AN OVERVIEW OF PEDIATRIC BULLOUS SKIN DISORDERS

Manar Ali Alghanim[1]*, Murad Mahmood Binjahlan[2], Ali Mudawi Alqahtani[3], Eman Hussain Alsaleh[4], Suliman Abdullah Alaqeel[5], Faris Aali Alotaibi[6], Waad Abdullah Aljubairah[7], Mushabbab Ali Al Alnuayr[3], Nidaa Qasem Khormi[8], Saleh Hashim Alrowaily[9], Sultan Alsharif [10], Ahmed Bushaybish Almehmadi [10], Amroo Khaled Noorelahi [10], Abdulghani Alzamzami [10]

ABSTRACT

Pediatric bullous skin disorders comprise a diverse group of conditions marked by blister formation on the skin, ranging in size and location. These disorders stem from various causes including genetic predispositions, immune system malfunctions, infections, and medication reactions. The appearance of blisters can be distressing, necessitating precise diagnosis and management strategies. Diagnosis involves a detailed medical history, comprehensive physical examination, and relevant laboratory tests to accurately identify and treat these dermatological conditions affecting children and adolescents. The physical examination is extensive, assessing not only the skin but also hair, nails, and mucous membranes for abnormalities. The classification of lesions into primary and secondary types, based on their origin and subsequent changes due to external factors, is critical for diagnosis. This study synthesizes information from a thorough literature review conducted across multiple databases and manual searches, highlighting the importance of microscopic examination, biopsy, and various laboratory tests in diagnosing skin diseases. It covers genetic disorders like epidermolysis bullosa, autoimmune conditions including bullous pemphigoid, alongside infectious diseases such as Impetigo and fungal infections.

Keywords: Pediatric bullous skin disorders, epidermolysis bullosa, bullous pemphigoid, impetigo, fungal infections

[1]* Primary Healthcare, Ministry of Health, Dammam, Saudi Arabia
[2] Department of Emergency Medicine, Mecca Health Cluster, Mecca, Saudi Arabia
[3] North of Farsha Primary Healthcare Center, Abha Primary Health Care, Aseer, Saudi Arabia
[4] Department of Emergency Medicine, Prince Saud bin Jalawi Hospital, Al Ahsa, Saudi Arabia
[5] Department of Family Medicine, Ministry of Health, Uyun Al Jawa, Saudi Arabia
[6] Alfaisaliah Primary Healthcare Center, King Fahad General Hospital, Jeddah, Saudi Arabia
[7] Department of Pediatrics, Maternity and Children Hospital, Al Ahsa, Saudi Arabia
[8] College of Medicine, Jazan University, Jazan, Saudi Arabia
[9] Department of Pediatrics, Maternity and Children Hospital, Arar, Saudi Arabia
[10] Department of Pediatrics, Al Thager Hospital, Jeddah, Saudi Arabia

***Corresponding Author:** Manar Ali Alghanim
*Primary Healthcare, Ministry of Health, Dammam, Saudi Arabia, Email: manaralghanim@outlook.com

DOI: 10.53555/ecb/2023.12.11.89

INTRODUCTION

Pediatric bullous disorders present a spectrum of conditions characterized by blistering on the skin, ranging from small to large sizes, potentially affecting any area of the body. These conditions can stem from a variety of causes including genetic factors, immune system dysregulation, infections, or reactions to medications, making accurate diagnosis and effective management crucial. The appearance of blisters in children can cause considerable concern, underscoring the importance of identifying the specific disorder to develop an appropriate treatment plan. Understanding the etiology and characteristics of these blisters is essential for healthcare providers to address the disorder effectively, ensuring the child's health and well-being. Proper diagnostic and therapeutic approaches are key to mitigating the impact of these conditions, facilitating better health outcomes for affected children and providing reassurance to their families amidst the challenges posed by pediatric bullous skin disorders (1, 2).

Diagnosing pediatric and adolescent dermatological conditions demands an integrated approach, encompassing an in-depth medical history, a meticulous physical examination, and requisite laboratory testing. Critical historical information vital for diagnosis includes the rash or lesion's onset, duration, changes over time, associated symptoms, and outcomes from any prior treatments. This detailed evaluation is paramount for the precise identification and management of skin disorders in young patients. By thoroughly understanding the history and clinical presentation, along with targeted diagnostic testing, healthcare providers can tailor treatment strategies effectively, addressing the unique challenges presented by skin conditions in this age group. This comprehensive diagnostic process is essential for ensuring accurate treatment and care for pediatric and adolescent patients facing various skin diseases (3).

Diagnosing skin conditions requires a multifaceted physical examination that goes well beyond simple visual inspection. This process includes the palpation of the skin to evaluate its texture and the structures beneath. Additionally, a thorough examination encompasses the assessment of the hair, nails, and mucous membranes for any abnormalities. Such comprehensive evaluations are essential for identifying subtle nuances that might indicate specific dermatological issues. It is imperative to accurately document these observations to monitor changes over time effectively. This meticulous record-keeping is fundamental for tracking the evolution or resolution of the skin condition across subsequent visits. By having detailed documentation, healthcare providers gain a deeper insight into the disease's trajectory, significantly enhancing the ability to make well-informed decisions about treatment options and overall patient care. This approach not only aids in the precise management of the condition but also supports a more personalized patient care plan, tailored to the individual's specific needs and the progression of their skin condition (4, 5).

METHODOLOGY

This study is based on a comprehensive literature search conducted on 5 March 2023, 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 pediatric bullous skin disorders. There were no restrictions on date, language, participant age, or type of publication.

DISCUSSION

The accurate identification and classification of skin lesions are crucial for diagnosing skin disorders. The diversity of dermatological terminology, while rich, can be complex due to variations in usage. Essential for both documentation and inter-clinician communication, the standardized terms covering the primary lesion type, secondary features, color, shape, and distribution, ensure a thorough examination and patient care **(Table 1)** (3). Diagnosing skin diseases often involves microscopic examination of skin scrapings and biopsies. Laboratory tests like auto-antibody titers, aldolase levels, cultures, creatine kinase, and serology tests including complete blood counts and metabolic panels, play a crucial role in diagnosis

Table. 1 Summarize dermatological findings for primary lesions, secondary lesions, color, and configuration (3).

Category	Lesion Type	Description
Primary Lesions	Macule	Flat, defined skin color change <1cm
	Patch	Large macule, >1cm in diameter
	Papule	Small, elevated, solid lesion <5mm across
	Plaque	Larger elevated area, diameter >5mm, characterized by width
	Nodule	Deeper, solid lesion, 5mm-2cm, extending into underlying tissue
	Tumor	Large nodule, diameter >2cm
	Pustule	Pus-filled elevation, originating from papules/vesicles
	Vesicle	Small, fluid-filled blister <5mm
	Bulla	Large vesicle, >5mm
	Wheal	Flat, raised area from skin edema, seen in allergic reactions
	Abscess	Pus-filled nodule/tumor
Secondary Lesions	Scale	Loose, superficial skin flakes
	Lichenification	Thickened skin with pronounced markings
	Crust	Dried serum/pus, forming scabs
	Erosion	Loss of the epidermis
	Ulcer	Deeper wound reaching the dermis
	Sinus	Tunnel in dermis opening to skin surface
	Atrophy	Skin thinning, loss of hair/glands
	Excoriation	Scratch marks
	Fissure	Deep cracks in skin
Color	Erythema	Red skin due to increased blood supply
	Purpura/Petechiae	Bleeding into the skin, small red/purple spots
	Hyperpigmentation	Darkened skin color
	Hypopigmentation	Skin color paler than normal
Configuration	Linear	Straight line pattern
	Herpetiform	Clustered pattern
	Annular	Ring-shaped
	Nummular	Coin-shaped
	Dermatomal	Nerve pathway distribution
	Photodistributed	Sun-exposed areas

Common pediatric bullous skin disorders

When introducing pediatric bullous skin disorders, it is helpful to categorize them based on their underlying causes. They may be genetic disorders, autoimmune disorders infectious disorders, fungal infections, and viral infections.

Genetic disorders

These are inherited conditions that children are born with. They are caused by genetic mutations that affect the skin's structure or function, leading to blister formation.

Epidermolysis Bullosa

Epidermolysis Bullosa (EB) is classified as a group of hereditary blistering disorders caused by genetic mutations affecting essential proteins within the basement membrane zone (BMZ). EB is categorized into four primary types, EB simplex (EBS), junctional EB (JEB), dystrophic EB (DEB), and Kindler syndrome (6). Typically, EB symptoms manifest at birth or during early childhood, with the late-onset subtype of JEB appearing between 5 to 8 years of age (1). Diagnosis is achieved through immunofluorescence antigen mapping,

transmission electron microscopy, and genetic analysis (6). The clinical features in both children and adults vary based on the EB subtype, with some complications developing over time, particularly in older individuals. Severe forms of EB are associated with complications like malnutrition, osteopenia, iron deficiency, and delayed growth, whereas milder forms may cause blisters primarily on hands and feet seasonally **(Figure 1)** (1). The likelihood of developing squamous cell carcinoma (SCC) significantly escalates in individuals with the generalized severe subtype of recessive DEB (RDEB), starting with a 7.5% risk by age 20 and increasing to 90% by age 55 (7). Similarly, the risk for melanoma is heightened in patients with RDEB, generalized severe, and EBS, generalized severe. Conditions such as Kindler syndrome and generalized EBS may see an improvement or reduction in blistering over time (6). Although there is no cure for EB, advancements are being made in treatment approaches (8), with management strategies for both children and adults focusing on wound care, infection prevention, and comprehensive multidisciplinary care. Trials with systemic therapies like phenytoin, tetracyclines, cyclosporine, and etanercept have shown some success (8). Specific therapies, including thalidomide and cyclosporine, have been effective against epidermolysis bullosa pruriginosa, while isotretinoin showed promise in a phase I trial for RDEB, potentially aiding in SCC chemoprevention despite causing increased skin fragility (1). Research into cell therapies, such as the use of allogeneic fibroblasts, mesenchymal stromal cells, bone marrow transplantation, and gene and protein therapies, continues to evolve.

Autoimmune disorders

Autoimmune bullous skin disorders occur when the body's immune system mistakenly attacks healthy cells, in this case, components of the skin (1). They encompass a range of conditions characterized by blister formation on the skin and mucous membranes, each with unique clinical features, pathogenetic mechanisms, and treatment strategies, supported by a diverse array of research and clinical findings **(Table 2).**

Table. 2 summarizes the characteristics, treatments, and outcomes of various autoimmune bullous skin disorders.

Disorder	Characteristics	Treatment & Outcomes	References
Paraneoplastic Pemphigus (PNP)	Associated with cancers. Severe stomatitis common. Childhood cases show lichenoid lesions.	Tumor removal improves skin lesions; limited success with adjuvant immunosuppressants.	(9-12)
Bullous Pemphigoid (BP)	Autoantibodies against BP antigens. Itchy, tense bullae. Pediatric cases have specific involvement patterns.	Steroids and dapsone. Other options include cyclosporine and mycophenolate mofetil.	(13, 14)
Mucous Membrane Pemphigoid (MMP)	Mucosal scarring. Heterogenous antigens.	Steroids, dapsone, azathioprine, erythromycin. Aggressive treatment for ocular disease.	(15-18)
Epidermolysis Bullosa Acquisita (EBA)	Blisters with potential scarring. More inflammatory in children.	Dapsone, steroids, and mycophenolate mofetil.	(1)
Linear Immunoglobulin A Bullous Dermatosis (LABD)	Subepidermal blisters. Mimics bullous pemphigoid in adults.	Dapsone as primary treatment. Options include sulfapyridine and corticosteroids.	(19-22)
Dermatitis Herpetiformis (DH)	Linked to celiac disease.	Gluten-free diet and dapsone for symptoms.	(1)
Pemphigus Vulgaris (PV)	Flaccid blisters and erosions. Autoantibodies to desmogleins.	Corticosteroids, azathioprine, mycophenolate mofetil, rituximab for severe cases.	(1)
Pemphigus Foliaceus (PF)	Cutaneous eruption without mucosal involvement.	Systemic corticosteroids and dapsone. Mycophenolate mofetil and rituximab also used.	(1)

Infectious disorders

They are caused by pathogens such as bacteria, viruses, or fungi that invade the skin and cause infections, leading to blister formation.

Bacterial infections

Impetigo

This common skin infection can manifest in two forms. The non-bullous type often starts with group A beta-hemolytic streptococci infection, quickly followed by *Staphylococcus aureus* colonization, usually after minor skin injuries like insect bites. It presents as small blisters or pustules that burst, creating a distinctive honey-colored crust. New lesions can emerge swiftly, especially in areas prone to moisture, such as the diaper region, where fungal or gram-negative bacterial superinfections may occur. Bullous impetigo, predominantly affecting children aged 2 to 5, features large, thin-walled blisters caused by *Staphylococcus aureus*-produced toxins. These blisters can break open, leaving crusty residues. While rare, complications can include cellulitis and acute post-streptococcal glomerulonephritis. Topical mupirocin is the usual treatment, except in cases with fever or poor patient compliance, where systemic antibiotics like dicloxacillin or clindamycin might be prescribed (23, 24).

Cellulitis and Erysipelas

Cellulitis involves the deeper skin layers, presenting as warm, tender, and red skin, often stemming from an entry wound. Erysipelas, however, affects the upper dermis and is marked by a raised, sharply defined red area, typically on the face or legs. Both conditions can exhibit fever and lymphadenopathy, with group A strep being a common cause. Oral antibiotics such as penicillin or erythromycin are effective treatments, with dicloxacillin offering additional staph protection. Severe infections might need intravenous (IV) antibiotics, and the most extreme cases, like necrotizing fasciitis, require urgent surgery and targeted IV therapy (3).

Erythema Chronicum Migrans

A hallmark of Lyme disease, this rash emerges days to weeks post-tick bite, expanding from a red spot into a large ring with central clearing. Lyme disease symptoms include fever and fatigue, and early treatment with amoxicillin or doxycycline is crucial for recovery (3).

Folliculitis

Commonly triggered by *Staphylococcus aureus*, this condition presents as small, red, pustular lesions often centered around hair follicles. Risk factors include friction and diabetes. Initial treatment involves topical antibiotics, with systemic antibiotics as a backup. Pseudomonas folliculitis, linked to hot tub use, features similar lesions confined to swimsuit areas and usually resolves without treatment, though severe cases may need oral ciprofloxacin. Hot tub maintenance is essential for prevention (3).

Fungal infections

Fungi are versatile organisms that can thrive in various environments. Fungal infections vary widely, with scalp infections being notably common in children, posing a risk of permanent hair loss if not promptly addressed. These infections include yeast infections caused by Candida and Malassezia, as well as dermatophyte infections known as tinea (25).

Viral infections

The presentation of viral infections can range widely, from localized conditions like papilloma virus-induced warts to the widespread skin manifestations of chicken pox from varicella virus infection. Warts are prevalent and typically harmless, falling into four main categories: the common wart (verruca vulgaris) the plantar wart (verruca plantaris), the flat wart (verruca plana), and the genital wart (condyloma accuminata). Notably, half of all common warts in children naturally disappear without any treatment (3). Warts are diagnosed based on medical history and the appearance of these recognizable growths. Common warts are often seen as verrucous papules on the hands or limbs, whereas plantar warts appear on the foot soles, disrupting skin lines and showing dark spots due to thrombosed vessels. Flat warts, typically painless, are flat papules or plaques that can be pink, flesh-toned, or slightly darker, usually found on the face. Genital warts present as flesh-colored or pink verrucous papules without symptoms. Differential diagnosis for genital warts includes conditions such as molluscum contagiosum and folliculitis. A 5% acetic acid application may turn genital warts white, although this test can give both false-positive and false-negative results. The most accurate method for identifying human papilloma virus (HPV) is through a DNA probe for HPV DNA. Treatments for warts vary, with many resolving on their own. Common warts may be treated with 17% salicylic acid applications or cryosurgery using liquid nitrogen. Plantar warts, challenging to remove, can be treated similarly or with CO2 laser vaporization for a 90% success chance. Reports indicate that imiquimod 5% cream, especially effective for genital warts, may also work well on the sole's thick

skin, particularly when combined with cryosurgery (26). Imiquimod is believed to stimulate immune responses, recommended to be applied three times weekly for up to 16 weeks. Flat warts may be treated with topical tretinoin cream twice daily. Podophyllin is the first-choice treatment for genital warts, achieving cure rates as high as 98%.34 Alternatives include liquid nitrogen cryosurgery, imiquimod, and CO2 laser, with up to a 97% cure rate (3). Molluscum Contagiosum is a poxvirus family infection, usually appearing as flesh-colored or pink papules with a central dimple on children's trunks and faces, or the genitals and inner thighs of sexually active people. It typically resolves on its own within 18 months. Treatment, more urgent for immunocompromised patients, can include papule curretage, liquid nitrogen cryosurgery, or incision and expression. Sexual health screenings are advised for genital lesions (3).

Particular consideration when treating pediatric patients

When administering medical treatment to pediatric patients, it is crucial to not only consider the standard side effects of medications but also to evaluate how these treatments might specifically impact children's growth and development. For example, the use of systemic corticosteroids is associated with delayed growth, and tetracyclines can lead to permanent discoloration of teeth. Another significant consideration is the impact of certain medications, like rituximab, on the immune system. Rituximab can affect the body's response to vaccine-preventable diseases, which is particularly relevant in the context of treating pediatric autoimmune bullous diseases (AIBD). Although the evidence is limited, existing literature suggests that rituximab's influence on B and T cells can impair vaccine effectiveness. Consequently, it is advised by experts to complete necessary vaccinations prior to initiating rituximab treatment if possible. If vaccination before rituximab treatment is not feasible, an optimal vaccine response may not be achieved until at least 6 months following the last dose of rituximab (1). This guidance underscores the importance of careful planning and consideration of immunization status in pediatric patients requiring rituximab or similar immune-modulating therapies.

CONCLUSION

Pediatric bullous skin disorders represent a complex group of conditions that require careful evaluation and management. The impact on affected children and their families can be significant, not only due to the physical symptoms but also because of the potential for long-term complications and the psychological impact of chronic skin conditions. Early and accurate diagnosis, followed by a tailored, multidisciplinary approach to treatment, is essential for optimizing outcomes and improving the quality of life for these patients.

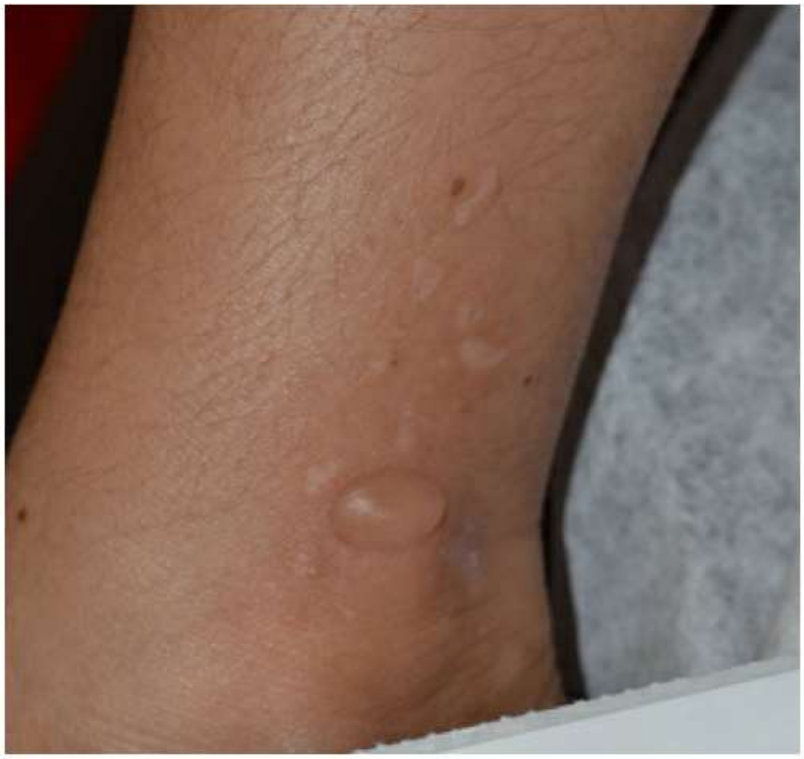

Figure 1. Generalized epidermolysis bullosa simplex (1).

REFERENCES

1. Schultz B, Hook K. Bullous diseases in children: a review of clinical features and treatment options. Pediatric Drugs. 2019;21(5):345-56.
2. Ashton R, Fassihi H. Pediatric Autoimmune Bullous Disease: A Literature Review and Update on Management. Pediatrics In Review. 2022;43(6):309-21.
3. Sanfilippo AM, Barrio V, Kulp-Shorten C, Callen JP. Common pediatric and adolescent skin conditions. Journal of Pediatric and Adolescent Gynecology. 2003;16(5):269-83.
4. Kasper DL, Fauci AS, Hauser SL, Longo DL, Jameson JL, Loscalzo J. General Examination of the Skin. Harrison's Manual of Medicine, 19e. New York, NY: McGraw-Hill Education; 2016.
5. Burgin S. Examining Scalp, Hair, Nails, Mucous Membranes, and Lymph Nodes. Guidebook to Dermatologic Diagnosis. New York, NY: McGraw-Hill Education; 2021.
6. Fine J-D, Bruckner-Tuderman L, Eady RAJ, Bauer EA, Bauer JW, Has C, et al. Inherited epidermolysis bullosa: Updated recommendations on diagnosis and classification. Journal of the American Academy of Dermatology. 2014;70(6):1103-26.
7. Fine J-D, Johnson LB, Weiner M, Li K-P, Suchindran C. Epidermolysis bullosa and the risk of life-threatening cancers: The National EB Registry experience, 1986-2006. Journal of the American Academy of Dermatology. 2009;60(2):203-11.
8. Rashidghamat E, McGrath JA. Novel and emerging therapies in the treatment of recessive dystrophic epidermolysis bullosa. Intractable & Rare Diseases Research. 2017;6(1):6-20.
9. Han S-P, Fu L-S, Chen L-J. Masked pemphigus among pediatric patients with Castleman's disease. International Journal of Rheumatic Diseases. 2019;22(1):121-31.
10. Ohzono A, Sogame R, Li X, Teye K, Tsuchisaka A, Numata S, et al. Clinical and immunological findings in 104 cases of paraneoplastic pemphigus. British Journal of Dermatology. 2015;173(6):1447-52.
11. Tsuchisaka A, Numata S, Teye K, Natsuaki Y, Kawakami T, Takeda Y, et al. Epiplakin Is a Paraneoplastic Pemphigus Autoantigen and Related to Bronchiolitis Obliterans in Japanese Patients. Journal of Investigative Dermatology. 2016;136(2):399-408.
12. Daneshpazhooh M, Moeineddin F, Kiani A, Naraghi ZS, Firooz A, Akhyani M, et al. Fatal Paraneoplastic Pemphigus After Removal of Castleman's Disease in a Child. Pediatric dermatology. 2012;29(5):656-7.
13. Waisbourd-Zinman O, Ben-Amitai D, Cohen AD, Feinmesser M, Mimouni D, Adir-Shani A, et al. Bullous pemphigoid in infancy: Clinical and epidemiologic characteristics. Journal of the American Academy of Dermatology. 2008;58(1):41-8.
14. Das D, Bandyopadhyay D. Juvenile pemphigoid nodularis: Report of a rare case. Indian Dermatology Online Journal. 2014;5(2):189-92.
15. Kharfi M, Khaled A, Anane R, Fazaa B, Kamoun MR. Early Onset Childhood Cicatricial Pemphigoid: A Case Report and Review of the Literature. Pediatric dermatology. 2010;27(2):119-24.
16. Kahn E, Spence Shishido A, Yancey KB, Lawley LP. Anti-Laminin-332 Mucous Membrane Pemphigoid in a 9-Year Old Girl. Pediatric dermatology. 2014;31(3):e76-e9.
17. Tavakolpour S. The role of intravenous immunoglobulin in treatment of mucous membrane pemphigoid: A review of literature. Journal of Research in Medical Sciences. 2016;21(1).
18. Maley A, Warren M, Haberman I, Swerlick R, Kharod-Dholakia B, Feldman R. Rituximab combined with conventional therapy versus conventional therapy alone for the treatment of mucous membrane pemphigoid (MMP). Journal of the American Academy of Dermatology. 2016;74(5):835-40.
19. Antiga E, Torchia D, Caproni M, Fabbri P. Linear immunoglobulin A bullous dermatosis. Expert Review of Dermatology. 2009;4(5):495-508.
20. Jabłońska S, Chorzelski TP, Rosinska D, Maciejowska E. Linear IgA bullous dermatosis of childhood (chronic bullous dermatosis of childhood). Clinics in dermatology. 1991;9(3):393-401.
21. Yamagami J, Nakamura Y, Nagao K, Funakoshi T, Takahashi H, Tanikawa A, et al. Vancomycin Mediates IgA Autoreactivity in Drug-Induced Linear IgA Bullous Dermatosis. Journal of Investigative Dermatology. 2018;138(7):1473-80.
22. Ho JCC, Ng PLP, Tan SH, Giam YC. Childhood Linear IgA Bullous Disease Triggered by Amoxicillin-Clavulanic Acid. Pediatric dermatology. 2007;24(5):E40-E3.
23. Wooldridge WE. Managing skin infections in children. Postgraduate medicine. 1991;89(4):109-12.
24. Scales JW, Fleischer AB, Krowchuk DP. Bullous impetigo. Archives of pediatrics & adolescent medicine. 1997;151(11):1168-9.

25. Berg D, Erickson P. Fungal skin infections in children: new developments and treatments. Postgraduate Medicine. 2001;110(1):83-94.
26. Sparling JD, Checketts SR, Chapman MS. Imiquimod for plantar and periungual warts. CUTIS-NEW YORK-. 2001;68(6):397-9.