Cutaneous manifestations suggestive of systemic diseases in pediatrics

N. Paredes Salfate*, L. Noguera Morel**

*Dermatologist. Valparaíso. Chile - **Dermatologist. Department of Dermatology. Hospital Universitario Infantil Niño Jesús. Madrid. Spain

Abstract

Cutaneous manifestations may be the first clue to an underlying systemic disease in childhood and, in some cases, may precede involvement of other organs. The aim of this review is to summarize the skin patterns with the greatest clinical value for raising suspicion of systemic disease in pediatric patients. The article addresses atypical urticarial lesions, purpura and vasculitis, cutaneous signs of rheumatologic disorders, mastocytosis with possible systemic involvement, and skin manifestations associated with systemic malignancies. Particular attention is given to warning signs, the main associated diseases, and the key elements of differential diagnosis. Initial complementary tests and referral criteria according to clinical suspicion are also outlined. Early recognition of specific skin patterns may shorten diagnostic delay, guide focused investigation, and help identify potentially serious conditions. A systematic dermatological examination should be considered an essential part of the comprehensive assessment of children with suspected systemic disease.

Resumen

Las manifestaciones cutáneas pueden constituir la primera pista de una enfermedad sistémica en la edad pediátrica y, en algunos casos, preceder a la afectación de otros órganos. El objetivo de este artículo es revisar los patrones cutáneos de mayor utilidad clínica para orientar la sospecha diagnóstica en pediatría. Se abordan lesiones urticariformes atípicas, púrpura y vasculitis, signos cutáneos de enfermedades reumatológicas, mastocitosis con potencial afectación sistémica y manifestaciones cutáneas de neoplasias malignas sistémicas. Se destacan los hallazgos semiológicos que deben alertar al pediatra, las principales entidades asociadas y las claves para el diagnóstico diferencial. Asimismo, se resumen las pruebas complementarias iniciales más útiles y los criterios de derivación según la sospecha clínica. El reconocimiento precoz de determinados patrones cutáneos permite acortar el tiempo diagnóstico, priorizar el estudio dirigido y detectar situaciones potencialmente graves. La exploración dermatológica sistemática debe formar parte de la valoración integral del niño con sospecha de enfermedad sistémica.

Key words: *Cutaneous manifestations; Systemic disease; Child; Vasculitis; Dermatoses.*

Palabras clave: Manifestaciones cutáneas; Enfermedad sistémica; Niño; Vasculitis; Dermatosis.

Introduction

Certain skin patterns in childhood may represent the first manifestation of a systemic disease and lead to an early diagnosis.

The skin, by virtue of its accessibility and extent, is an organ of great value in the recognition of systemic diseases with cutaneous expression. In pediatrics, certain dermatologic lesions can act as early markers of inflammatory, autoimmune, autoinflammatory, hematologic, neoplastic, or mast cell involvement, and may precede the appearance of manifestations in other organs. Their early identification can facilitate a timely diagnosis and avoid delays in the workup of potentially serious conditions.

This article reviews the cutaneous manifestations with the greatest clinical

Corresponding author: luceronoguera@gmail.com

OBJECTIVES

- To recognize the main skin patterns that may suggest systemic disease in childhood.
- To distinguish benign, self-limited cutaneous lesions from those that constitute warning signs.
- To identify the most characteristic dermatologic manifestations of vasculitis, rheumatologic diseases, mastocytosis, and systemic malignancies.
- To assess the role of the primary care pediatrician in the early detection and initial follow-up of these patients.

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value for suspecting systemic disease in childhood. The main lesional patterns, associated entities, warning features, differential diagnosis, and the initial approach available to the pediatrician are described, with particular attention to those situations that require priority or urgent referral[1].

We will now describe the main cutaneous manifestations to be considered in childhood for raising suspicion of a systemic condition.

Atypical urticarial lesions

Long-lasting, painful, or residual wheals, or wheals that are resistant to antihistamines, should raise suspicion of urticarial vasculitis and/or autoinflammatory syndromes.

Conventional urticaria is characterized by the appearance of wheals: erythematous, edematous lesions that blanch on pressure, are evanescent and pruritic, last less than 24 hours, and resolve without leaving residual lesions or hyperpigmentation. A duration longer than 24 hours or the presence of erythematous-violaceous macules that leave residual hyperpigmentation (Fig. 1) upon resolution should attract attention and raise the differential diagnosis of urticarial vasculitis[2].

Figure 1. Poorly defined residual brownish macule on the forearm.

Urticarial vasculitis (UV)

UV is a rare form of small-vessel vasculitis characterized by recurrent episodes of wheal- or hive-like lesions that persist for prolonged periods. In addition to their duration or the presence of residual lesions, other features may raise suspicion of UV:

- Lesions that do not blanch on pressure.
- A sensation of pain or burning at the lesions.
- Resistance to antihistamines.

Although it is usually idiopathic, it may be secondary to infections, medications such as NSAIDs, or appear in the context of rheumatologic diseases such as systemic lupus erythematosus (SLE)[3].

Unlike conventional urticaria, this condition results from inflammatory damage to the walls of dermal blood vessels, displaying a histopathologic pattern of leukocytoclastic vasculitis with fibrinoid necrosis and neutrophil-rich infiltrates[2]. The gold standard for confirming the diagnosis is skin biopsy, which allows identification of vascular inflammation and fibrinoid deposits.

It may occur with normal complement levels (normocomplementemic UV) or with low $C1_q$, C3, and C4 levels (hypocomplementemic UV)[2]; the latter may have systemic manifestations, such as fever, arthritis or arthralgia, ocular involvement including conjunctivitis, episcleritis, and uveitis, lymphadenopathy, and, in some cases, involvement of other organs such as the lungs, kidneys, heart, and central nervous system[3].

Urticaria in autoinflammatory diseases

Another feature to be considered in patients with urticaria is the duration of disease and the response to standard treatments such as antihistamines. In children, urticaria flares typically last less than 6 weeks to be considered acute urticaria; flares lasting more than 6 weeks should raise suspicion of chronic urticaria. Chronic urticaria may be idiopathic or may serve as a marker of systemic inflammatory disease.

If, in addition, the urticarial flares are recurrent and accompanied by symptoms and signs of systemic inflammation, such as fever and elevation of acute-phase reactants, a systemic autoinflammatory syndrome should be considered and ruled out[4].

Purpuric lesions and vasculitis

Palpable purpura, the presence of livedo, necrosis, or association with systemic features should raise suspicion of vasculitis or an underlying inflammatory disease.

The appearance of purpuric maculopapular lesions is the classic manifestation of vasculitis. IgA vasculitis (Henoch-Schönlein purpura) is the most common systemic vasculitis in childhood[5]. It is characterized by:

- Erythematous-violaceous purpuric or petechial macules and papules that do not disappear on pressure (non-blanching).
- A typical distribution on the lower extremities and buttocks, although in very young children it may involve the back and upper extremities.
- It may be associated with subcutaneous edema of the scalp, hands, and feet, especially in infants.

In addition to palpable purpura, patients often present with abdominal or joint pain, and there may be renal involvement with hematuria and/or proteinuria[5]. The classic tetrad consists of purpura, arthralgia/arthritis (especially of the knees and ankles), abdominal pain (which may be complicated by intussusception), and nephropathy.

Prognosis is determined by renal involvement, which occurs in 20-80% of children and is the most important prognostic factor. Follow-up with urinalysis and blood pressure monitoring is required for at least 6-12 months. Skin biopsy is not necessary in typical cases, but it is recommended for atypical eruptions in order to exclude other vasculitis[6].

Vasculitis in autoinflammatory diseases

The skin is frequently the first site of manifestation of complex genetic syndromes that present with vascular inflammation.

- Familial Mediterranean fever (FMF): associated with a higher frequency of vasculitis than the general population, particularly polyarteritis nodosa (PAN) and IgA vasculitis. PAN associated with FMF typically presents with subcutaneous nodules

Figure 2. Periungual erythema (**A**) with (**B**) dilated capillaries on dermoscopy.

and a much earlier age of onset than the idiopathic form[7].

- ADA2 deficiency (ADA2D): characterized by systemic small- and medium-vessel vasculopathy/vasculitis. The most common cutaneous manifestation is livedo racemosa (7074% of cases), followed by PAN-like cutaneous nodules.

Other significant pediatric vasculitis:

- Kawasaki disease: although it is a medium-vessel vasculitis, it manifests as a polymorphic exanthem, edema, and palmoplantar erythema with subsequent periungual desquamation.
- Polyarteritis nodosa (PAN): in children, it affects the skin and muscles, presenting with livedo reticularis, purpura, necrosis, and tender subcutaneous nodules along the course of vessels[8].
- Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis: these include granulomatosis with polyangiitis and microscopic polyangiitis; in children, they typically present with palpable purpura or a petechial eruption in nearly 50% of cases[8].
- Takayasu arteritis: a large-vessel vasculitis that in children may present with livedo reticularis, purpura, and erythema nodosum[8].

Characteristic manifestations of rheumatologic diseases

Certain skin lesions, such as the heliotrope rash, Gottron papules, or the malar rash, are key to the recognition of pediatric rheumatologic diseases.

In juvenile dermatomyositis there are pathognomonic lesions:

- Heliotrope rash: a violaceous or lilac discoloration of the upper eyelids, often accompanied by edema[9].
- Gottron papules: scaly, violaceous, or erythematous papules located symmetrically over the joints (knuckles, elbows, knees)[9].
- In addition, there are other signs, such as changes in the periungual fold (telangiectasias and thickened cuticles –Fig. 2–) and the shawl sign (erythema on the neck and shoulders).

In childhood-onset SLE, cutaneous manifestations (77%) are the second most common finding, after renal involvement (84%)[9].

- Malar rash: a butterfly-shaped erythema over the cheeks and bridge of the nose, sparing the nasolabial fold; it is the most frequent acute manifestation, present in 74% of pediatric cases[9].
- Subacute cutaneous lupus: less common in children, characterized by photosensitive annular or psoriasiform lesions, often associated with anti-Ro/SSA antibodies.
- Chronic discoid cutaneous lupus: erythematous-scaly plaques that may leave scarring lesions and scarring alopecia, usually located on sun-exposed areas.
- Patients may also present with photosensitivity, non-scarring alopecia, oral ulcers, vasculitic and purpuric lesions, and livedo reticularis or racemosa (Fig. 3) associated with systemic disease activity, and Raynaud phenomenon[8].

Neonatal lupus is uncommon; the lesions are usually transient and appear within the first weeks or months of life (before 4-6 months of age). The most characteristic finding is "raccoon eyes" periorbital erythema, with erythematous, sometimes scaly annular plaques (Fig. 4), predominantly on the face and scalp, and less so on the extremities and trunk. It occurs in 4-16% of children of mothers positive for anti-Ro/SSA or anti-La/SSB antibodies[10].

Mastocytosis

Cutaneous mastocytosis in children usually has a benign course, but certain clinical findings warrant assessment for systemic involvement.

Figure 3. Necrotic ulcer with livedo racemosa.

Figure 4. Annular lesions in an infant.

It is a clonal myeloid disorder defined by an increase and accumulation of mast cells in one or more organs[11], caused by somatic or germline (much less common) variants of the proto-oncogene *KIT1*[12]. The skin is the most frequently affected organ in childhood mastocytosis.

Cutaneous manifestations in children include two main forms; according to the classification proposed by Torrelo A et al., a hallmark feature of mastocytosis in young children is the Darier sign, which consists of the formation of a wheal or blister upon rubbing the lesion (Fig. 5)[13].

1. **Classic: adult type, mostly monomorphic.** One or multiple erythematous maculopapules, <5 mm, less prominent Darier sign, minimal or no blister formation, with few systemic symptoms. It may persist beyond adolescence, although 50-70% of cases regress spontaneously.

2. **Well-differentiated: pediatric type, mostly polymorphic.** One or multiple macules, papules, plaques, and nodules of red to brownish-tan color of variable size; it may even progress to erythroderma. The Darier sign is positive and easily inducible, with possible blister formation. Patients may present with systemic symptoms such as *flushing* and abdominal pain. It usually resolves during adolescence.

If the Darier sign is evident or reported by the parents, rubbing the skin lesions is not recommended; likewise, eliciting the Darier sign should be avoided in large skin lesions to prevent possible massive degranulation of dermal mast cells[13].

Cutaneous manifestations of systemic malignancies

Infiltrated violaceous lesions, cutaneous nodules, or a blueberry muffin-like rash may be the presenting feature of a systemic malignancy.

These manifestations are due to secondary skin infiltration or cutaneous metastasis; among them, the following stand out:

- Leukemia cutis: an uncommon presentation of extramedullary leukemia, occurring in 10-15% of children with acute myeloid leukemia (AML) and less frequently, in 5.8%[14] with acute lymphoblastic leukemia (ALL). It may present as maculopapules or nodules, isolated or diffuse, ranging in color from reddish-brown to violaceous, *blueberry muffin rash* in neonates, and gingival hyperplasia.
- Lymphoma cutis: usually a solitary plaque or nodule, erythematous and infiltrated, located on the head or neck. The most common types in children are non-Hodgkin lymphomas, such as high-grade B- or T-cell lymphomas. They may be accompanied by systemic symptoms such as fever, weight loss, or lymphadenopathy.
- Cutaneous metastases from solid tumors: in children, the most common are rhabdomyosarcoma and neuroblastoma, presenting as plaques, infiltrated nodules, or subcutaneous tumors, generally painless[15].

Table I summarizes the key lesions, the main suspected diagnosis, and the most useful initial actions in clinical practice.

Role of the Primary Care Pediatrician

The primary care (PC) pediatrician plays a fundamental role in the early detection, prioritization of the initial workup, and appropriate referral of children with suspected systemic disease.

When evaluating a child with skin lesions suggestive of systemic disease, the PC pediatrician should perform a focused history, assessing duration, the evanescent or persistent nature of the lesions, associated symptoms, fever, arthralgia, muscle weakness, abdominal pain, weight loss, lymphadenopathy, family history, and drug exposure. The examination should include an accurate morphologic description of the lesions, their distribution, the presence of purpura, livedo, edema, mucosal signs, and findings of extracutaneous involvement.

Depending on the clinical suspicion, an initial workup may be requested with complete blood count, blood chemistry, acute-phase reactants, urinalysis, and targeted immunologic or complementary tests. Priority or urgent referral should be made when there are extensive purpuric lesions, cutaneous necrosis, impaired general condition, suspicion of systemic vasculitis, signs of connective tissue disease, relevant systemic symptoms, or infiltrative lesions suggestive of hematologic or neoplastic disease.

In addition, the PC pediatrician is key to identifying warning signs, avoiding diagnostic delays, and coordinating initial follow-up with dermatology and other involved pediatric specialties.

Figure 5. A. Oval erythematous-brownish plaque. **B.** Erythema and edema over the plaque after rubbing the lesion: positive Darier sign.

Table I. Practical orientation table. Summary of the key lesions, the main suspected diagnosis, and the most useful initial actions in clinical practice

Skin pattern	*Warning clues*	*Main suspected diagnosis*	*Initial workup/referral*
Wheals >24 hours	Pain, residual pigmentation, and poor response to antihistamines	Urticarial vasculitis/ autoinflammation	Complete blood count, CRP/ESR, complement, urinalysis; consider biopsy and referral
Palpable purpura	Abdominal pain, arthralgia, hematuria, and necrosis	IgA vasculitis or other vasculitis	Complete blood count, coagulation, urinalysis, blood chemistry; renal follow-up and referral according to severity
Heliotrope rash/ Gottron papules/malar rash	Proximal weakness, photosensitivity, and oral ulcers	Juvenile dermatomyositis/ systemic lupus erythematosus	Creatine kinase, ANA, autoimmune panel; referral to rheumatology/ dermatology
Brownish lesions with Darier sign	Blisters, flushing, digestive symptoms, and organomegaly	Mastocytosis	Serum tryptase; referral if systemic symptoms are present
Infiltrated nodules/ blueberry muffin	Fever, lymphadenopathy, weight loss, and cytopenias	Systemic malignancy	Urgent workup and referral to pediatric hematooncology

Conflict of interest

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Statement on the use of artificial intelligence

A generative artificial intelligence tool was used solely to support the improvement of readability and linguistic revision of the manuscript. The authors reviewed, edited, and assumed final responsibility for the content.

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Asterisks indicate the level of interest of the article in the authors' opinion.

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A very useful review for differentiating urticarial vasculitis from common urticaria and guiding the initial workup of atypical wheals.

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A recommended article for its synthesis of the clinical features, renal prognosis, and follow-up of IgA vasculitis in childhood.
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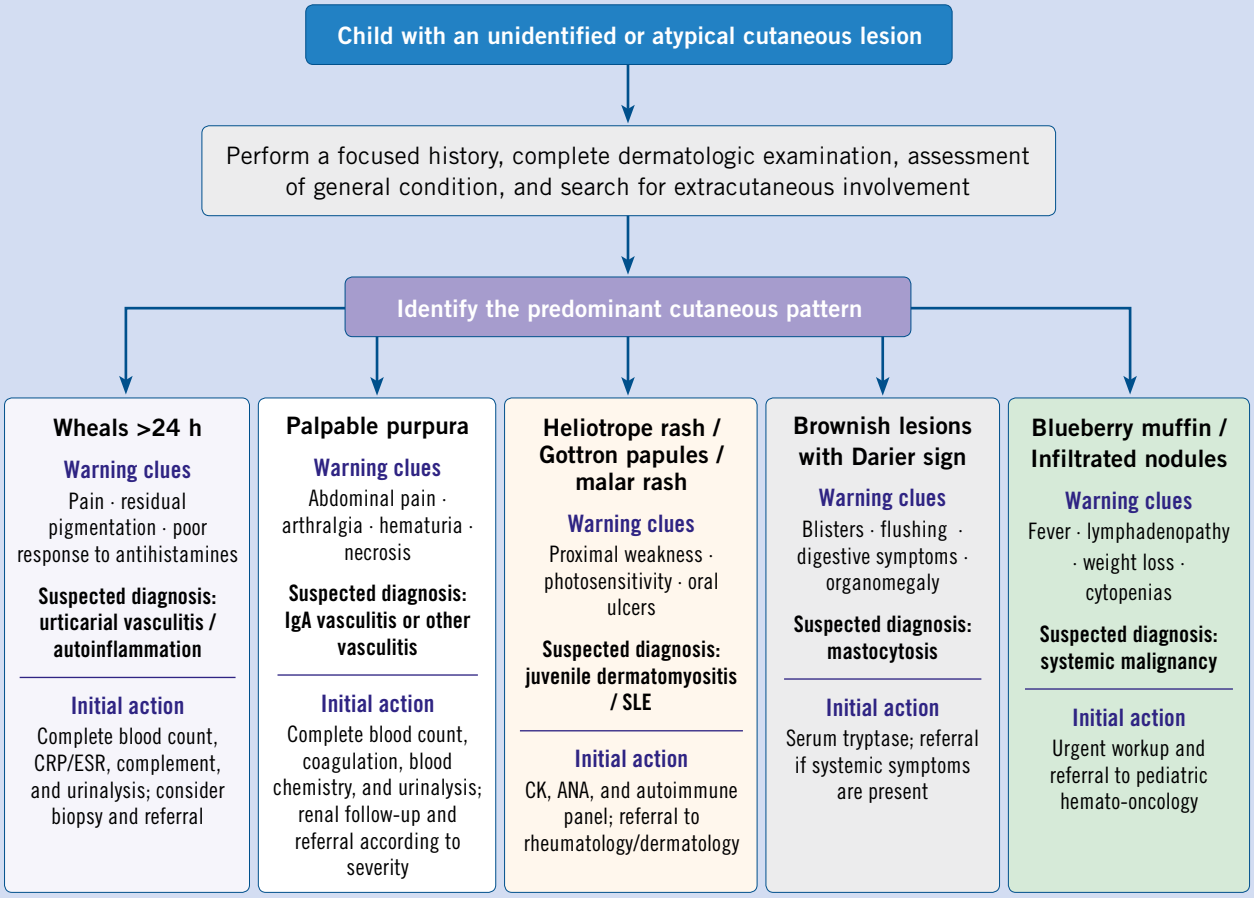
Reference of particular interest for understanding pediatric mastocytosis and its potential systemic implications.

Action algorithm for cutaneous manifestations suggestive of systemic disease in pediatrics
(Initial assessment guided by lesional pattern, warning signs, and targeted workup/referral)



Key idea: in the presence of warning signs or systemic involvement, prioritize targeted workup and specialist referral.

Accreditation quiz

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Clinical case

An 11-year-old girl with no relevant past medical history attends the clinic because of the appearance, over the past 10 days of red, swollen wheals on the abdomen, thighs, and legs, initially interpreted as urticaria. The mother provides photographs from the onset showing that the lesions persist for more than 24 hours, some are painful, and there are residual brownish patches from the first lesions that appeared. She reports pain in the ankles and wrists, low-grade fever, and increased fatigue. She has no respiratory difficulty or angioedema. She has been taking desloratadine 5 mg/day with no clear improvement.

On physical examination, edematous, ill-defined erythematous-violaceous plaques are observed, some with a faint purpuric center, located on the thighs, abdomen, and arms. They do not blanch completely on pressure. No frank joint swelling is noted, but there is pain on movement of both wrists and knees. In addition, brownish hyperpigmented macules are seen at sites where lesions had been present the previous week. There are no mucosal lesions or palpable lymphadenopathy.

Laboratory tests show a moderate elevation of acute-phase reactants and complement consumption. Urinalysis shows no abnormalities. A skin biopsy is performed, which reports leukocytoclastic vasculitis consistent with urticarial vasculitis.

Given the clinical presentation and laboratory findings, the etiologic workup is expanded to rule out an associated autoimmune disease, and the patient is referred to pediatric dermatology and rheumatology for joint evaluation and treatment.

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41. Which of the following findings is more suggestive of urticarial vasculitis than of conventional urticaria? Choose the CORRECT answer:

a. Intense pruritus with disappearance within a few hours.
b. Evanescent lesions without residual changes.
c. Painful wheals that persist for more than 24 hours.
d. Rapid response to antihistamines.
e. Associated dermographism.

42. Which of the following lesions is most characteristic of juvenile dermatomyositis? Choose the CORRECT answer:

a. Erythema nodosum.
b. Gottron papules.
c. Cholinergic urticaria.
d. Keratosis pilaris.
e. Grouped vesicles.

43. In a child with palpable purpura on the lower extremities, abdominal pain, and arthralgia, the most likely DIAGNOSIS is:

a. Cutaneous mastocytosis.
b. IgA vasculitis.
c. Acute urticaria.
d. Juvenile dermatomyositis.
e. Metastatic neuroblastoma.

44. Which of the following findings warrants assessment for systemic involvement in a child with cutaneous mastocytosis? Choose the CORRECT answer:

a. Isolated macules without symptoms.
b. Mild Darier sign.
c. *Flushing* of marked intensity and gastrointestinal symptoms.
d. Stable, small lesions.
e. Occasional pruritus.

45. Which cutaneous finding should particularly alert the clinician to a possible systemic malignancy? Choose the CORRECT answer:

a. Multiple molluscum contagiosum.
b. Eczematous plaques in flexural areas.
c. Infiltrated violaceous nodules associated with fever and lymphadenopathy.
d. Acute urticaria after a viral infection.
e. Common warts.

Clinical case

46. In the case presented, which CLINICAL FEATURE most strongly suggests the differential diagnosis with conventional urticaria?

a. Trunk location.
b. The absence of angioedema.
c. Persistence of the lesions for more than 24 hours with residual hyperpigmentation.
d. The patient's age.
e. The low-grade fever.

47. Which is the MOST USEFUL TEST to confirm the diagnosis in this context?

a. Patch test.
b. Skin biopsy.
c. Abdominal ultrasound.
d. Isolated ANA.
e. Chest X-ray.

48. Once the diagnosis is confirmed, which APPROACH is the most appropriate?

a. Continue antihistamines on demand only.
b. Perform no further studies if the patient improves.
c. Expand the etiologic workup and consider specialist referral.
d. Discontinue all medication and observe at home.
e. Start empirical antibiotics.

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