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Skin eruptions in children: drug hypersensitivity vs viral exanthema

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Abstract:

Childhood rashes or exanthemas are common and are usually relatively benign. There are many causes of rash in children, including mainly viruses, and less often bacterial toxins, drugs, allergens, and other diseases. Viral exanthema often appears while children are taking a medication in the course of a viral infection; it can mimic drug exanthema, and is perceived as a drug allergy in 10% of cases. In the vast majority of cases, the distinction between virus induced and drug induced skin eruption during the acute phase is not possible. The drugs most commonly implicated are beta-lactams (BL) and nonsteroidal anti-inflammatory drugs (NSAIDs). Viruses, commonly Epstein Barr virus (EBV), human herpesvirus 6 (HHV6) and cytomegalovirus (CMV), and the bacterium *Mycoplasma pneumoniae*, may cause exanthema either from the infection itself (active or latent) or because of interaction with drugs that are taken simultaneously. Determination of the exact diagnosis requires a careful clinical history and thorough physical examination. Haematological and biochemical investigations and histology are not always helpful in differentiating between the two types of exanthema. Serological and polymerase chain reaction (PCR) assays can be helpful, although a concomitant acute infection does not exclude drug hypersensitivity. A drug provocation test (DPT) is although considered the gold standard for the diagnosis, is not preferred by the patients. Skin tests are not well tolerated,

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and *in vitro* tests, such as the basophil activation test and lymphocyte transformation, are of low sensitivity and specificity and their relevance is debatable. Based on current evidence, we propose a systematic clinical approach for timely differential diagnosis and management of rashes in children who present a cutaneous eruption while receiving a drug.
Key words: children, drug allergy, drug hypersensitivity, exanthema, virus

Key Message:

Childhood rashes or exanthemas are common and are usually relatively benign. Viral exanthema often appears while children are taking a medication in the course of a viral infection. It can mimic drug exanthema, and is perceived as a drug allergy in 10% of cases. Viruses may cause exanthema either from the infection itself (active or latent) or because of interaction with drugs that are taken simultaneously. We propose a systematic clinical approach which is crucial for timely differential diagnosis and management of rashes in children who present a cutaneous eruption while receiving a drug.

Introduction:

Childhood rashes or exanthemas are fairly common and are usually relatively benign with a self-limited course. The estimated incidence of exanthema in children is 158.3/10,000 (CI 142.3–174.4). [1] Exanthemas have an abrupt onset, affecting several areas of the body simultaneously.[2] As shown in Table 1, there are many possible causes of these rashes, including mainly viruses, and less often bacterial toxins, drugs, allergens and other diseases (e.g., autoimmune diseases, Kawasaki disease).[3,4] Following implementation of comprehensive immunization programmes in infancy, the classic forms of viral exanthemas have become less common, with an increase in the incidence of atypical exanthemas. Viral exanthemas can clinically mimic drug-induced exanthema (DIE), and often appear while children are taking a drug in the course of a viral infection. In such a situation, the exanthema is perceived as a drug allergy in about 10% of cases.[5,6] The drugs most frequently implicated are beta-lactams (BL) and nonsteroidal anti-inflammatory drugs (NSAIDs).[7]

This may lead doctors and parents to empirical use of an alternative drug, which could place an extra financial burden on the health insurance system and/or the family, increase antibiotic resistance, and ultimately result in ineffective treatment.[8] After a full allergy work-up, however,

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less than10% of these children will be confirmed to have a drug allergy.[9] In a study of 88 children, who were taking BL and presented a non-immediate exanthema, the majority tested positive for a viral infection, mainly enterovirus and herpes viruses, while they had a negative response to an oral drug provocation test (DPT), and thus no drug allergy was confirmed.[10] We have shown similar results, when testing revealed that certain exanthemas that developed during BL treatment were of infective origin, mainly from mycoplasma.[11]

Viruses may cause exanthemas either because of the infection (active or latent) or because of the interaction with drugs that are taken simultaneously.[12] Many viruses are implicated in exanthemas, with the most common being the Epstein Barr virus (EBV),[13] human herpesvirus 6 (HHV-6)[14]and cytomegalovirus (CMV).[15] Since a rash in childhood is a disquieting situation, the exact diagnosis of the specific exanthema subtype is decisive. In the case of drug allergy, immediate cessation of the culprit drug limits the severity of the rash and the systemic complications. A careful clinical history (prodromal symptoms, contact, chronology of the exanthema development, in relation to the drug exposure timeline, the morphological pattern of the exanthema, seasonality, pruritus, the body areas affected, etc.) and a thorough physical examination are important in establishing the cause of the exanthema.[2,4] The parents, however, often do not often remember the exact history. Haematological, biochemical investigations and histology are not routinely performed, and are not always helpful in differentiating between these two types of exanthema.[2] Serum specific antibodies testing for virus and polymerase chain reaction (PCR) assays can be helpful in the diagnostic process, although a concomitant acute infection does not exclude drug hypersensitivity (e.g., amoxicillin hypersensitivity in EBV infection).[4]

Skin tests pose special problems, such as tolerability, and many parents do not agree for a drug provocation test (DPT) on their child, which is the gold standard for the diagnosis of DIE. *In vitro* tests, such as the basophil activation test (BAT) and the lymphocyte transformation test (LTT), are not readily available, are of low sensitivity and specificity, and their relevance is debatable.[7] The BAT has not any indication in exanthematic reactions to drugs. The main objective of this review was, based on the currently available evidence, to propose a systematic clinical approach for the timely differential diagnosis and management of cutaneous eruptions in children who are receiving a drug.

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The mechanism of DIE

Viral exanthemas may be triggered directly (infectious exanthema) by specific pathogens, as in the case of the "classic" childhood diseases (Table 1).[16] The skin manifestation may result, alternatively, from an immune response (indirect or parainfectious exanthema) between the virus and antibody, or a cell-mediated response to the virus.[17] There is a well-established assumption that the concurrent use of drugs during certain infections increases the occurrence of DIE. In this instance, DIE is not thought to be generated by true drug allergy, but is principally the outcome of impermanent and shifting pathogen-mediated immune changes. The reaction usually does not recur on re-administration of the drug.[18]

a. Virally induced polyclonal T-cell activation

The suggestion that EBV is associated with DIE in patients with infectious mononucleosis (IM) has been broadly welcomed in the medical community, but a few studies have failed to generate recurrence of symptoms after drug re-challenge.[13,19] The mechanism of DIE most commonly proposed with respect to IM is that the viral load and the increasing numbers of activated CD8+ T-lymphocytes lead to a rise in the levels and activity of interferon-γ (IF-γ) and interleukin-2 (IL-2). Consequently, the activity of the type 2 helper T-lymphocytes (Th2 cells) is inhibited, which leads to suppressed release of the characteristic Th2 cell cytokines IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13.[20] It appears that adequate IL-10 activity is required to maintain immune tolerance and to limit immune responsiveness to certain antigens.[21] It is assumed that a crucial factor in the susceptibility to DIE seen in IM is suppression of IL-10 activity[22], which is accompanied by an increase in activated type 1 helper T-lymphocytes (Th1 cells), a known contributor to the development of non-immediate hypersensitivity reactions (NIR).[21] Consequently, the antibiotic molecules in the context of EBV-mediated immune changes set the stage for a hypersensitivity reaction, with presentation of an erythematous, maculopapular cutaneous eruption.

Certain antibiotics, notably penicillin, used concomitantly with chemotherapeutic drugs in the treatment of leukaemia, were observed to be independently associated with development of a morbilliform rash. A suggested mechanism for the pathogenesis of these cutaneous eruptions is that the profound $CD4^+$ lymphopenia, including regulatory T cells, induced by these purine analogues results in hypersensitivity and decreased drug tolerance.[23]

b. Affinity between amoxicillin and viral molecules

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The high affinity of BL with viral antigens can be considered a putative triggering mechanism for DIE. Specifically, viral infections could be a co-factor for activating drug specific T cells, which would otherwise undergo apoptosis, and a long-lasting DHR would not be developed. [24] It is thought that HHV-6, EBV and CMV reactivation emerges as a drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, or as other severe cutaneous adverse drug reactions (SCARs), giving rise to considerable aberration in the pathological phenotype of severe drug rashes.[25] Specifically, it has been shown that amoxicillin acts directly on herpesvirus replication, producing a flare in patients with DRESS.[26] This situation resulted in a transient state of immunosuppression and extensive non-specific immune system feedback, leading to a failure of tolerance to other drugs also, in particular anticonvulsants.[27]

c. Suppressed drug detoxification

Because of defective drug detoxication mechanisms (low plasma glutathione levels), DHR are more likely to evolve in patients suffering from human immunodeficiency virus (HIV) infection.[28] A similar mechanism of suppressed detoxification during EBV infection could be responsible for skin reactions. In support of this hypothesis, aminopenicillins and sulphonamides have been associated with a morbilliform rash in patients with HIV at a frequency related to the decline in immune function.[29]

Clinical Presentation

Viral induced exanthema (VIE)

Viral exanthemas have an abrupt onset and may be macular, papular, maculopapular, urticarial or vesicular, according to the virus implicated, and the mucosa may be involved. The distribution of the rash may be central (rubella, measles, roseola, parvovirus B19, EBV-infectious mononucleosis) or peripheral (hand-foot-mouth disease). Prodromal symptoms such as fever or malaise may precede the appearance of the rash.[30]

Drug Induced Exanthem (DIE)

The clinical presentation of a DIE is sometimes very difficult to be differentiated from urticaria. Exanthem is defined as an acute eruptive, widespread distribution of multiple small, round to oval erythematous macules and /or papules with different degrees of confluence. The morphology of the wheal in urticaria (single and temporary) and its duration (disappear in 24 hours) contrasts with an exanthem, which is characterized by a cellular infiltrate and lasts several

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days.[4]Urticaria is the most common manifestation of immediate drug reactions (IRs) and usually appear within 1 h after drug intake. The majority of IRs are mediated by IgE antibodies, *but* also can be mediated by COX-1 inhibition or by MRGPRX2 (Mas-related G protein–coupled receptor member X2), which depends on the type of drug that induced them[31]. Maculopapular exanthems (MPE) are the most common manifestation of non immediate drug reactions (NIRs). They primarily appear with erythematous macules and infiltrated papules, which often involve trunk and the proximal extremities in a symmetric distribution[4,31,32] MPE appear mostly 7-12 day of treatment, but not rarely after therapy was already stopped. Severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP*)* belong to severe NIRs. NIRs are mediated by T cells. The exanthema in SJS/TEN usually appear 4 to 28 days after start of therapy and it is painful with macules or blisters and sloughing of the skin and mucosal involvement and malaise may be profound.[33] While the exanthema in DRESS usually appear 2 to 8 weeks after start of therapy and is maculopapular but without erosions in the mucosa. Facial oedema, fever, lymphadenopathy, eosinophilia and involvement of many organs are usually present.[34,35] In AGEP, the exanthema is pustular, and accompanied by fever and oedema. It may start on day 3 or 5[4,31]

The complexity of the different clinical manifestations of NSAIDS hypersensitivity are due to the specific mediated mechanism. The reactions could be allergic and are classified into selective NSAID-induced wheals and/ or angioedema or anaphylaxis, and selective NSAID-induced delayed reactions, like maculopapular exanthema. In addition, the reactions could be non-immunological, cross-intolerant and are classified into NSAID-exacerbated respiratory disease, NSAID-exacerbated cutaneous disease (wheals and/or angioedema), NSAID-induced urticaria/angioedema or anaphylaxis[32]

It is important to highlight the difficulty in differentiating the VIE from the DIE, especially in their onset. Fever and malaise may precede the onset of the VIE, which is usually sudden, whilst a DIE appears after an exposure to a drug. However, fever may herald the onset of a more severe type of drug reaction.The DIE often spreads centripetally from the trunk to the extremities and is symmetrical. Lesions may coalesce into large plaques and may get severe in dependent areas, such as the back. They are usually pruritic with involvement of mucus membranes and other organs. In contrast, enanthems, which involve the mucous membranes, are more commonly associated with an infectious aetiology. In the same line, a child with VIE rarely experiences pruritus or other systemic complications and the exanthem tends to start

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on the face and acral sites with subsequent progression to involve throughout the trunk. The type of lesions is not always clearly determined. DIE is commonly characterized by erythematous macules or small papules, but a VIE could have the same lesions. The clinician must be concise that the clinical presentation is dynamic and can change within hours.

Diagnosis

a. Diagnostic approach in children with a skin eruption

Identification of the causative factor of a rash can be difficult when one or several different drugs are taken during the course of an infection. For accurate diagnosis, a rational approach is required, as shown in Figure 1. It may be helpful to examine the patient first, to establish the appearance and distribution of the exanthema, and then proceed with a relevant line of questioning.

The occurrence of a viral exanthem-more prevalent during spring/summer, the specific morphology and parts of the body that are affected, the presence of an enanthem, the vaccination status, and a history of contact with sick people or of a recent trip can lead to a specific viral diagnosis.[35,36] Some viral exanthemas are characteristic of a specific viral cause, making the diagnosis simple, but in the post-immunization era the majority are non-typical, which renders the diagnosis difficult.[30] Viral infections have an incubation period varying from 1 to 15 days, and the skin lesions resolve within 1 to 2 weeks.[30] For DHR diagnosis a careful, focused history is needed, which should include the initial drug dose and duration, along with relevant signs and symptoms. In many cases the children are brought for diagnosis, months or even years, after the appearance of the exanthema. Photographs may be shown to the doctor that can help in some cases. It is important to record all the drugs that were taken before and during the time of the reaction.[35] In DHR the rash may appear days or weeks after the beginning of medication, and its duration can reach 2 weeks after cessation of the suspected drug.[37] Mild NIR often appears 6-10 days after the beginning of administration when the drug is taken for the first time, and within 3 days when the drug is taken for second time. However, when the drug is taken for second time the initial symptoms already may appear within few hours and develop into a typical exanthem after 1 or 2 days.[4] The duration of the rash is up to two weeks after the last drug intake.[36]

Whilst the initial approach to a child with an exanthem begins with the detailed history, many times it renders inconclusive. The patient's age may help narrow the possible diagnoses. For example, acute maculopapular rashes in younger children are usually caused by viral infections, whereas in older children

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they are usually caused by drug reactions. Although, it is important to determine the type of lesions, it subsequently becomes difficult since such as macules, papules, vesicles, plaques, or pustules could be common morphological features. Furthermore, an exanthem that develops within 3 days of a drug being initiated for an infection is more likely to be secondary to the infection because of the time required for hypersensitivity to develop in a patient and previously sensitised to a particular drug. DIE classically appears 7 to 14 days after the start of a new medication, although it may appear sooner or later.

b. In vivo testing

To exclude the diagnosis of DHR, an allergic work-up is required, which should ideally be carried out 4-6 weeks after the complete resolution of all clinical symptoms[38-40]. According to the current guidelines, the diagnostic procedure for immediate reaction (IR) with or without anaphylaxis, includes skin testing with the suspected drug, either skin prick tests (SPT) or intradermal test (IDT).[40] If the skin tests are negative, a DPT can be performed.[6] SPTs, and especially IDTs, are not well tolerated by younger children as they are painful, fact that discourages parents from having them tested.[7] In addition, while their negative predictive value is very high, many false positive results have been reported, giving a sensitivity of less than 10%.[41,42] Regarding NIR, the utility of skin tests has been questioned in patients with isolated benign rash during BL treatment, and the direct application of DPT is suggested by the guidelines of the European Academy of Allergy and Clinical Immunology (EAACI) for the management of drug hypersensitivity in children.[7] Although the direct procedure of DPT without skin testing has been welcomed by parents and children, with a consequent increase in the numbers of patients having an allergic work-up, the current the evidence is low, and skin tests are still recommended .[7] DPT, however, remains the gold standard and is important in the management of children with a suspicion of drug allergy.

For suspected benign NIR, skin tests are of limited diagnostic value and direct DPT is recommended. In this respect, one-tenth of the maximum single unit dose should be given in the first place and, if tolerated, a full dose 1-7 days after, depending on the time interval of the index reaction[43]. The optimal doses and dosing schedule for DPT differ according to each protocol applied.[35,44,45] , as consensus is lacking. DPTs should not be performed in the case of SCARs.[7]

c. In vitro testing

Tests supporting VIE

Infections can be detected by serology, and direct detection of the virus is possible by polymerase chain reaction (PCR). These methods can be of help, especially in the case of an

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atypical exanthem and/or when there is underlying disease (e.g., anaemia) or immunosuppression).[2] In these atypical cases, a widespread papular/purpuric eruption with vesicobullous or pustular lesions and indurated pigmented nodules/plaques may cause confusion.[46,47,48] . It is important to take into consideration that a positive serological test does not preclude the diagnosis of an DHR, because some skin reactions may occur in the context of a viral infection or reactivation (e.g., DRESS with HHV-6 or maculopapular exanthema with EBV, with drugs). A complete blood count (CBC), and serological testing for CMV, EBV, HHV, HSV, Parvovirus B-19, adenovirus and *Mycoplasma pneumoniae* serology could helpful.

Tests supporting DIE

Studies have shown that it is possible to differentiate DIE from some VIE in children, by monitoringthe immunological response. Specifically, studies by phenotypic immunofluorescence analysis and Reverse Transcriptase -PCR have revealed that children with DIE have a stronger skin-homing T cell response and their peripheral blood mononuclear cells express a Th1 cytokine pattern while children with VIE tend to have a Th0 cytokine pattern [47,48]. This may help discriminate between the two causes of reaction, especially during the onset and the progress of the disease. In the same line, another study showed that maculopapular exanthema induced by drugs several chemokines, produced by cutaneous cells, are involved in the recruitment of cytotoxic T cells from peripheral blood. The determination of the precise chemokines are important to define the correct targets in the affected tissue[49].

Furthermore, the quantification of IgE antibodies, mainly relevant for BL, particularly the benzyl penicilloyl and the amoxicilloyl determinants, are of low diagnostic value in children.[7,10]

Many DHR are considered systemic, involving not only the skin but possibly internal organs also.[50] Evaluation can be made with CBC, renal and liver function tests and urinalysis. Imaging studies, mainly chest X-ray computed tomography (CT) are necessary in suspected severe DHR, i.e., DRESS, to identify interstitial pneumonitis or pleural effusion.[51]

The BAT and the sulphidoleukotriene release test can be applied when the test for specific IgE to a drug is negative or not available, although only small series have been reported.[52,53] BAT has been suggested as a useful diagnostic tool in the caseof IR to BL, and recent studies for non BL have shown encouraging results for BAT [54,55], but further paediatric studies are needed to confirm its value.[54]

The LTT attempts to quantify T-cell activation in response to a drug, but, although promising in adults, it appears to be of low diagnostic value for benign NIR to BL, non-BL and NSAIDs in children.[56-58] The LTT can help identify causes of SCARs, when DPT is strongly

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contraindicated. SCARs in 54 children were recently investigated, and LTT sensitivity towards BL or carbamazepine was reported up to 80% [59], although a study on adults revealed lower sensitivity (25% - 75%), and the performance of LTT is influenced by the culprit drug and the type of reaction.[60] Specifically, positivity is particularly high when the LTT is combined with measurement of cytokines and cytotoxic markers (cyto-LTT).[61] The true diagnostic value of LTT remains to be determined in large paediatric studies.

Skin biopsy can be helpful, although it is not indicated in all cases, and cannot indicate the causative drug. Specifically, in maculopapular and urticarial exanthemas, biopsies are often non-specific and are unwarranted, and are not routinely recommended. In the case of suspected SCARs, however, skin biopsy should be performed.

In this context, histopathology contributes to the initial diagnosis and to the prognosis, by guiding early discontinuation of the culprit drug, which otherwise may cause severe complications.[62] Specific immunohistochemical markers examined in biopsies taken at about 72 hours after the onset of drug exanthema, compared with biopsies obtained within 24 hours of the eruption, indicated a higher diagnostic output from fully evolved lesions.[36] Significant dermal lymphocytic infiltration has been found in a percentage of 50-100% of DIE biopsies[36,63-65], in decisive differentiation from VIE, in which dermal lymphocytic infiltration was detected in 20.8% cases only.[36]

Another distinguishing feature between the two types of exanthema is dermal eosinophilic infiltration, which was also found in a significantly higher number of biopsies from DIE (36-62.5%)[35,57-60] compared with VIE (16.6-20%).[36,66] It was noted, however, that 12.5% of DIE and 20.8% of VIE biopsies showed no infiltrate.[36]

Several specific genetic polymorphisms of the human leukocyte antigen (HLA alleles) have been demonstrated to be strongly associated with SCARs, and some of them have been proposed as valid genetic markers for prediction of these life-threatening reactions.[67]

Skin testing (SPT, IDT) and DPT is a recommended procedure for the diagnosis of a suspected DIE. Blood tests are used to exclude DIE and particularly the severe forms of DHR, which may cause organ dysfunction and haematological abnormalities. Furthermore, viral serology(IgM antibodies against respective viruses)and PCR may be useful to exclude VIE. Histology form the skin lesion is not routinely undertaken as it is not diagnostic of a drug or a virus cause. However,

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it contributes to the prognosis for an DIE, by guiding early discontinuation of the culprit drug. LTT and BAT can not differentiate DIE from VIE.

Differential Diagnosis

The differential diagnosis in a child with a rash is very wide ranging, and the clinical history is of paramount importance. Several specific signs are pathognomonic for certain diseases. Clues, such as the onset of symptoms before the appearance of the rash, typical morphological characteristics and administration of a new drug in the recent past, should be clarified. It is necessary to identify the type of skin lesions, the size, colour, distribution, arrangement and configuration of the lesions, and possible changes. Palpation of cutaneous lesions provides additional information, such as firmness, tenderness, mobility, temperature, and blanching with pressure. It is of note that maculopapular exanthemas do not evolve to SCARs, which may sometimes appear to be similar, commencing with an innocent exanthem or a morbilliform maculopapular eruption. SCARs can be very challenging at the onset, and alarm signs should be mucosal lesions, bullae, Nikolsky sign, facial oedema and fever.[68]

Precise morphological descriptions are critical in establishing the differential diagnosis, and the presence or absence of associated symptoms are also important (Table 2).

Treatment

In most viral cases the rash is benign, self-limited, and resolves spontaneously without treatment.[69]

In case of a confirmed DHR, treatment consists of discontinuation of the culprit drug, although this is not always feasible. If a patient is taking several medications, it may be difficult to identify the causative drug, and sequential with drawal might be considered, taking into account the type of reaction.[68] Urticarial reactions and mild maculopapular morbilliform exanthemas can be managed symptomatically, with antihistamines for the pruritus.[70] In the case of an anaphylactic reaction the anaphylaxis protocol should be followed.[40] SJS/TEN require urgent and active treatment, with several drugs, including corticosteroids, immunosuppressive anti-inflammatory drugs (cyclophosphamide, cyclosporin), intravenous immunoglobulins (IVIG) and tumour necrosis factor-α (TNF-α) inhibitors (anti-TNFαa agents).[71]

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Future needs

The high production of current omics technologies, allows the quantitative measurement of many putative targets (e.g. DNA, RNA, protein, metabolite) and identifies potential adverse drug reactions with the target [72]. Furthermore, omics approaches generate the etiology of complex diseases, such as genetic, environmental or even infectious agents [73].These technologies have individuallycontributed medical progress, providing a more concise view of the disease state.

Concluding Remarks

Exanthema is one of the most common reasons for paediatric consultation. When a drug is taken during the course of an infection the differential diagnosis between VIE and DIE may be difficult. It is important to consider the entire clinical presentation, the location and appearance of the rash, the clinical course and the associated symptoms in making the appropriate diagnosis. True allergy is not common in children, and overdiagnosis of drug allergy is a problem in the paediatric population, giving rise to increased health costs and bacterial resistance, because of the use of alternative antibiotics. BL and NSAIDS are the most commonly suspected drugs. An allergic work-up is crucial to the identification of true drug allergy, which should be conducted more than 4 weeks after the initial presentation of the exanthema.

References

1.Vega Alonso T, Gil Costa M, Rodriguez Recio MJ, de la Serna Higuera P. Incidence and clinical characteristics of maculopapular exanthemas of viral aetiology. Atencion primaria 2003;32(9):517-23.

2.Folster-Holst R, Kreth HW. Viral exanthems in childhood--infectious (direct) exanthems. Part 1: Classic exanthems. JDDG 2009;7(4):309-16.

3.Goodyear HM, Laidler PW, Price EH, Kenny PA, Harper JI. Acute infectious erythemas in children: a clinico-microbiological study. Br J Dermatol 1991;124(5):433-8.

4.Brockow K, Ardern-Jones MR, Mockenhaupt M, et al. EAACI position paper on how to classify cutaneous manifestations of drug hypersensitivity. Allergy 2019;74(1):14-27.

5.Zambonino MA, Corzo JL, Munoz C, et al. Diagnostic evaluation of hypersensitivity reactions to beta-lactam antibiotics in a large population of children. Pediatr Allergy immunol 2014;25(1):80-7.

This article is protected by copyright. All rights reserved

Accepted Article

6.Abrams E, Netchiporouk E, Miedzybrodzki B, Ben-Shoshan M. Antibiotic Allergy in Children: More than Just a Label. Int Arch Allergy Immunol 2019;180(2):103-12.
7.Gomes ER, Brockow K, Kuyucu S, et al. Drug hypersensitivity in children: report from the pediatric task force of the EAACI Drug Allergy Interest Group. Allergy 2016;71(2):149-61.
8.Ventola CL. The antibiotic resistance crisis: part 1: causes and threats. P T. 2015; 40(4): 277-83.
9.Graham F, Caubet JC. Diagnosis of drug causality in non-immediate drug hypersensitivity in children. Expert Rev Clin Pharmacol 2018;11(7):655-8.
10.Caubet JC, Kaiser L, Lemaitre B, Fellay B, Gervaix A, Eigenmann PA. The role of penicillin in benign skin rashes in childhood: a prospective study based on drug rechallenge. Pediatr Allergy Immunol 2011;127(1):218-22.
11.Atanaskovic-Markovic M, Gaeta F, Medjo B, et al. Non-immediate hypersensitivity reactions to beta-lactam antibiotics in children - our 10-year experience in allergy work-up. Pediatr Allergy immunol 2016;27(5):533-8.
12.Atanaskovic-Markovic M, Caubet JC. Management of drug hypersensitivity in the pediatric population. Expert Rev Clin Pharmacol 2016;9(10):1341-9.
13.Dibek Misirlioglu E, Guvenir H, Ozkaya Parlakay A, et al. Incidence of Antibiotic-Related Rash in Children with Epstein-Barr Virus Infection and Evaluation of the Frequency of Confirmed Antibiotic Hypersensitivity. Int Arch Allergy Immunol 2018;176(1):33-8.
14.Tohyama M, Hashimoto K, Yasukawa M, et al. Association of human herpesvirus 6 reactivation with the flaring and severity of drug-induced hypersensitivity syndrome. Br J Dermatol 2007;157(5):934-40.
15.Ozcan D, Seçkin D, Bilezikçi B, Arslan H. The role of human herpesvirus-6, Epstein–Barr virus and cytomegalovirus infections in the etiopathogenesis of different types of cutaneous drug reactions. Int J Dermatol 2010;49(11):1250-4.
16.Folster-Holst R, Kreth HW. Viral exanthems in childhood. Part 3: Parainfectious exanthems and those associated with virus-drug interactions. JDDG 2009;7(6):506-10.
17.Cherry JD. Viral exanthems. Curr Probl Pediatr 1983;13(6):1-44.
18.Thompson DF, Ramos CL. Antibiotic-Induced Rash in Patients With Infectious Mononucleosis. Ann Pharmacother 2017;51(2):154-62.

This article is protected by copyright. All rights reserved

Accepted Article

19.Chovel-Sella A, Ben Tov A, Lahav E, et al. Incidence of rash after amoxicillin treatment in children with infectious mononucleosis. Pediatrics 2013;131(5):e1424-7.
20.Banerjee I, Mondal S, Sen S, Tripathi SK, Banerjee G. Azithromycin-induced rash in a patient of infectious mononucleosis - a case report with review of literature. JCDR 2014;8(8): Hd01-2.
21.Schulke S. Induction of Interleukin-10 Producing Dendritic Cells As a Tool to Suppress Allergen-Specific T Helper 2 Responses. Front Immunol 2018;9:455.
22.Jog NR, Chakravarty EF, Guthridge JM, James JA. Epstein Barr Virus Interleukin 10 Suppresses Anti-inflammatory Phenotype in Human Monocytes. Front Immunol 2018;9:2198.
23.Wang RF, Li D, Kuehn GJ, Andritsos LA, Grever MR, Kaffenberger BH. Antibiotic exposure is associated with cutaneous adverse events in hairy cell leukemia patients treated with purine analogues. J Am Acad Dermatol 2019;80(6):1762-4.
24.Remy MM. Dengue fever: theories of immunopathogenesis and challenges for vaccination. Inflamm Allergy Drug Targets 2014;13(4):262-74.
25.Hirahara K, Kano Y, Mitsuyama Y, Takahashi R, Kimishima M, Shiohara T. Differences in immunological alterations and underlying viral infections in two well-defined severe drug eruptions. Clin Exp Dermatol 2010;35(8):863-8.
26.Mardivirin L, Valeyrie-Allanore L, Branlant-Redon E, et al. Amoxicillin-induced flare in patients with DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms): report of seven cases and demonstration of a direct effect of amoxicillin on Human Herpesvirus 6 replication in vitro. EJD 2010;20(1):68-73.
27.Oskay T, Karademir A, Erturk OI. Association of anticonvulsant hypersensitivity syndrome with Herpesvirus 6, 7. Epilepsy research 2006;70(1):27-40.
28.Para MF, Finkelstein D, Becker S, Dohn M, Walawander A, Black JR. Reduced toxicity with gradual initiation of trimethoprim-sulfamethoxazole as primary prophylaxis for Pneumocystis carinii pneumonia: AIDS Clinical Trials Group 268. J Acquir Immune Defic Syndr 2000;24(4):337-43.
29.Coopman SA, Johnson RA, Platt R, Stern RS. Cutaneous disease and drug reactions in HIV infection. N Engl J Med 1993;328(23):1670-4.
30.Knöpfel N, Noguera-Morel L, Latour I, Torrelo A. Viral exanthems in children: A great imitator. Clin Dermatol 2019;37(3):213-26.

This article is protected by copyright. All rights reserved

Accepted Article

31.Atanaskovic-Markovic M. What is new in beta-lactam allergy in children? Pediatr Allergy Immunol 2020; doi: 10.1111/pai.13375.

32. Mori F, Atanaskovic-Markovic M, Blanca-Lopez N, et al. A Multicenter Retrospective Study on Hypersensitivity Reactions to Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) in Children: A Report from the European Network on Drug Allergy (ENDA) Group. J Allergy Clin Immunol Pract 2020;8(3):1022-1031.e1

33.Atanasković-Marković M, Medjo B, Gavrović-Jankulović M, Ćirković Veličković T, Nikolić D, Nestorović B. Stevens-Johnson syndrome and toxic epidermal necrolysis in children. Pediatr Allergy Immunol 2013;24(7):645-9.

34. Zhang C, Van DN, Hieu C, Craig T. Drug-induced severe cutaneous adverse reactions: Determine the cause and prevention. Ann Allergy Asthma Immunol 2019;123(5):483-7.

35. Norton AE, Konvinse K, Phillips EJ, Broyles AD. Antibiotic Allergy in Pediatrics. Pediatrics 2018;141(5).

36.Singh S, Khandpur S, Arava S, et al. Assessment of histopathological features of maculopapular viral exanthem and drug-induced exanthem. J Cutan Patholo 2017;44(12):1038-48.

37.Muzumdar S, Rothe MJ, Grant-Kels JM. The rash with maculopapules and fever in children. Clin Dermatol 2019;37(2):119-28.

38.Demoly P, Adkinson NF, Brockow K, et al. International Consensus on drug allergy. Allergy 2014;69(4):420-37.

39.Graham F, Tsabouri S, Caubet JC. Hypersensitivity reactions to beta-lactams in children. Curr Opin Allergy Clin Immunol 2018;18(4):284-90.

40.Atanaskovic-Markovic M, Gomes E, Cernadas JR, et al. Diagnosis and management of drug-induced anaphylaxis in children: An EAACI position paper. Pediatr Allergy Immunol 2019;30(3):269-76.

41.Ibáñez MD, Rodríguez Del Río P, Lasa EM, et al. Prospective assessment of diagnostic tests for pediatric penicillin allergy: From clinical history to challenge tests. Ann Allergy Asthma Immunol 2018;121(2):235-44.e3.

42.Mill C, Primeau MN, Medoff E, et al. Assessing the Diagnostic Properties of a Graded Oral Provocation Challenge for the Diagnosis of Immediate and Nonimmediate Reactions to Amoxicillin in Children. JAMA pediatrics 2016;170(6):e160033.

This article is protected by copyright. All rights reserved

Accepted Article

43. Romano A, Atanaskovic-Markovic M, Barbaud A, et al. Towards a more precise diagnosis of hypersenzitivity to beta-lactams-an EAACI position paper. Allergy 2020;75(6):1300-1315.

44. Moral L, Caubet JC. Oral challenge without skin tests in children with non-severe beta-lactam hypersensitivity: Time to change the paradigm? Pediatr Allergy Immunol 2017;28(8):724-7.

45.Vezir E, Dibek Misirlioglu E, Civelek E, et al. Direct oral provocation tests in non-immediate mild cutaneous reactions related to beta-lactam antibiotics. Pediatr Allergy Immunol 2016;27(1):50-4.

46.Drago F, Ciccarese G, Gasparini G, et al. Contemporary infectious exanthems: an update. Future Microbiol 2017;12:171-93.

47. Torres MJ, Corzo JL, Leyva L, et al. Differences in the immunological responses in drug- and virus-induced cutaneous reactions in children. Blood Cells Molec Dis. 2003;30(1):124-131.

48. Posadas SJ, Leyva L, Torres MJ, et al. Subjects with allergic reactions to drugs show in vivo polarized patterns of cytokine expression depending on the chronology of the clinical reaction. J Allergy Clin Immunol. 2000;106(4):769-776.

49. Fernandez TD, Mayorga C, Torres MJ, et al. Cytokine and chemokine expression in the skin from patients with maculopapular exanthema to drugs. *Allergy*. 2008;63(6):712-719.

50.Bircher AJ. Uncomplicated drug-induced disseminated exanthemas. Chem Immunol Allergy 2012;97:79-97.

51.Guillon JM, Joly P, Autran B, et al. Minocycline-induced cell-mediated hypersensitivity pneumonitis. Ann Int Med 1992;117(6):476-81.

52.Gamboa PM, Garcia-Aviles MC, Urrutia I, Antepara I, Esparza R, Sanz ML. Basophil activation and sulfidoleukotriene production in patients with immediate allergy to betalactam antibiotics and negative skin tests. J Investig Allergol Clin Immunol 2004;14(4):278-83.

53.Aranda A, Mayorga C, Ariza A, et al. In vitro evaluation of IgE-mediated hypersensitivity reactions to quinolones. Allergy 2011;66(2):247-54.

54.Kuyucu S, Mori F, Atanaskovic-Markovic M, et al. Hypersensitivity reactions to non-betalactam antibiotics in children: an extensive review. Pediatr Allergy Immunol 2014;25(6):534-43.

This article is protected by copyright. All rights reserved

Accepted Article

55.Ben Said B, Berard F, Bienvenu J, Nicolas JF, Rozieres A. Usefulness of basophil activation tests for the diagnosis of IgE-mediated allergy to quinolones. Allergy 2010;65(4):535-6.
56.Pichler WJ, Tilch J. The lymphocyte transformation test in the diagnosis of drug hypersensitivity. Allergy 2004;59(8):809-20.
57.Beeler A, Zaccaria L, Kawabata T, Gerber BO, Pichler WJ. CD69 upregulation on T cells as an in vitro marker for delayed-type drug hypersensitivity. Allergy 2008;63(2):181-8.
58.Caubet JC, Frossard C, Fellay B, Eigenmann PA. Skin tests and in vitro allergy tests have a poor diagnostic value for benign skin rashes due to beta-lactams in children. Pediatr Allergy Immunol 2015;26(1):80-2.
59.Liccioli G, Mori F, Parronchi P, et al. Aetiopathogenesis of severe cutaneous adverse reactions (SCARs) in children: A 9-year experience in a tertiary care paediatric hospital setting. Clin Exp Allergy 2020;50(1):61-73.
60.Mayorga C, Ebo DG, Lang DM, et al. Controversies in drug allergy: In vitro testing. J Allergy Clin Immunol 2019;143(1):56-65.
61.Bergmann MM, Caubet JC. Role of in vivo and in vitro Tests in the Diagnosis of Severe Cutaneous Adverse Reactions (SCAR) to Drug. Curr Pharm Des 2019;25(36):3872-80.
62.Ortonne N, Valeyrie-Allanore L, Bastuji-Garin S, et al. Histopathology of drug rash with eosinophilia and systemic symptoms syndrome: a morphological and phenotypical study. Br J Dermatol 2015;173(1):50-8.
63.Naim M, Weyers W, Metze D. Histopathologic features of exanthematous drug eruptions of the macular and papular type. Am J Dermatopathol 2011;33(7):695-704.
64.Bellini V, Pelliccia S, Lisi P. Drug- and virus- or bacteria-induced exanthems: the role of immunohistochemical staining for cytokines in differential diagnosis. Dermatitis 2013;24(2):85-90.
65.Gerson D, Sriganeshan V, Alexis JB. Cutaneous drug eruptions: a 5-year experience. J Am Acad Dermatol 2008;59(6):995-9.
66.Wang EC, Lee JS, Tan AW, Tang MB. Fas-ligand staining in non-drug- and drug-induced maculopapular rashes. J Cutan Pathol 2011;38(2):196-201.
67.Pavlos R, Mallal S, Ostrov D, Pompeu Y, Phillips E. Fever, rash, and systemic symptoms: understanding the role of virus and HLA in severe cutaneous drug allergy. J Allergy Clin Immunol Pract 2014;2(1):21-33.

This article is protected by copyright. All rights reserved

Accepted Article

68.Noguera-Morel L, Hernandez-Martin A, Torrelo A. Cutaneous drug reactions in the pediatric population. Pediatr Clin North Am 2014;61(2):403-26.
69.Allmon A, Deane K, Martin KL. Common Skin Rashes in Children. Am Fam Physician 2015;92(3):211-6.
70.Peroni A, Colato C, Zanoni G, Girolomoni G. Urticarial lesions: if not urticaria, what else? The differential diagnosis of urticaria: part II. Systemic diseases. J Am Acad Dermatol 2010;62(4):557-70; quiz 71-2.
71.Ardern-Jones MR, Friedmann PS. Skin manifestations of drug allergy. Br J Clin Pharmacol 2011;71(5):672-83.
72. Paananen J, Fortino V.An omics perspective on drug target discovery platforms. Briefings in Bioinformatics 2020; 21(6):1937–1953.
73. Hasin Y, Seldin M, Lusis A. Multi-omics approaches to disease. Genome biology 2017;18(1):83.
74.Drago F, Paolino S, Rebora A, et al. The challenge of diagnosing atypical exanthems: a clinico-laboratory study. J Am Acad Dermatol 2012;67(6):1282-8.
75.Broliden K, Tolfvenstam T, Norbeck O. Clinical aspects of parvovirus B19 infection. J Int Med 2006;260(4):285-304.
76.Feder HM, Bennett N, Modlin JF. Atypical hand, foot, and mouth disease: a vesiculobullous eruption caused by Coxsackie virus A6. Lancet Infect Dis 2014;14(1):83-6.
77.Di Lernia V, Mansouri Y. Epstein-Barr virus and skin manifestations in childhood. Int J Dermatol 2013;52(10):1177-84.
78.Tsai J, Nagel MA, Gilden D. Skin rash in meningitis and meningoencephalitis. Neurology 2013;80(19):1808-11.
79.Kang JH. Febrile Illness with Skin Rashes. Infect Chemother 2015;47(3):155-66.
80.McKinnon HD Jr, Howard T. Evaluating the febrile patient with a rash. Am Fam Physician 2000;62(4):804-16.
81.Caputo R, Gelmetti C, Ermacora E, Gianni E, Silvestri A. Gianotti-Crosti syndrome: a retrospective analysis of 308 cases. J Am Acad Dermatol 1992;26(2 Pt 1):207-10.
82.Oberlin KE. Vesiculobullous and pustular diseases in newborns. Cutis 2017;100(4):E18-e21.
83.Patterson J, Sammon M, Garg M. Dengue, Zika and Chikungunya: Emerging Arboviruses in the New World. WestJEM 2016;17(6):671-9.

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Accepted Article

84.Miron D, Luder A, Horovitz Y, et al. Acute human parvovirus B-19 infection in hospitalized children: A serologic and molecular survey. Pediatr Infect Dis J 2006;25(10):898-901.
85.John CC, Niermann M, Sharon B, Peterson ML, Kranz DM, Schlievert PM. Staphylococcal toxic shock syndrome erythroderma is associated with superantigenicity and hypersensitivity. Clin Infect Dis 2009;49(12):1893-6.
86.Yawalkar N. Maculopapular Drug Eruptions. In Pichler WJ (ed). Drug Hypersensitivity, Basel, Karger 2007:242-50.
87.Heelan K, Shear NH. Cutaneous drug reactions in children: an update. Paediatr Drugs 2013;15(6):493-503.
88.Levy M, Koren G, Dupuis L, Read SE. Vancomycin-induced red man syndrome. Pediatrics 1990;86(4):572-80.
89.Spigarelli MG, Hurwitz ME, Nasr SZ. Hypersensitivity to inhaled TOBI following reaction to gentamicin. Pediatr Pulmonol 2002;33(4):311-4.
90.Blanca-López N, Andreu I, Torres Jaén MJ. Hypersensitivity reactions to quinolones. Curr Opin Allergy Clin Immunol 2011;11(4):285-91.
91.Barni S, Butti D, Mori F, et al. Azithromycin is more allergenic than clarithromycin in children with suspected hypersensitivity reaction to macrolides. J Investig Allergol Clin Immunol 2015;25(2):128-32.
92.Blanca-López N, Cornejo-García JA, Pérez-Alzate D, et al. Hypersensitivity Reactions to Nonsteroidal Anti-inflammatory Drugs in Children and Adolescents: Selective Reactions. J Investig Allergol Clin Immunol 2015;25(6):385-95.
93.Gold M, Goodwin H, Botham S, Burgess M, Nash M, Kempe A. Re-vaccination of 421 children with a past history of an adverse vaccine reaction in a special immunisation service. Arch Dis Child 2000;83(2):128-31.
94.Park J, Matsui D, Rieder MJ. Multiple antibiotic sensitivity syndrome in children. Can J Clin Pharmacol 2000;7(1):38-41.
95.Platt R, Dreis MW, Kennedy DL, Kuritsky JN. Serum sickness-like reactions to amoxicillin, cefaclor, cephalexin, and trimethoprim-sulfamethoxazole. J Infect Dis 1988;158(2): 474-7.
96.Quint T, Wöhrl S, Kinaciyan T. Fixed drug eruption caused by fluconazole-An underdiagnosed but recurrent problem. Contact Derm 2019;80(3):172-3.

This article is protected by copyright. All rights reserved

Accepted Article

97.Gómez-Traseira C, Rojas-Pérez-Ezquerra P, Sánchez-Morillas L, et al. Paracetamol-induced fixed drug eruption at an unusual site. Recent Pat Inflamm Allergy Drug Discov 2013;7(3):268-70.
98.Ott H. Hypersensitivity Reactions to Drugs. In Irvine AD, Hoeger PH, Yan AC (ed) Harper's Textbook of Pediatric Dermatology1,2 Blackwell Publishing Ltd 2011:183.1-183.14.
99.Clindamycin. Acute genralised exantematous pustulosis in a chiled:case repost. Reactions Weekly. 2015;1539(1):p98.
100.De A, Das S, Sarda A, Pal D, Biswas P. Acute Generalised Exanthematous Pustulosis: An Update. Indian J Dermatol 2018;63(1):22-9.
101.Zaouak A, Ben Salem F, Charfi O, Hammami H, Fenniche S. Acute generalized exanthematous pustulosis induced by terbinafine in a child confirmed by patch testing. Int J Dermatol 2019;58(2):e42-e3.
102.Coster A, Aerts O, Herman A, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome caused by first-line antituberculosis drugs: Two case reports and a review of the literature. Contact Derm 2019;81(5):325-31.
103.Maarouf M, Wickenheiser M, Krase JM, Wolter S, Shi VY. Trimethoprim-sulfamethoxazole-induced drug reaction with eosinophilia and systemic symptoms in a child with congenital renal disease. Pediatr Dermatol 2018;35(6):e391-e2.
104.Atanasković-Marković M, Janković J, Tmušić V, et al. Hypersensitivity reactions to antiepileptic drugs in children. Pediatr Allergy Immunol 2019;30(5):547-52.
105.Dewan AK, Quinonez RA. Allopurinol-induced DRESS syndrome in an adolescent patient. Pediatr Dermatol 2010;27(3):270-3.
106.Finkelstein Y, Soon GS, Acuna P, et al. Recurrence and outcomes of Stevens-Johnson syndrome and toxic epidermal necrolysis in children. Pediatrics 2011;128(4):723-8.
107.Kidon M, Blanca-Lopez N, Gomes E, et al. EAACI/ENDA Position Paper: Diagnosis and management of hypersensitivity reactions to non-steroidal anti-inflammatory drugs (NSAIDs) in children and adolescents. Pediatr Allergy Immunol 2018;29(5):469-80.
108.Schachner LA, Hansen RC. Pediatric dermatology. Churchill Livingstone (ed), Tapa dura 1988.
109.Morelli JG, Tay YK, Rogers M, Halbert A, Krafchik B, Weston WL. Fixed drug eruptions in children. J Pediatr 1999;134(3):365-7.

This article is protected by copyright. All rights reserved

Accepted Article

110.Weinborn M, Barbaud A, Truchetet F, Beurey P, Germain L, Cribier B. Histopathological study of six types of adverse cutaneous drug reactions using granulysin expression. Int JDermatol 2016;55(11):1225-33.

Table 1. Common causes and types of exanthema in children

Types	**Cause**	**Reference**
Viral		
Maculopapular eruptions	CMV	(46)
	Measles virus	(4, 30, 37)
	Rubella virus	(46)
	Roseola virus	(46)
	HHV6	(74)
	Zika virus	(37)
	Parvovirus B19	(75)
	Coxsackie virus (Hand, foot mouth disease)	(76)
	EBV(Infectious mononucleosis)	(77)
	West Nile virus	(78)
	Adenovirus	(79)
	Parainfluenza virus	(2)
Diffuse erythema with desquamation	Kawasaki disease	(79)
	Rubeola	(80)
Vesicobullous or pustular eruptions	Gianotti-Crosti syndrome	(30), (81)
	Varicella-zoster virus	(2)
	Herpes simplex virus	(82)
	Dengue fever	(83)
Urticarial eruptions	Adenovirus	(80)
	Parvovirus B19	(84)

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Bacterial		
Maculopapular eruptions	GAS (scarlet fever) *Rickettsia rickettsii* (Rocky Mountain spotted fever) *Neisseria meningitidis* (meningococcemia) *Mycoplasma pneumoniae* Chlamydia	(37) (78) (78) (79) (79)
Diffuse erythema with desquamation	Staphylococcal scalded skin syndrome Toxic shock syndrome	(30) (85)
Vesicobullous or pustular eruption	Impetigo	(30)
Urticarial eruptions	*Mycoplasma pneumoniae*	(11, 80)
Disease State		
Maculopapular eruption	Kawasaki disease	(37)
Erythematous rash	Autoimmune disease (SLE, dermatomyositis)	(85)
Purpuric rash	Henoch-Shönlein purpura	(30)
Drug (Time interval from intake to reaction)		
Exanthematous or morbilliform drug eruptions (4–14 days after start of use)	BL NSAIDs Antiepileptics Sulphonamides	(86, 87)
Urticarial Drug Eruptions (Typically within 1-6 hours)	BL Vancomycin Aminoglycosides Quinolones	(11) (88) (89) (90)

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	Sulphonamides Macrolides NSAIDs Vaccines	(54) (91) (92) (93)
Serum sickness-like Reactions *(7-21 days after start of use)*	BL (especially cefaclor) Macrolides Sulphonamides	(7, 35) (94) (95)
Fixed Drug Eruption *(30 minutes to 8 hours after readministration)*	BL Quinolones Fluconazole Sulphonamides Tetracyclines Paracetamol Antihistamines	(35) (90) (96) (4) (87) (97) (98)
Acute Generalized Exanthematous Pustulosis (AGEP) *(1–12 days after start of use)*	BL (especially aminopenicillins) Clindamycin Sulphonamides Quinolones Antifungals	(6, 35) (99) (100) (100) (101)
Drug reaction with eosinophilia and systemic symptoms (DRESS) *(2–8 weeks after start of use)*	BL Vancomycin Tetracyclines Rifampicin Sulphonamides Antiepileptics Allopurinol	(6, 30, 35) (59) (59) (102) (103) (104) (105)

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Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis (SJS/TEN) *(4–28 days after start of use)*	BL Sulphonamides Macrolides Antiepileptics NSAIDs	(6, 35, 59) (106) (59) (104) (107)

BL: Beta-Lactams, NSAIDs: nonsteroidal anti-inflammatory drugs**,** CMV: Cytomegalovirus, EBV: Epstein Barr virus, GAS: group A streptococcus, HHV6: Human herpes virus 6, SLE: systemic lupus erythematosus

Table 2: Clinical features of viral and drug induced exanthemas in children

	Viral induced	**Drug induced**	**Reference**
Prodromal symptoms	Fever Malaise	Pruritus Involvement of other systems	(2, 30)
Onset	Sudden	After exposure to a (new)drug	(37)
Areas of body affected	Central or peripheral	Whole body Same site (in case of fixed drug eruption)	(108) (109)
Pruritus	No	Yes	(87)
Morphology			(4, 30, 37, 110)
1. Appearance			
Topography	Central or peripheral	symmetrical	
Dermatomal distribution	Yes/No	No	
Extensor surfaces	Yes/No	Yes/No	
Mucosal involvement	Yes/No	Yes/No	

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2. Special features			
Colour	Bright red erythematous rose	erythematous	
Blanching	Yes/No	Yes	
Palpable	Yes/No	Yes	
Presence of petechiae	Yes/No	No	
Resolution	Without treatment	Usually 24-36 hours with treatment, up to 2 weeks after cessation of the drug involved	(36)
Complications	Bacterial superinfection	Life-threatening condition	(7, 30)

Figure 1. Algorithm of how to approach a patient with an exanthem

PCR: Polymerase chain reaction, DPT: Drug provocation test: DH: Drug hypersensitivity, SCARs: Severe Cutaneous Adverse Reactions

*contraindicated in SCARs

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Figure 1. Algorithm of how to approach a patient with an exanthem

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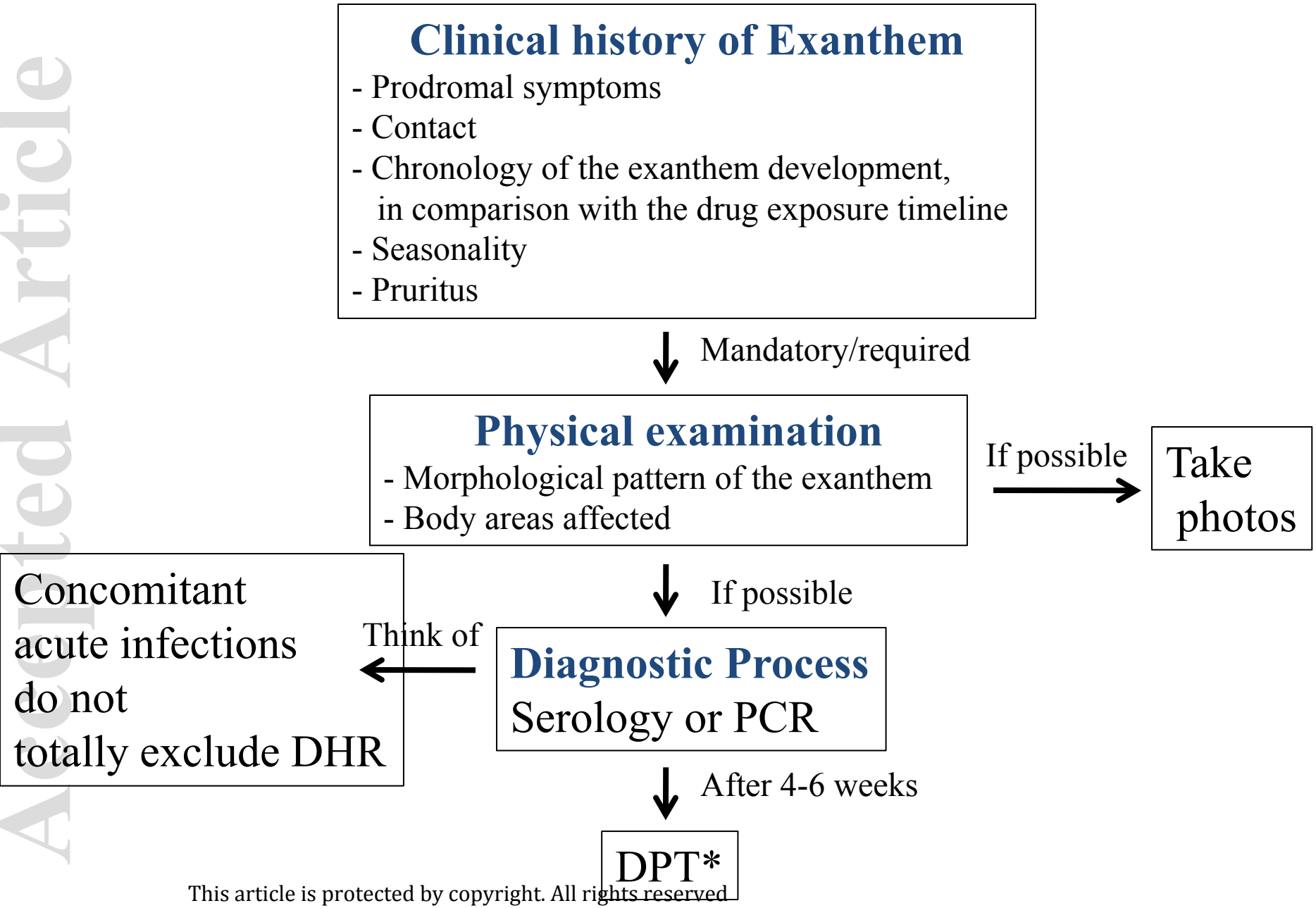

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PCR: Polymerase chain reaction, DPT: Drug provocation test: DH: Drug hypersensitivity, SCARs: Severe Cutaneous Adverse Reactions

*contraindicated in SCARs

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