Rash with fever in children: a clinical approach

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Introduction

A febrile child with rash often presents a diagnostic challenge. Those providing healthcare for children need to know when this common symptom combination is a benign versus a more serious clinical presentation. With scrupulous, methodical history taking and careful serial physical examination, it is usually possible to make a diagnosis and choose an appropriate treatment. This article gives a brief overview of the common infectious and non-infectious conditions in children that present with fever and rashes and the tips as to how to easily identify them. The distinct morphological features and distribution of the rash along with a characteristic cluster of systemic features may give important clues to the likely cause. The importance of a thorough history cannot be over-emphasized.

A thorough history is vital and often leads to a diagnosis. The main points to be clarified are summarized in Box 1 (below).

Age

The age of the child can give some idea regarding probable aetiologies. Viral exanthema like measles, roseola infantum (Sixth disease), Epstein–Barr virus and enteroviral infections commonly occur in infants and children ≤3 years of age. Most cases of Kawasaki disease and Staphylococcal scalded skin syndrome also occur in children ≤5 years of age. The age of occurrence of Varicella, Rubella, and erythema infectiosum overlaps with these conditions, extending from 3 to 10 years of age.

Meningococcal septicaemia shows two peak ages of occurrence – the first in children ≤5 years and a second between 15 and 24 years. Systemic lupus erythematosus, juvenile dermatomyositis, rheumatic fever, polyarteritis nodosa and Wegener's granulomatosis usually affect older children (more than 6–7 years) while Henoch–Schönlein purpura (HSP) occurs between 2 and 8 years and systemic onset juvenile idiopathic arthritis is usually seen in children of less than 1 year of age.

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History taking in a child with a fever and rash

- onset
- duration and type of fever
- evolution of rash
- temporal association between fever and rash
- sequence of distribution of rash
- **blanching or non-blanching**
- associated symptoms suggestive of systemic illness
- presence of similar rashes in close contacts
- any contact with infection or travel abroad e.g. Dengue, ZIKA virus epidemic
- recent intake of medicines
- exposure to allergens, pets e.g. likely household triggers should be taken into account

Box 1

Examination

Careful physical examination entails close examination of the rash and salient features of systemic involvement. After careful examination of the systems, it is helpful to describe accurately the morphology and distribution of any rash. An accurate description of the primary and secondary features helps to establish the likely diagnosis (See Box 2). Examination should conclude with looking at lymph nodes, finger tips, genitalia, oral mucosa, nails, and hair. If mucosal involvement is apparent, then genitalia should also be examined. Systemic examination should look specifically for features like hepatosplenomegaly (Epstein Barr viral infection), heart murmurs (infective endocarditis, rheumatic fever) and include a targeted neurological examination.

Morphology

Some of the common conditions and the differential diagnoses based on morphology of rash are shown in Table 1.

Describing rashes

Primary features:

- Macule – non-palpable lesion <1 cm diameter
- Papule – palpable lesion <0.5 cm in diameter
- Patch – non-palpable lesion >1 cm diameter
- Nodule – palpable lump >0.5 cm in diameter
- Vesicle – blister <0.5 cm (containing clear fluid)
- Bulla – blister >0.5 cm
- Pustule – vesicle containing pus

Secondary features:

- Excoriation – scratch mark
- Lichenification – thickening of skin caused by rubbing
- Necrosis
- Scarring – usually secondary to trauma, skin may become stretched and atrophic, or raised within the site of trauma. If it is hypertrophic or extends beyond the original trauma, it is described as being *keloid*
- Erosion – partial loss of epidermis
- Ulcer – full thickness loss of epidermis

Box 2

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Rash morphology and likely causes in children with fever

Macular or maculopapular rash	Generally tend to be due to viral exanthem. Measles, Rubella, Dengue, Roseola infantum (Sixth disease), erythema infectiosum (Fifth disease), Epstein—Barr virus, Chikungunya fever, adenovirus, Enterovirus, Brucellosis, *Rickettsial* infections, SLE, systemic juvenile idiopathic arthritis. Drug Rash when associated with fever, check eosinophils and liver function tests.
Vesicular rash	*Varicella zoster*, *Herpes simplex*, enterovirus.
Petechial or purpuric rash	Meningococcal septicaemia, Dengue fever, Chikungunya fever, papular purpuric gloves and socks syndrome, Rickettsial infections, *Yersinia pestis*, *Borrelia*, *Bartonella*, HSP, cutaneous vasculitis.
Urticarial rash	Coxsackievirus, *Yersinia enterocolitica*, *Borrelia*, *Coxiella burnetti*, urticarial vasculitis.
Nodular rash	Erythema nodosum - seen in Tuberculosis, *Mycoplasma*, *Yersinia enterocolitica*, Fungal infections, *Bartonella*, sarcoidosis, inflammatory bowel disease.

Table 1

Petechial rashes

Petechiae are small (less than 3 mm) non-blanching intradermal haemorrhages. They are called purpura if larger than 3 mm. Petechiae with fever are often a cause of panic if a child presents to emergency care portals as they may indicate bacterial septicaemia. However, the most common causes of petechiae are viral illnesses. They also occur with malignancies and several vasculitides.

A child with petechial rash must be assessed thoroughly. Check the vital signs (heart rate, respiratory rate and temperature) and look for signs of shock (delayed capillary refill time, hypotension). Then assess for any signs of URTI, meningitis, or lymphadenopathy.

Palpable purpura

Any purpura which is raised or tender is suggestive of vasculitis, e.g. HSP. In the presence of typical features of HSP (abdominal pain, arthralgia and typical appearance/distribution) further investigation may not be required. If you suspect vasculitis from another cause then it is helpful to test antinuclear antibody (ANA), Complement C3 and C4, ASOT, DNAse B and undertake an urinanalysis.

Investigation of non-palpable petechial or purpuric rashes

Thrombocytopenia secondary to any pathology is a cause of petechiae. Investigations in petechial rashes should include full blood count (FBC), blood film and a coagulation screen (APTT/PTT).

In child with fever and petechial rash, it is important to maintain a high clinical suspicion for meningococcal infection. If suspected then blood should be sent for blood culture, blood glucose, CRP, blood gas, meningococcal PCR and intravenous antibiotics should be given without delay.

Associated clinical features

It cannot be emphasized enough that the type of rash and clinical features associated with the rash point to the diagnosis making confirmatory laboratory diagnosis unnecessary in many instances. An aetiological approach based on associated systemic features is given below (Table 2).

Relationship of rash with day of onset of fever

Fever often precedes the appearance of any rash. As a rough rule of thumb, the following mnemonic helps to correlate the day of fever and the rash which will help in diagnosis (Box 3).

Clinical features that help reach a diagnosis in children with fever and rash

a. Prodrome of upper respiratory tract infection	Measles, rubella, erythema infectiosum, roseola infantum, Varicella zoster, adenoviruses, coxsackievirus, EBV, scarlet fever
b. Fever of acute onset	Measles, rubella, erythema infectiosum, roseola infantum, Varicella zoster, adenoviruses, coxsackievirus, EBV, scarlet fever, toxic shock syndrome, meningococcemia, infective endocarditis, leptospirosis, Kawasaki disease, systemic onset juvenile idiopathic arthritis, rheumatic fever
c. Fever of insidious onset	SLE, juvenile dermatomyositis, polyarteritis nodosa, Wegener's granulomatosis
d. Relapsing fever	*Borrelia*, *Bartonella quintana*
e. Polyarthritis of small joints/myalgia	Chikungunya fever, Dengue fever, leptospira, systemic onset juvenile idiopathic arthritis, systemic lupus erythematosus, polyarteritis nodosa, juvenile dermatomyositis
g. Hepatosplenomegaly with lymphadenopathy	EBV, leptospirosis, *Borrelia*, Brucellosis
h. Hemorrhagic manifestations	Dengue fever, Chikungunya fever, meningococcemia, HSP
i. Multi-organ failure, hypotension, shock	Dengue fever, meningococcemia, toxic shock syndrome

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The timing of rash in feverish children can predict likely aetiology

Very **S**ick **P**atients **M**ust **T**ake **D**ouble **T**ablets	
Varicella	1st day of fever
Scarlet fever	2nd day of fever
Small **P**ox	3rd day of fever
Measles	4th day of fever
Typhus	5th day of fever
Dengue	6th day of fever
Typhoid	7th day of fever

Box 3

Prodrome of upper respiratory tract infection

A prodrome of malaise, fever, catarrhal symptoms and sore throat before the appearance of any rash usually suggests viral exanthema. Virological confirmation is not necessary and the pattern and distribution of the rash are often diagnostic (See Figures 1–4).

Diseases mimicking viral exanthema

Kawasaki Disease (KD) is often misdiagnosed as viral infection due to common features. This can be a serious issue as untreated KD may develop coronary aneurysms which may remain undiagnosed. KD is diagnosed by a set of clinical parameters without any specific laboratory investigation criteria. Absence of prodrome of respiratory symptoms, non-exudative conjunctivitis, distribution of the rash predominantly over the trunk, oedema over hands and feet with desquamation, and a raised ESR, help differentiate KD from viral infection. A high index of suspicion and experience is required to identify atypical cases of KD which

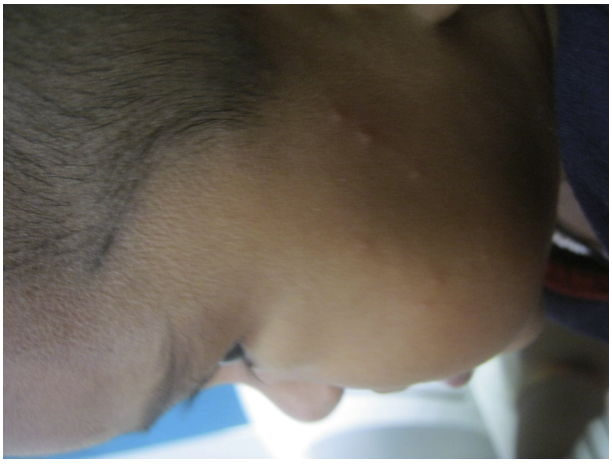

Figure 1 Hand Foot Mouth disease – Multiple discrete erythematous papules with surrounding erythema over face.

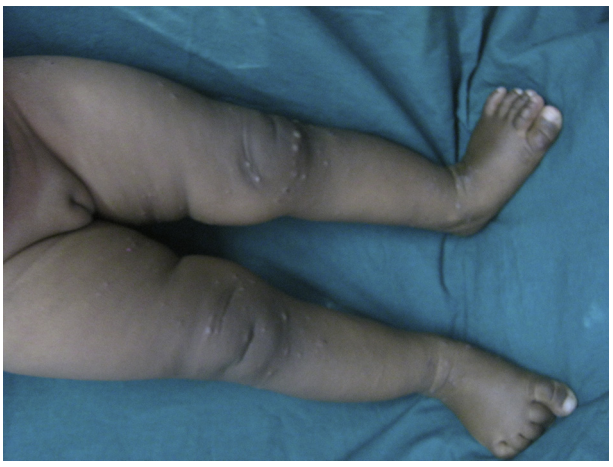

Figure 2 Over lower extremities.

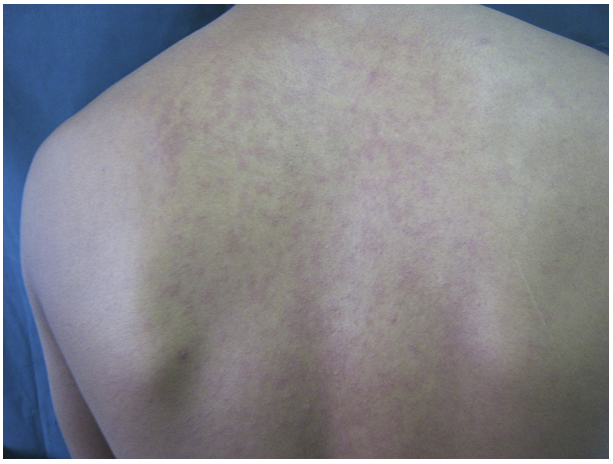

Figure 3 Diffuse erythematous morbilliform rash on the back.

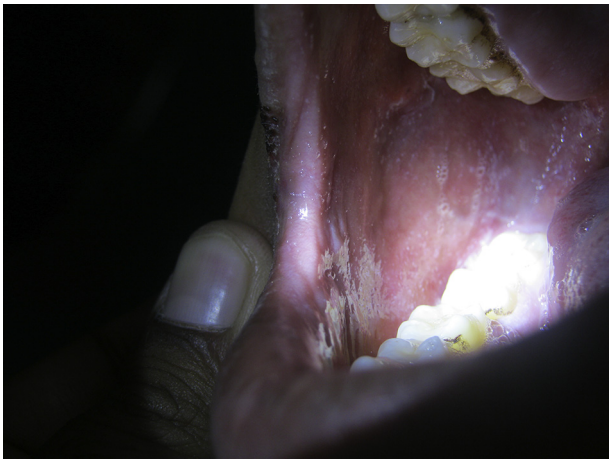

Figure 4 Kopliks spots.

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have fever with few of the characteristic clinical features, but are still at risk of developing coronary aneurysms.

Scarlet Fever (SF) is sometimes difficult to differentiate from KD, both having scarlatiniform rash and strawberry tongue. Absence of rapid clinical response to anti-Streptococcal antibiotics within 24–48 hours would go in favour of KD. The typical transient nature of rash with Koebner phenomenon differentiates systemic-onset juvenile idiopathic arthritis from viral exanthema, KD, leptospirosis, and SF. (Koebner phenomenon or isomorphic response refers to skin lesions appearing along lines of trauma/pressure).

Figure 5 Diffuse erythematous well defined to ill defined maculopapular rashes secondary to Phenytoin.

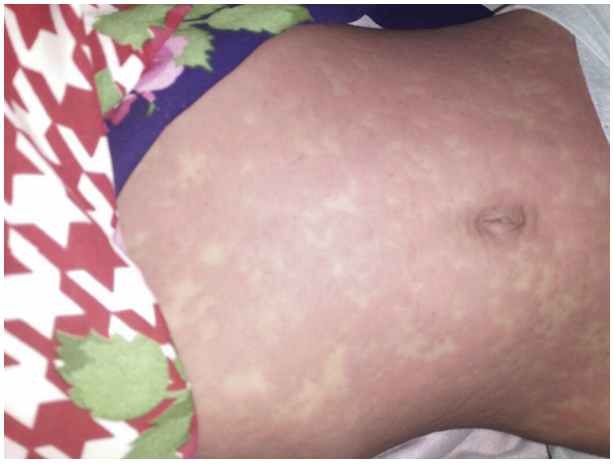

Figure 6 On abdomen.

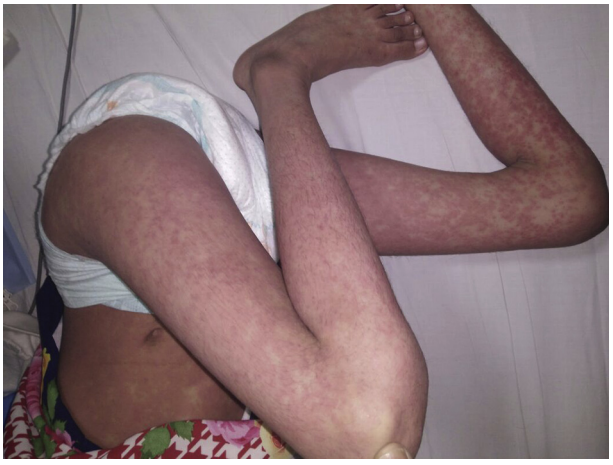

Figure 7 On lower extremities.

Drug-induced eruptions (Figures 5–7) are very common and are sometimes difficult to differentiate from viral exanthema. Even though the former are more likely to be urticarial, intensely erythematous and pruritic, they could also present with maculopapular rashes, vasculitis, bullae and erosions as in Toxic Epidermal Necrolysis (TEN) or Steven Johnson Syndrome.

DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) is another differential with extensive rash, fever, lymphadenopathy, haematological abnormalities, hepatitis, involvement of kidneys, lungs, heart and pancreas.

Steven Johnson Syndrome (SJS) which involves the skin and mucous membranes mimics SF or KD. In SJS, erythematous macules develop central necrosis resulting in vesicles, bullae, and denuded areas. Such vesiculo-bullous lesions are absent in SF or KD. TEN, also triggered by drugs, consists of sudden onset (within 24–48 hours) widespread blister formation, confluent or morbilliform erythema, skin tenderness, and positive Nikolsky's sign*. (**Nikolsky's sign is present when the outer epidermis separates easily from the basal layer on exertion of firm sliding manual pressure*).

A temporal relationship between appearance or worsening of rash and intake of drugs, morphology of the rash, its characteristic pruritic nature, and presence of eosinophilia in blood are suggestive of drug-induced rash. Sometimes biopsy can be helpful in confirming the diagnosis of a drug eruption.

Insidious onset fever

Insidious onset fever, relatively higher age of presentation, and characteristic distribution of rash allow easy identification of collagen vascular diseases. The commoner features are summarized in Table 3.

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Clinical features of collagen vascular diseases

SLE	a. malar (butterfly) rash over cheeks and nasal bridge
	b. non-deforming arthritis
	c. tendinitis
	d. serositis
	e. nephritis
	f. photosensitivity
	g. discoid lesions
	h. peri-ungal telangiectasia
	i. palatal or nasal mucosa erosions
	j. livedo reticularis
	k. Raynaud's phenomenon
	l. scarring alopecia
JD	a. periorbital violaceous heliotrope rash
	b. proximal myopathy
	c. dysphagia
	d. constipation
	e. Gottron papules over metacarpals, knees, and/or elbows
	f. oedema—periorbital/generalized
	g. calcinosis—later in course of disease
KD	a. persistent high 'spiking' fever (>5 days)
	b. bilateral non-exudative conjunctivitis
	c. lymphadenopathy
	d. cracked lips, strawberry tongue
	e. desquamation of fingers/toes in recovery phase
	f. coronary artery aneurysm
	g. erythema of palms and soles
	h. oedema of hands and feet
sJIA	a. faint, erythematous, salmon-coloured, macular rash
	b. Koebner phenomenon positive
	c. quotidian fever (many times a day)
	d. arthritis
	e. serositis

Fever with Rash Algorithm from Patient UK website.

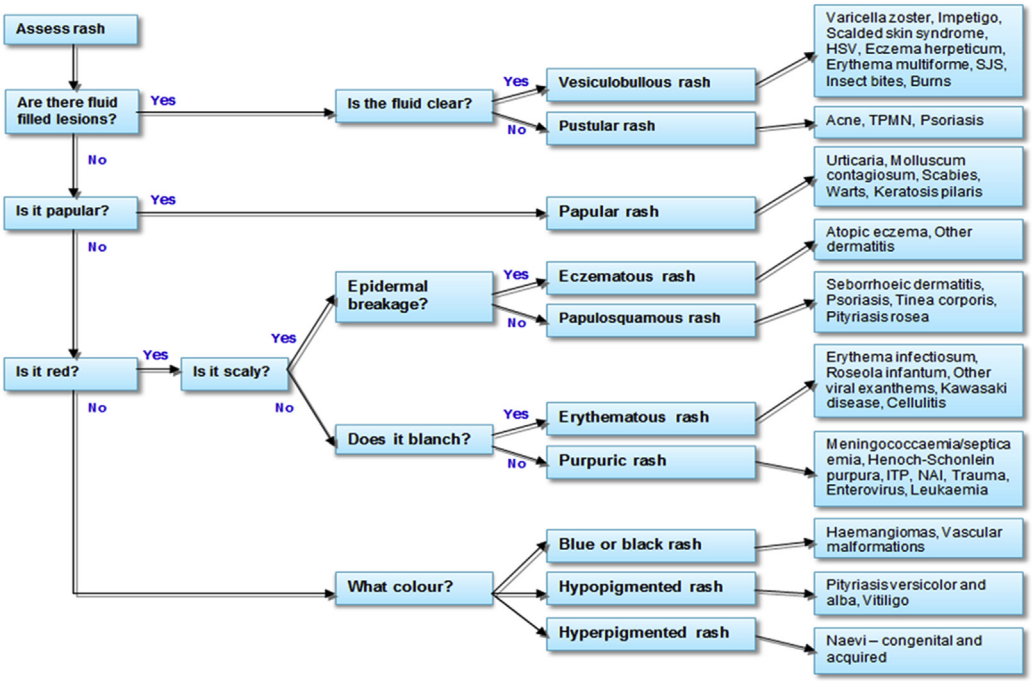

Table 3

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Conclusion

Fever presenting with rashes in children has a long list of possible diagnoses. A stepwise approach consisting of proper history taking, identifying the morphological type of lesion, and ultimately correlating these in the background of appropriate clinical milieu will go a long way in identifying the aetiology, ordering the appropriate investigations and management. ◆

FURTHER READING

1 Textbook of paediatric dermatology. 2nd edn. Arnold Oranje, NP: John Harper, 2006.

2 Kang JH. Febrile illness with skin rashes. *Infect Chemother* 2015; **47:** 155–66.

3 Sarkar R, Mishra K, Garg VK. Fever with rash in a child in India. *Indian J Dermatol Venereol Leprol* 2012; **78:** 251–62.

4 Ghosh SK, Bandyopadhyay D, Ghosh A, et al. Mucocutaneous features of hand, foot, and mouth disease: a reappraisal from an outbreak in Kolkata. *Indian J Dermatol Venereol Leprol* 2010; **76:** 564–6.

5 Drago F, Rampini E, Rebora A. Atypical exanthems: morphology and laboratory investigations may lead to an aetiological diagnosis in about 70% of cases. *Br J Dermatol* 2002; **147:** 255–60.

6 Keighley CL, Saunderson RB, Kok J, Dwyer DE. Viral exanthems. *Curr Opin Infect Dis* 2015; **28:** 139–50.

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