Review Article

Fever with rash in a child in India

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INTRODUCTION

Fever with exanthem is common in childhood and a cause of anxiety among parents. Many of them are benign viral exanthems without much clinical significance. Reassurance and supportive therapy are all that is needed in such cases. However, a physician must be aware of the distinguishing features of the serious illnesses which may be associated with major complications with substantial morbidity and mortality.

There are a large number of infectious and noninfectious conditions presenting as exanthematous fevers. Many of them have a characteristic combination of clinical features. The rash is also morphologically different in different diseases. This review attempts to give an overview of the causes, epidemiology, salient clinical features, and diagnostic clues of fever with rash in the pediatric age group, particularly in the Indian context.

The common causes of fever with rash in children are shown in Table 1.

EPIDEMIOLOGY

Viral exanthems are by far the most common cause of fever with rash in children.¹⁻³ There are a number of viruses causing various cutaneous manifestations associated with systemic symptoms. Rubeola or measles caused by a paramyxovirus is a major public health problem with significant mortality and morbidity, especially in developing countries.⁴ The incidence of the disease has declined substantially in industrialized countries.⁵ Measles is transmitted by droplet infection and commonly affects children between 6 months and 3 years of age, with a trend toward higher age group in the developed countries.⁶ In India, epidemics occur in winter and early spring. The number of cases have decreased (i.e., 40,840 cases and 44 deaths in 2009) in the country since the implementation of Universal Immunization Programme.

Another life-threatening exanthematous fever in children which deserves special mention is dengue fever. The arbovirus transmitted by Aedes aegypti mosquito causes explosive epidemics in the monsoon
Table 1: Common causes of fever with rash in a child

### Infectious Causes

#### Viral infections
- Measles, rubella, varicella, adenovirus, herpes simplex virus types 1 and 2, HHV-6, HHV-7, EBV, coxsackie, dengue, chikungunya, influenza A and B, hepatitis B, Lassa*, Marburg*, Ebola* Hantavirus*

#### Bacterial infections
- Staphylococcus aureus, Group A streptococcus, Neisseria meningitidis, Listeria monocyctogenes, Salmonella typhi, Yersinia pestis, Yersinia enterocolitica, Bartonella quintana, Borrelia, Leptospira

#### Rickettsial infections (diseases)
- R. prowazekii (Epidemic typhus), R. typhi (Murine typhus), R. tsutsugamushi (Scrub typhus), R. conorii (Indian tick typhus), R. rickettsii (Rocky mountain spotted fever), R. akari (rickettsial pox), Coxiella burnetti (Q fever), Rochalimaea quintana (Trench fever)

### Noninfectious Causes

#### Collagen vascular diseases
- Systemic juvenile rheumatoid arthritis, SLE, juvenile dermatomyositis, KD, HSP, polyarteritis nodosa, Wegener’s granulomatosis

#### Drug hypersensitivity rash
- SJS, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, leucocytoclastic vasculitis

*Not seen in India

season in India. There has been an increasing trend over the years with 15,509 cases, having a case fatality rate of 0.57 in 2009. The disease occurs in all ages and both sexes are equally affected.[8]

Another dengue-like illness is chikungunya fever, which is also transmitted by the same vector and in the same season. Its incidence is also on the rise in India with a massive epidemic occurring in 2006 affecting nearly 1.39 million cases spread over 213 districts in 15 states.[9–11]

On the other hand, most of the other viral exanthems are self-limiting without serious complications. Herpes simplex infections are ubiquitous without any seasonal variation. Infected individuals harbor latent infection responsible for recurrences, with highest seroprevalence seen in the developing countries.[12]

Varicella and rubella mainly affect children between 3 and 10 years of age, both being transmitted by droplet infection.[13,14] Human herpes virus 6 (HHV6) and Epstein–Barr virus (EBV) infections occur in infancy and early childhood.[2,15] By the end of the second year, almost 100% children are seropositive for HHV6.[3]

Both viruses are transmitted by contaminated saliva. Enteroviruses, known to cause numerous exanthems in children, occur round the year in tropical and subtropical areas. They are highly contagious, transmitted via contact with nasal/oral secretions, aerosol droplets and fecal material. Infants less than 1 year of age account for more than 25% of the cases with high incidences seen among male sex and conditions with poor hygiene and low socioeconomic status. Epidemics of hand foot and mouth disease (HFMD) are caused by coxsackievirus A16 or Enterovirus71, whereas coxsackievirus A9, A10, B1, through B3 and B5 cause sporadic cases.[14]

Parvovirus B19 infections occur mainly in winter and spring transmitted via respiratory droplets. The classic exanthem of this virus is erythema infectiosum (EI) which is most common between 4 and 10 years of age. The other exanthem caused by the same virus is Poplar purpuric gloves and socks syndrome (PGS), which occurs mainly in young adults.[2]

Cutaneous eruptions with fever also occur in many bacterial infections. Children are known to have various staphylococcal skin infections without much clinical significance. However, staphylococcal scalded skin syndrome (SSSS) and toxic shock syndrome (TSS) are potentially fatal conditions caused by the same organism. SSSS or Ritter’s disease occurs predominantly in infants and children less than 5 years of age. TSS occurs mostly in menstruating girls between 15 and 25 years, but is also seen in nonmenstruating girls and children where the infection occurs from nasal packs, wounds, sinusitis, tracheitis, etc.[16]

Group A streptococci (GAS) is responsible for causing scarlet fever (SF), erysipelas, and acute rheumatic fever (RF), each of which is associated with high fever and characteristic rash.[17] The incidence of SF is maximum between 2 and 10 years,[18,19] RF affecting children between 5 and 15 years of age has been reported to occur in 1–3% of those with prior streptococcal infections.[20]

The incidence of endemic meningococcal disease is low in India with occasional outbreaks, mainly in the cities of north India, usually occurring in winter and almost always caused by the serogroup A.[21,22] Highest incidence is seen in children younger than 5 years with a second peak between 15 and 24 years. Most infections are acquired from a colonized adult or a patient with meningococcal disease.[23–25]
Leptospirosis has been known to occur in India since long, especially in areas with heavy monsoon, animal rearing practices, and unplanned urbanization.[26-30] Outbreaks have been reported from Orissa after the supercyclone in 1999 and from Mumbai in 2000 and 2005.[25] As many as 232 cases have been reported from a hospital in north India between 2004 and 2008.[26] Children usually acquire this infection by direct or indirect contact with urine of infected dogs.[28]

A discussion on infectious causes of fever with rash is incomplete without mentioning the myriad of rickettsial diseases [Table 1], which are largely underdiagnosed, but are an important cause of febrile rash in children in India.[51-33] Transmission can be via mites, rat fleas,ouse, or tick.

Noninfectious causes of febrile rash include drug eruptions and collagen vascular diseases (CVD). Adverse cutaneous drug eruptions occur in approximately 2–3% of hospitalized patients.[34,35] Most of them are mild and self-limited, resolving with the withdrawal of the offending drug. Severe and potentially life-threatening eruptions occur in approximately 1 in 1000 hospitalized patients.[36] Of these, toxic epidermal necrolysis (TEN) has been reported to have high mortality rates ranging from 20 to 70%.[37]

Notable among the CVD are systemic lupus erythematosus (SLE), systemic onset juvenile chronic arthritis (sJCA), and vasculitis. Lupus has a female preponderance, female to male ratio being 4:1 before puberty and 8:1 after puberty. Onset of the disease is usually after 8 years and its prevalence varies from 4 to 250/1,00,000.[38] sJCA is commonly seen in young children often less than 1 year of age with no sex predilection.[39] Among the vasculitides, Kawasaki disease (KD) and Henoch–Schonlein purpura (HSP) are worthy of mention. KD has increasingly been reported from different parts of the world since its first publication in English medical literature in 1974.[40] Prevalence of KD is highest among Asians, intermediate in blacks, and lowest in whites.[41-43] 85% of the cases are below 5 years of age. It is underreported in India,[44,45] the true incidence is expected to be higher and there are increasing reports from centers in India that KD has replaced HSP as the commonest vasculitic disorder in hospitalized children.[46,47] HSP is a common cause of hospital admission in children with an overall estimated incidence of 9/100,000, with a peak age of 2–8 years and male to female ratio of 2:1.[48,49] The other CVD like juvenile dermatomyositis (JD), Wegener’s granulomatosis (WG), and polyarteritis nodosa (PAN) are relatively less common. The occurrence of JD and WG in girls is two to three times more common than boys with a mean age of 6–7 years.[50,51] PAN occurs equally in boys and girls with a mean age of 9 years.[52]

**CLINICAL FEATURES**

Many of the above mentioned causes have a characteristic combination of signs and symptoms. Measles is characterized by a distinct prodromal phase with fever, rhinorrhea, cough, and conjunctival congestion. Koplik spots consisting of gray white sand-like lesions with surrounding erythema in the buccal mucosa opposite the lower second molar tooth are pathognomonic. Erythematous, confluent, maculopapular rash develops usually on the fourth day of fever, beginning behind the ears and forehead and progressing downward. The rash resolves in the same order with residual brownish discoloration and desquamation which fades over the next 10 days.[53]

The rash of rubella consists of minute, discrete macules, in contrast to the confluent rash of measles. The rash appears within 24 hours of onset prodromal symptoms, spreads rapidly from face to trunk and extremities and disappears altogether by the third day. Posterior cervical and postauricular lymphadenopathy, although not pathognomonic, is commonly seen.[13,14]

On the other hand, the rash of varicella occurs in crops, which evolves through the stages of macule, papule, vesicle, and crusts involving mainly the trunk and proximal end of extremities [Figure 1]. Fever subsides 2–4 days after appearance of rash and the rash disappears after 3–7 days, leaving behind hypo- or hyperpigmented macules persisting for days to weeks.[13,54]

In infectious mononucleosis, fever, pharyngeal inflammation, generalized lymphadenopathy, and hepatosplenomegaly are associated with a maculopapular rash which may take the form of erythema multiforme or urticaria. The exanthem occurs in 3–13% of cases and increases to 50% if treated with ampicillin or amoxicillin.[15,55,56]

Children with dengue fever present with sudden onset of high grade fever associated with facial flushing,
headache, myalgia, arthralgia, and abdominal pain. Within 48 hours of onset of fever, a transient generalized macular rash develops. Fever may subside after 2–7 days, only to reappear after 1–2 days, demonstrating the typical biphasic pattern. The critical phase begins at defervescence, marked by some warning signs like intense abdominal pain, persistent vomiting, mucosal bleeding, clinical fluid accumulation, lethargy, and tender hepatomegaly. This second phase is associated with a generalized morbilliform maculopapular rash sparing the palms and soles [Figure 2]. The extent of plasma leakage decides whether patient recovers from this phase or progresses to the next phase of severe dengue. Severe dengue is defined by one or more of the following: (a) shock from plasma leakage; (b) severe bleeding; and (c) severe organ impairment.\(^{(37,38)}\)

Chikungunya fever is characterized by high fever with rigors, accompanied by intense joint pain, headache, myalgia, and rash. The arthritis is polyarticular, migratory involving small joints. The joint pain tends to persist for long. The rash is itchy, transient, maculopapular, distributed over trunk, and extremities, appearing 4–8 days after fever and arthritis.\(^{(39–41,56)}\)

The lesions of herpes simplex types 1 and 2 are in the form of single or grouped vesicles varying from 2 to 10 mm, on a mildly erythematous base. Fever blisters are the most common presentation of recurrent HSV-1 infection, primarily seen over lips, nose, chin, cheek, or oral mucosa. Occasionally, erythema multiforme or Steven–Johnson Syndrome may be seen.\(^{(12,53)}\)

Children infected with HHV6 exhibit a sudden high fever lasting for 3–5 days. With cessation of fever, discrete macular or maculopapular rash erupt, known as exanthem subitum (ES), over neck and trunk which begins to disappear in a few hours. These children have a 10% risk of febrile convulsions. Pityriasis rosea (PR), commonly affecting adolescents and young adults, has been considered to be associated with HHV6 and HHV7. After a prodromal period, the rash begins with a primary or “herald patch.” Within 1–2 weeks, morphologically identical but smaller lesions appear on the trunk and proximal extremities. The lesions are distributed along the lines of cleavage and have a ring of scales surrounding them.\(^{(2,3)}\)

Erythema infectiosum (EI) caused by Parvovirus B19 is seen as a homogenous erythema over the cheeks demonstrating the typical “slapped cheek” appearance, associated with a reticulate maculopapular rash over the proximal extremities and occasionally over distal extremities and trunk. The rash undergoes repeated fading and recurrence triggered by local irritants, high temperature, and emotional stress. Parvovirus B19 also causes PPGS which consists of edema and erythema of both hands and feet with associated petechiae and purpura. The eruption may extend on to dorsal surfaces but ends abruptly at wrists and ankles and is frequently associated with burning and itching. Oral erosions, vesicles, lip edema, and petechiae over hard palate, pharynx, and tongue may also be seen.\(^{(11,3,14,54)}\)

Enteroviruses are responsible for a large number of exanthems. HFM disease is most common. After a prodrome of 2–4 days, large (2–8 mm), oval, gray blisters with erythematous base develop over hands, feet, and buttocks. Painful aphthous ulcers are seen in the mouth. The rash resolves in 5–7 days.\(^{(14,54)}\)

Gianotti–Crosti syndrome, also called papular acrodermatitis of childhood, affects children between 1 and 6 years of age. Many viruses have been implicated to cause this disease, namely hepatitis B, EBV, cytomegalovirus, and coxsackievirus. The rash that follows a prodrome of fever and respiratory symptoms is composed of symmetric, homogenous, flat-topped pink-brown papules distributed classically on cheeks, extensor extremities, and buttocks. Hemorrhagic or moist eczematous papules may also be seen. The rash lasts for around 15–20 days, sometimes longer.\(^{(1,2,14)}\)

Staphylococcal infections in children range from furuncles, carbuncles, folliculitis, bullous impetigo (which may or may not be associated with fever) to TSS and SSSS (which are associated with high temperatures). TSS is an acute multisystem disease characterized by high fever, vomiting, diarrhea, conjunctival congestion, strawberry tongue and diffuse, dark, and sunburn-like rash. This is accompanied by altered sensorium, disseminated intravascular coagulation, and hypotension. Symptoms resolve by 7–10 days, associated with desquamation of palms and soles. SSSS affecting predominantly children below 5 years consists of a scarlatiniform erythema transforming into a wrinkled paper appearance with peeling of large sheets of epidermis. Healing occurs within 10–15 days without scarring.\(^{(10,60,61)}\)

SF caused by GAS is characterized by a rash and strawberry tongue appearing 1–2 days after an upper
respiratory tract infection. The rash is typically diffuse, erythematous, blanchable, and finely papular (like sandpaper) beginning around the neck spreading over trunk and extremities, sparing the face. The rash fades with desquamation after 3–4 days.\textsuperscript{[18,19]} Erysipelas, also caused by GAS, is a well-circumscribed, indurated, tender rash arising abruptly with high fever. Erythema marginatum is one of the major diagnostic criteria of acute RF, which is a nonsuppurative complication of prior GAS infection. The rash consists of erythematous, serpiginous, macular, nonpruritic rash with central pallor, primarily occurring over trunk and extremities, sparing the face.\textsuperscript{[17]}

Enterococcal and viridans group of streptococci are known causes of bacterial endocarditis, cutaneous manifestations of which include petechiae, splinter hemorrhages, Osler’s nodes, and Janeway’s spots.\textsuperscript{[53]}

Meningococcemia is characterized mainly by fever with petechiae, but other transient lesions resembling a viral maculopapular rash may also be seen. The petechiae are often raised with a “smudged” appearance involving trunk and extremities. Gangrenous hemorrhagic areas resembling purpura fulminans are seen in fulminant meningococcemia which is also associated with adrenal hemorrhage, hypotension, multiorgan failure (MOF) with or without meningitis.\textsuperscript{[21-23,25,62]}

Disease with \textit{Yersinia enterocolitica} manifests as diarrhea and enterocolitis and infrequently septicemia. Erythema nodosum, arthritis, and uveitis may develop as reactive complications. Septicemic plague caused by \textit{Yersinia pestis} presents with initial generalized erythema followed by petechiae and purpura.\textsuperscript{[63]}

The clinical features of leptospirosis encompass a wide spectrum ranging from asymptomatic infection at one extreme to MOF at the other. Symptomatic children present with a biphasic pattern, beginning with abrupt onset of high fever with chills, headache, severe tenderness over lower half of the body, conjunctival suffusion, hepatosplenomegaly (HSM), and generalized lymphadenopathy (LAD). After a brief period of well-being, the second phase occurs characterized by a transient (<24 hours) rash in 10% of cases. The rash may be urticarial, petechial-purpurial or desquamating type. Meningitis and uveitis may occur in this phase.\textsuperscript{[64,65]}

Borrelia infections are known to cause fever with rash. Notable among them are Lyme disease and relapsing fever. Erythema migrans, an annular rash, is typical of Lyme disease. It may be uniformly erythematous or may take the form of a target lesion with necrosis and vesicles in the center. Axilla, periumbilical area, thigh, and groin are the usual sites. The rash enlarges to average 15 cm with a sharply demarcated peripheral reddish band about 1–2 cm wide and resolves without treatment in 4 weeks. Relapsing fever consists of recurrent febrile and afebrile periods, each lasting 2–7 days. Usually the terminal part of the primary febrile episode is associated with a diffuse, erythematous macular, or petechial rash over trunk and shoulders lasting 1–2 days. Jaundice, splenomegaly, lymphadenopathy, and CNS features may also be seen.\textsuperscript{[66]}

Trench fever, caused by \textit{Bartonella quintana} is characterized by fever for about a week, followed by recurrent fevers, usually every 5 days, associated with a nonspecific macular rash, severe headache, neck, back, and shin pain.\textsuperscript{[67]}

Rickettsial fevers usually have varying combination of features including fever, headache, myalgia, hepatosplenomegaly, and lymphadenopathy along with rash. The rash is macular or maculopapular, occasionally petechial. The diseases may be associated with a typical painless eschar with an erythematous rim at the site of vector bite.\textsuperscript{[31-33,68]}

Drug eruptions, although mostly morbilliform and exanthematous, can present with various patterns, the knowledge of which can help the clinician determine the causative medication and the most appropriate treatment. Acute generalized exanthematous pustulosis (AGEP) is characterized by acute-onset fever associated with generalized scarlatiniform erythema and many small, sterile, follicular pustules. Antibiotics are the predominant cause, others being mercury exposure or UV radiation. AGEP resolves spontaneously by 7–10 days followed by desquamation over a few days.\textsuperscript{[69]}

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome or drug-induced hypersensitivity syndrome, usually caused by anticonvulsants, is characterized by the triad of fever, skin eruption, and internal organ involvement.\textsuperscript{[70]}

Stevens–Johnson syndrome (SJS) is a serious
mucocutaneous illness with systemic symptoms characterized by the presence of flat, atypical target lesions [Figure 3], epidermal detachment comprising less than 10% of the total body surface area (BSA) and involvement of two or more mucosal sites. TEN is a life-threatening condition characterized by high fever associated with widespread (involving more than 30% of BSA) confluent erythema followed by necrolysis. An epidermal involvement between 10–30% of BSA has been referred to as SJS-TEN overlap. Anticonvulsants, especially carbamazepine and phenytoin, are most frequently implicated in causing SJS and TEN. Other drugs include antibiotics like sulphonamides, penicillins, and fluoroquinolones as well as NSAIDs.\[^{[71,72]}\]

Another severe drug eruption includes leucocytoclastic vasculitis, characterized by blanching erythematous macules, replaced later by palpable purpura. Fever, myalgias, arthritis, and abdominal pain may be present. It typically appears 7–21 days after the onset of drug therapy.\[^{[73]}\]

Antibiotics have also reported to cause serum sickness and serum sickness-like cutaneous eruptions which begin with erythema on the sides of the fingers, hands, and toes and progress to a widespread morbilliform or urticarial eruption. Multiorgan involvement, fever, arthralgia, and arthritis are common.\[^{[74]}\]

In contrast to drug-induced and infectious febrile rashes, CVDs are usually characterized by insidious onset, low-grade, indolent fever with nonspecific constitutional symptoms like fatigue, anorexia, and weight loss. However, high spiky fever is seen in sJCA and KD. Children with KD present with a remittent or continuous fever for about 1–2 weeks without a prodrome of respiratory symptoms. The acute phase is characterized by erythema and/or edema of hands and feet, polymorphous erythema over body and extremities, bilateral nonexudative conjunctival injection, redness, dryness and fissuring of lips, a strawberry tongue, and nonsuppurative cervical lymphadenopathy. Fever and all the acute signs subside in the subacute phase, except conjunctivitis. This phase (last for about 2 weeks) is associated with desquamation, thrombocytosis, and coronary aneurysms [Figure 4]. Convalescent phase begins with disappearance of all clinical features and lasts for the next 2–4 weeks till ESR and CRP normalizes.\[^{[46,47]}\] The clinical manifestations of the different CVDs have been summarized in Table 2.

**DIAGNOSTIC APPROACH**

A febrile child with rash often presents a diagnostic challenge for physicians. The distinct morphological features and distribution of the rash along with a characteristic cluster of systemic features may give a clue to the clinician. A thorough history including onset, duration and type of fever, temporal association between fever and rash, sequence of distribution of rash, associated symptoms, presence of similar lesions in close contacts, recent intake of medicines, and hygiene status of the household should be taken. Careful physical examination entails close examination of the rash and salient features of systemic involvement.

**AGE**

Age of the child can give some idea regarding probable etiologies. Viral exanthems like measles, ES, EBV, and enteroviral infections commonly occur in infants and children below 3 years of age. Most of the cases of KD and SSSS are children below 5 years of age. The age of occurrence of varicella, rubella, and EI overlaps with that of the above mentioned conditions, extending from 3 to 10 years of age. Meningococcemia shows two peak ages of affection—children less than 5 years and between 15 and 24 years. SLE, JD, RF, PAN, and WG affect older children above 6–7 years while HSP occurs between 2 and 8 years and sJCA usually seen in less than 1 year. On the other hand, dengue and chikungunya fevers affect all age groups.

**MORPHOLOGY OF RASH**

The differential diagnoses based on morphology of rash is shown in Table 3

**ASSOCIATED CLINICAL FEATURES**

It cannot be more emphasized 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 etiological approach based on associated systemic features has been shown in Table 4.

**Prodrome of upper respiratory tract infection**

A prodrome of malaise, fever, catarrhal symptoms, and sore throat preceding the rash usually suggests viral exanthems like measles, rubella, ES, EI, varicella, coxsackievirus, EBV, and adenoviral infection. The
distinguishing features of these infections have been discussed earlier. Virological confirmation is not necessary.

Diseases mimicking viral exanthems

KD is often misdiagnosed as viral infections 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, nonexudative conjunctivitis, distribution of the rash predominantly over the trunk, edema over hands and feet with desquamation, and a raised ESR, differentiate KD from the above mentioned viral infections. A high index of suspicion and experience is required to identify atypical cases of KD which have fever with few of the characteristic clinical features, but develop coronary aneurysm. SF is sometimes difficult to differentiate from KD, both having scarlatiniform rash and strawberry tongue. Absence of rapid clinical response to antistreptococcal antibiotics within 24–48 hours would go in favor of KD. The typical transient nature of rash with Koebner phenomenon differentiates sJCA from viral exanthems, KD, leptospirosis, and SF.

Drug-induced eruptions are very common and often difficult to differentiate from viral exanthems. The former are more likely to be urticarial, intensely erythematous and pruritic, and may or may not be associated with the prodromal features of viral fevers. SJS involving skin and mucous membrane mimics SF...
Table 2: Clinical manifestations of collagen vascular diseases presenting with fever and rash

<table>
<thead>
<tr>
<th>Disease</th>
<th>Description and distribution of mucocutaneous lesions</th>
<th>Associated clinical features of other systems</th>
</tr>
</thead>
<tbody>
<tr>
<td>s JCA</td>
<td>Faint, erythematous, salmon-colored, macular rash, 2–5 mm, in groups, evanescent, Koebner phenomenon positive</td>
<td>Quotidian fever, arthritis, HSM, LAD, serositis</td>
</tr>
</tbody>
</table>
| SLE     | a. Malar or butterfly rash over cheeks and nasal bridge  
b. Photosensitive rash  
c. Discoid lesions  
d. Periungual telangiectasia  
e. Erosions on palatal and nasal mucosa  
f. Livedo reticularis  
g. Raynaud’s phenomenon  
h. Subacute psoriasiform/annular/urticarial lesions  
i. Alopecia | Insidious onset fever, non deforming arthritis, tendinitis, serositis, hematologic abnormalities, HSM, LAD, neuropsychiatric features, lupus nephritis |
| JD      | a. Periorbital violaceous heliotrope erythema extending over bridge of nose and ears  
b. Gottron papules over metacarpals, knees, elbows  
c. Edema—periorbital/generalized  
d. Calcinosis—later in course of disease | Insidious onset fever, proximal myopathy, dysphagia, constipation, cardiac conduction defects, dilated cardiomyopathy |
| KD      | a. Erythema of palms and soles, edema of hands and feet  
b. Periungual desquamation in subacute phase  
c. Polymorphous exanthem  
d. Bilateral nonexudative conjunctival injection  
e. Erythema and cracking of lips, strawberry tongue, injection of oral and pharyngeal mucosa. | High grade, remittent fever, coronary aneurysm, myocarditis, pericarditis, arthritis, urethritis |
| HSP     | Initially maculopapular blanchable rash, later palpable purpura occurring in crops over dependent areas below waist, eyelids, lips, dorsum of hands, and feet | Arthritis (knees, ankles), hematemesis, melaena, intussusception, HSP nephritis |
| PAN     | Linear erythema with edema, palpable, painful nodules along the course of affected arteries | Fever, weight loss, abdominal pain, hypertension, hematuria, stroke, mononeuritis multiplex, myocarditis, arthritis, arthralgia |
| WG      | Palpable purpuric nodules | Chronic sinusitis, hemoptysis, uveitis, corneal conjunctival lesions, hematuria, proteinuria |

Table 3: Differential diagnoses based on morphology of rash

<table>
<thead>
<tr>
<th>Macular or maculopapular rash</th>
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<tbody>
<tr>
<td>Measles, rubella, dengue, ES, EI, drug rash, infectious mononucleosis, chikungunya fever, adenoviral infections, enteroviral infections, brucellosis, rickettsial infections, SLE, systemic onset juvenile chronic arthritis</td>
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<tr>
<td><strong>Diffuse erythema/scarlatiniform rash with desquamation</strong></td>
<td></td>
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<tr>
<td>Scarlet fever, SJS, drug-induced toxic epidermolysis, staphylococcal and streptococcal toxic shock syndrome, KD</td>
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<tr>
<td><strong>Vesicular rash</strong></td>
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<tr>
<td>Varicella, herpes simplex, enteroviral infections, SJS</td>
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<tr>
<td><strong>Petechial or purpuric rash</strong></td>
<td></td>
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<tr>
<td>Meningococccemia, dengue fever, chikungunya fever, papular purpuric gloves and socks syndrome, rickettsial infections, Yersinia pestis, Borrelia, Bartonella, HSP, cutaneous vasculitis</td>
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<tr>
<td><strong>Urticarial rash</strong></td>
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<tr>
<td>Infectious mononucleosis, coxsackievirus, Yersinia enterocolitica, Borrelia, Coxliella burnetti</td>
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<tr>
<td><strong>Nodular rash</strong></td>
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<tr>
<td>Erythema nodosum (seen in tuberculosis, drugs, Yersinia enterocolitica), Bartonella</td>
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or KD. In SJS, erythematous macules develop central necrosis resulting in vesicles, bullae, and denuded areas. Such vesiculobullous 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 sign. 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 (e.g., by showing eosinophils in morbilliform eruptions).[73]

**Circulatory failure**

Dengue and chikungunya are two of the conditions [Table 4] which may be associated with shock. Both are noted for absence of respiratory symptoms. In
Table 4: Differential diagnoses based on associated clinical features

<table>
<thead>
<tr>
<th>Type of RASH</th>
<th>Associated Conditions</th>
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<tbody>
<tr>
<td>a. Prodrome of upper respiratory tract infection</td>
<td>Measles, rubella, EI, ES, varicella, adenoviruses, coxsackievirus, EBV, scarlet fever</td>
</tr>
<tr>
<td>b. Fever of acute onset</td>
<td>Measles, rubella, EI, ES, varicella, adenoviruses, coxsackievirus, Infectious mononucleosis, scarlet fever, toxic shock syndrome, meningococcemia, bacterial endocarditis, leptospirosis, KD, systemic onset juvenile chronic arthritis, acute RF</td>
</tr>
<tr>
<td>c. Fever of insidious onset</td>
<td>SLE, JD, polyarteritis nodosa, Wegener’s granulomatosis</td>
</tr>
<tr>
<td>d. Relapsing fever</td>
<td>Borrelia, Bartonella quintana</td>
</tr>
<tr>
<td>e. Polyarthritis of small joints/myalgia</td>
<td>Chikungunya fever, dengue fever, leptospirosis, systemic onset juvenile chronic arthritis, systemic lupus erythematosus, polyarteritis nodosa, JD</td>
</tr>
<tr>
<td>f. Arthritis involving large joints</td>
<td>Acute RF, HSP</td>
</tr>
<tr>
<td>g. Hemophagocytic lymphohistiocytosis</td>
<td>Infectious mononucleosis, leptospirosis, Borrelia, Brucellosis</td>
</tr>
<tr>
<td>h. Hemorrhagic manifestations</td>
<td>Dengue fever, chikungunya fever, meningococcemia, HSP</td>
</tr>
<tr>
<td>i. Multorgan failure, hypotension, shock</td>
<td>Dengue fever, meningococcemia, toxic shock syndrome, leptospirosis, chikungunya fever</td>
</tr>
</tbody>
</table>

fact, Ramos et al. concluded that presence of high fever, petechial rash, or mucosal bleed in the absence of cough and other respiratory symptoms has a very high positive predictive value of confirmed dengue infection.[78] Headache, myalgia, and arthralgia are seen in both diseases, with polyarticular arthralgia involving small joints and pruritic maculopapular rash more suggestive of chikungunya fever. Progressive leukopenia and a positive torniquette test are the earliest markers of probable dengue. Meticulous monitoring for warning signs described earlier can identify progression to critical phase before clinical signs of plasma leakage appear. Severe dengue consisting of shock, hemorrhage, and MOF must be differentiated from conditions with similar features like malaria, leptospirosis, and meningococcal or other bacterial shock. The hemorrhage in fulminant meningococcemia usually is in the form of purpura fulminans unlike dengue where gastrointestinal bleeding, petechiae, and purpura predominate. Although tender hepatomegaly may be seen in dengue, associated splenomegaly is suggestive of malaria and additional lymphadenopathy would indicate leptospirosis. Confirmation of diagnosis can be done by blood counts, blood culture for meningococcemia, peripheral smear and rapid antigen tests for malaria, serological tests for dengue, chikungunya, and leptospira.

Another exanthematous fever-associated circulatory failure includes TSS caused by *Staphylococcus aureus* and occasionally GAS. Females between 15 and 25 years of age are common victims with the typical sunburn-like rash and MOF as described earlier. Diagnosis is primarily clinical.

**Insidious onset fever**

Insidious onset fever, relatively higher age of presentation, and characteristic distribution of rash [Table 2] allow easy identification of CVD like SLE, JD, PAN, and WG. Diagnostic criteria of SLE are well established.[79] Typical clinical features, a positive antinuclear antibody (seen in more than 80% of cases), anti-Pm/Scl, and characteristic muscle biopsy findings confirm the diagnosis of JD. Typical findings of vasculitis on biopsy or angiography confirm PAN while antibodies to ANCA directed toward PR3 are specific for WG.

**CONCLUSION**

Exanthematous fevers in children have an exhaustive list of causes. A stepwise approach consisting of proper history taking, identifying the morphological type of lesion, and ultimately correlating the two in the background of appropriate clinical milieu will go a long way in identifying the etiology and ordering the appropriate investigations.

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**REFERENCES**


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Multiple Choice Questions

1. The rash of rubella is best described by which of the following morphological appearance?
   a. Confluent rash
   b. Discrete macules
   c. Morbilliform maculopapular rash
   d. Vesicles and crusts

2. A 15-month-old child has acute onset of high fever lasting for 3–5 days. The cessation of fever is associated with maculopapular rash over neck and trunk which begins to disappear within a few hours. What is the most likely diagnosis?
   a. ES
   b. Rubella
   c. EI
   d. Scarlet fever

3. The rash of dengue usually spares which part of the body?
   a. Face
   b. Upper limbs
   c. Lower limbs
   d. Palms and soles

4. Which of the following is characteristic of Kawasaki disease?
   a. Evanescent rash
   b. Petechiae
   c. Nonexudative conjunctival injection
   d. Palpable purpura

Contd...
Sarkar, et al. Fever and Rash in a Child

5. Salmon-colored, evanescent macular rash associated with quotidian fever, hepatosplenomegaly and lymphadenopathy. What is the most likely diagnosis?
   a. Indian tick typhus
   b. Leptospirosis
   c. Systemic onset juvenile chronic arthritis
   d. Erythema migrans

6. Which of the following is not a feature of Scarlet Fever?
   a. Strawberry tongue
   b. Sandpaper-like rash
   c. Annular rash
   d. Desquamation

7. A febrile prodrome of 2–4 days is followed by oval, gray blisters with erythematous base over hands and feet along with aphthous ulcers in the mouth. What is the causative organism?
   a. Epstein–Barr virus
   b. Parvovirus B19
   c. Human Herpes Virus 6
   d. Enterovirus

8. Strawberry tongue is seen in all of the following conditions except:
   a. Lyme disease
   b. Kawasaki disease
   c. Scarlet fever
   d. Toxic shock syndrome

9. Which of the following is not seen in toxic epidermal necrolysis?
   a. Positive Nikolsky sign
   b. Confluent erythema
   c. High fever
   d. Purpura fulminans

10. Trench fever is caused by which organism?
    a. *Borrelia*
    b. *Bartonella quintana*
    c. *Yersinia enterocolitica*
    d. Enterococcus

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Announcement

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