossible to replace, such as taxanes, platinum salts, to which they have previously experienced hypersensitivity reactions. Aspirin can also be administered to aspirin-sensitive individuals undergoing revascularization and to people with respiratory diseases that are made worse by aspirin owing to desensitization.[17] When there is no acceptable or suitable alternative and delay in treatment continuation could be fatal, hypersensitivity reactions to chemotherapeutic medicines provide severe management challenges. These reactions can have variety of symptoms and can be IgE mediated/ non-IgE mediated. Life-threatening hypersensitivity reactions must be promptly identified and treated. Risk stratification can direct therapeutic decision-making by identifying individuals who are at high risk of experiencing hypersensitivity reactions. Skin testing has significant predictive value for carboplatin hypersensitivity; however, it has not yet been demonstrated for oxaliplatin and taxane hypersensitivity.[18]

In every case of allergic hypersensitivity, the trigger must be stopped right away. Antihistamines, glucocorticoids, and occasionally epinephrine are used to treat acute responses. Glucocorticoids are typically used to treat delayed reactions.[8] Intravenous epidophyllotoxins may prevent hypersensitivity reactions via slow infusion, and if a reaction does occur, it is typically successfully treated with corticosteroids and antihistamines. It is advised that intravenous epidophyllotoxins be infused slowly because rapid infusion is frequently linked to hypotension. Infusions should last for at least 30 to 60 minutes. A preventive prescription of corticosteroids and antihistamines is typically beneficial in rechallenging patients who experience an allergic reaction. Patients who experience recurring responses to intravenous etoposide after using premedication may benefit from treatment with etoposide phosphate.[19]

Taxanes are a significant class of anti-cancer medications used to treat a range of cancers. However, the most widely used taxanes, paclitaxel and docetaxel, cause acute hypersensitivity reactions in approximately 5% to 10% of individuals. It is safe to re-expose almost all patients who have these reactions to taxanes, either through desensitization chall/enge.[20] Evaluation and management of hypersensitive reactions to chemotherapeutic agents is illustrated in (Figure 1). There is now substantial evidence that type I hypersensitivity reactions can be treated with the same quick desensitization techniques as anaphylactoid reactions. However, environments with only one-on-one nurse-patient care and those with immediate access to resuscitation personnel and resources should be used for initial rapid desensitization. Temporary tolerization is achieved in a short period of time. Standard methods provided for secure, continuous desensitization under identical circumstances in outpatient settings after initial desensitization, providing flexibility and enabling patients to continue taking part in clinical trials.[21] Clinical characteristics and effectiveness of management strategies for the hypersensitivity reactions needs to be studied and determined further as the present literature is mainly limited to books and scarce, more research studies including population-based surveys, clinical studies and trials are needed.

CONCLUSION

Early diagnosis and prompt management is essential in hypersensitivity reactions as it can lead to fatal complications also further research is needed to develop and test preventive strategies for hypersensitivity reactions to achieve optimal outcomes. Additionally, awareness and education by healthcare professionals among community regarding various allergies can also help in averting hypersensitivity reactions.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Warrington R, Watson W, Kim HL, Antonetti FR. An introduction to immunology and immunopathology. Allergy Asthma, Clin Immunol. 2011;7(1):S1.
2. Dispenza MC. Classification of hypersensitivity reactions. Allergy Asthma Proceedings. 2019;40(6):470-3.
3. Murphy KM WC. Janeway's immunobiology. 9th ed. New York: Garland Science, Taylor and Francis. 2017.
4. Schnyder B, Brockow K. Pathogenesis of drug allergy--current concepts and recent insights. Clin Exp Allergy. 2015;45(9):1376-83.
5. Posadas SJ, Pichler WJ. Delayed drug hypersensitivity reactions-new concepts. Clin Experimental Aller. 2007;37(7):989-9.
6. Tedner SG, Asarnoj A, Thulin H, Westman M, Konradsen JR, Nilsson C. Food allergy and hypersensitivity reactions in children and adults-A review. J Internal Med. 2022;291(3):283-302.
7. Justiz Vaillant AA VR, Zito PM. Immediate Hypersensitivity Reactions. StatPearls Treasure Island (FL): StatPearls Publishing. 2022.
8. Böhm R, Proksch E, Schwarz T, Cascorbi I. Drug Hypersensitivity. Deutsches Arzteblatt Int. 2018;115(29-30):501-12.
9. Bongrand P. Immunological bases and classification of allergy. Arch Pediatr. 1999;6(1):20s-28s.
10. Sheldon J, Wheeler RD, Riches PG. CHAPTER 30 - Immunology for clinical biochemists. In: Marshall WJ, Lapsley M, Day AP, Ayling RM, eds. Clinical Biochemistry: Metabolic and Clinical Aspects (Third Edition). Churchill Livingstone. 2014;560-603.
11. Lieberman P, Nicklas RA, Randolph C. Anaphylaxis--a practice parameter update 2015. Ann Allergy Asthma Immunol. 2015;115(5):341-84.

12. Holsapple MP, Kaminski NE. Immune System. In: Wexler P, ed. Encyclopedia of Toxicology (Second Edition). New York: Elsevier. 2005;573-96.
13. Salmon JE. 46 - Mechanisms of Immune-Mediated Tissue Injury. In: Goldman L, Schafer AI, eds. Goldman's Cecil Medicine (Twenty Fourth Edition). Philadelphia: W.B. Saunders. 2012;226-30.
14. King TC. 2 - Inflammation, Inflammatory Mediators, and Immune-Mediated Disease. In: King TC, ed. Elsevier's Integrated Pathology. Philadelphia: Mosby. 2007;21-57.
15. Fierer J, Looney D, Pechère J-C. 2 - Nature and Pathogenicity of Micro-organisms. In: Cohen J, Powderly WG, Opal SM, eds. Infectious Diseases (Fourth Edition). Elsevier. 2017;4-25.e21.
16. Dykewicz MS, Lam JK. Drug Hypersensitivity Reactions. Med Clin N Am. 2020;104(1):109-28.
17. Romano A, Torres MJ, Castells M, Sanz ML, Blanca M. Diagnosis and management of drug hypersensitivity reactions. J Allergy Clin Immunol. 2011;127(3):S67-73.
18. Tham EH, Cheng YK, Tay MH, Alcasabas AP, Shek LP. Evaluation and management of hypersensitivity reactions to chemotherapy agents. Postgraduate Med J. 2015;91(1073):145-50.
19. Lee C, Gianos M, Klaustermeyer WB. Diagnosis and management of hypersensitivity reactions related to common cancer chemotherapy agents. Ann Allergy Asthma Immunol. 2009;102(3):179-87.
20. Picard M, Galvão VR. Current Knowledge and Management of Hypersensitivity Reactions to Monoclonal Antibodies. J Allergy Clin Immunol Practice. 2017;5(3):600-9.
21. Castells M. Rapid desensitization of hypersensitivity reactions to chemotherapy agents. Curr Drug Safety. 2006;1(3):243-51.
22. Tham EH, Cheng YK, Tay MH, Alcasabas AP, Shek LPC. Evaluation and management of hypersensitivity reactions to chemotherapy agents. Postgraduate Med J. 2015;91(1073):145-50.

Cite this article as: Baik MA, Al Nihab AN, Al Aman AN, Al Ghareeb AR, Alaish MH, Al Awani AH et al. Classification and management of hypersensitivity reactions. Int J Community Med Public Health 2022;9:4731-6.