Review:

Approach to fever with rash in children
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Introduction

Rash may be hallmark of disease or nonspecific and an important clue to etiology of illness. Differential diagnosis is critical and recognition is key to making a good diagnosis.

Fever with rash is a common illness in childhood responsible for anxiety among parents. Generally fever with rash is considered benign viral exanthems without much clinical significance. In most cases reassurance and supportive therapy is all that is needed. However, a health care professional should be aware of signs and symptoms of the serious illnesses which may be associated with complications resulting in substantial morbidity and mortality.

Different patterns of lesions are:
- Papule: raised flat topped lesions with diameter <5 mm
- Nodule: >5 mm with raised rounded configuration
- Patch: macule >1 cm in size
- Plaque: papule >1 cm in size
- Vesicle: clear fluid filled <5 mm
- Bullae: fluid filled lesions > 5 mm
- Purpura: non blanching (bleeding into the skin(<5 mm: petechiae, >5 mm ecchymosis))

Classification of rash includes 5 types, that is, nodular, maculo-papular, vesico-pustular, urticarial, erythematous.

Organisation of rashes: confluent, linear, serpiginous, annular, dermatomal

Various definitions:
- Exanthem - Acute generalized eruption
- Enanthem - eruption involving mucus membrane
- Morbilliform - Erythematous macules & papules
- Scarlatiniform - confluent blanching erythema

Large number of infectious and noninfectious conditions present with exanthematous fevers. In this review, attempt has been made to provide an overview of the etiology, pathology, clinical presentation, differential diagnosis, investigations and management of fever with rash in the pediatric patients.

Detailed history taking must include age, site and details of onset of rash (location, duration, rate and direction of spread, pruritus, change of character), associated symptoms (fever, nasal congestion, sore throat, GI upset, joint pain), exposure to substances (drugs, chemicals, food, toxins, bites), history of travel, vaccination history, immune status or any cardiac abnormality.
**Table 1: Common causes of fever with rash in children**

<table>
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<th>Infectious causes</th>
<th>Measles, Rubella, Varicella, Herpes Simplex Virus Type I and 2, HHV-7, Adenovirus, EBV, Chikungunya, Dengue, Influenza A and B, Hepatitis B.</th>
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**Causes of fever with rash**

**Viral exanthems**

These are the most frequent causes of fever with rash in children (Mancini 1998). Some may lead to mortality and morbidity, especially in developing countries while others are self limiting.

**Viral fever prone to complications**

1. Rubeola or measles caused by a paramyxovirus is a major public health problem. These two cause significant mortality and morbidity, especially in developing countries. Measles is transmitted by droplet infection. It commonly affects children between 6 months and 3 years of age. Generally in India, epidemics occur in winter and early spring. In India, the incidence of measles is decreasing since the implementation of Universal Immunization Program. (Sarkar, Mishra et al. 2012)

2. Chikungunya is exanthematous fever transmitted by _Aedes egypti_ mosquito in monsoon. It's incidence is showing increasing trends in India with a massive epidemic in 2006.

3. Dengue is caused by arbovirus. It leads to life-threatening exanthematous fever. It is transmitted by _Aedes egypti_ mosquito leading to explosive epidemics in the monsoon season in India. It had case fatality rate of 0.57 in 2009. Dengue occurs in all ages and both sexes are equally affected. (Sarkar, Mishra et al. 2012)

**Viral fever: self limiting:**

1. Herpes simplex infections are widespread without any seasonal variation. Infected person carries latent infection responsible for recurrences.

2. Chickenpox, also known as varicella, is a highly contagious disease caused by varicella zoster virus commonly seen in children 3 to 10 years of age, both being transmitted by droplet
3. Rubella virus infection is transmitted by droplet infection and generally produces a mild fever and rash illness in children 3 to 10 years of age. (Singh, Narula et al. 2017)

4. Human herpes virus 6 (HHV6) infection occur in infancy and early childhood and is transmitted by contaminated saliva. By the end of the second year, almost 100% children are seropositive for HHV6.

5. Epstein-Barr virus (EBV) infection occur in infancy and early childhood and is transmitted by contaminated saliva. (Singh, Narula et al. 2017)

6. Enteroviruses infection occur round the year in tropical and subtropical areas and produce numerous exanthems in children. They are transmitted via contact with nasal/oral secretions, aerosol droplets and fecal material and are highly contagious. Infants account for > 25% of the cases. Coxsackievirus A16 or Enterovirus71, are responsible for epidemics of hand foot and mouth disease (HFM).

7. Parvovirus B19 infections generally occur in winter and spring. These are transmitted via respiratory droplets. The classic exanthem of this virus is erythema infectiosum (EI) which is most common in children between 4 and 10 years of age.

**Bacterial infections:**

Cutaneous eruptions with fever also occur in many bacterial infections.

1. Various staphylococcal skin infection occur in children. Staphylococcal scalded skin syndrome (SSSS) and toxic shock syndrome (TSS) are potentially serious conditions caused by the same organism occurs predominantly in infants and children < 5 years of age. TSS occurs mostly in menstruating girls between 15 and 25 years, but is also seen in non-menstruating girls and children where the infection occurs from nasal packs, wounds, sinusitis, tracheitis, etc. (Manders 1998)

2. Group A streptococci (GAS) is the cause for scarlet fever (SF), erysipelas, and acute rheumatic fever (RF). (Basetti, Hodgson et al. 2017) These conditions are associated with high fever and characteristic rash.

3. Meningococcal infection: The only natural reservoir of Neisseria meningitidis is the human nasopharyngeal mucosa. It commonly occurs in winters and is caused by the serogroup A. (Sinclair, Preziosi et al. 2010)

4. Rickettsial diseases: India is an integral component of “tsutsugamushi triangle” which depicts a part of the globe endemic to scrub typhus. (Sivarajan, Shivalli et al. 2016) It is caused by the arthropod-borne gram-negative obligately intracellular bacillus *Orientia tsutsugamushi*. Approximately 5 to 14 days after being bitten by an infected vector, a *Leptotrombidium* mite, patients begin to exhibit manifestations of infection such as non-specific flu-like symptoms, fever, rash, eschar at the bite site, headache, myalgia, cough, generalized lymphadenopathy, nausea, vomiting, and abdominal pain.

5. Leptospirosis: It a zoonosis known to occur in India since long, especially in areas with heavy monsoon, animal rearing practices, and unplanned urbanization. This infection may affect all
age groups and is acquired by direct or indirect contact with urine of infected dogs. (Sethi, Sharma et al. 2010)

**Noninfectious causes of febrile rash**

1. Systemic lupus erythematosus (SLE): It is more common in females, with a female to male ratio being 4:1 before puberty and 8:1 after puberty. It generally occurs after 8 years and its prevalence varies from 4 to 250/1,00,000. (D'Cruz 2006)

2. Systemic onset juvenile chronic arthritis (sJCA): It is commonly found in young children often < 1 year of age with no sex predilection. (Giancane, Alongi et al. 2017)

3. Kawasaki disease (KD): Prevalence of KD is highest among Asians

4. Henoch-Schonlein purpura (HSP)

5. Juvenile dermatomyositis (JD)

6. Wegener’s granulomatosis (WG)

7. Polyarteritis nodosa (PAN)

8. Drug eruptions: Skin adverse drug reactions (ADR) mostly are mild and self-limited, resolving with the withdrawal of offending drug. (Pudukadan and Thappa 2004) Severe and potentially fatal eruption arise in about 1 in 1000 hospitalized patients. (Sharma and Sethuraman 1996) Toxic epidermal necrolysis (TEN) has high mortality rates of 20 to 70%. (Guillaume, Roujeau et al. 1987)

**Clinical presentation**

**Measles:** It is characterized by a distinct prodromal phase with fever, rhinorrhea, cough, and conjunctival congestion. Koplik spots consist of gray white sand-like lesions, surrounded by erythema in the buccal mucosa opposite the lower second molar tooth are pathognomonic. Commencing behind the ears and forehead and going downward erythematous, confluent, maculopapular rash develops usually on the fourth day of fever which resolves in the same order. This is followed by residual brownish discoloration and desquamation which wanes in the next 10 days. (Rathi, Narendra et al. 2017)

**Rubella:** Rash is characterised by minute, discrete macules, in contrast to the confluent rash of measles. The onset of rash is 24 hours after 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. (Winter, Pramanik et al. 2017), (Vaidya, Kamble et al. 2016)

**Varicella:** The rash occurs in crops, it evolves through the stages of macule, papule, vesicle, and crusts involving mainly the trunk and proximal end of extremities. Generally fever subsides 2-4 days after appearance of rash and the rash fades by 3-7 days, leaving behind hypo- or hyperpigmented macules persisting for days to weeks. (Arvin 1996, Singh, Kaur et al. 2017)

**Dengue fever:** Children present with abrupt onset of high grade fever accompanied with facial flushing, headache, arthralgia, myalgia and abdominal pain. Post 48 hours of onset of fever, a transient generalized macular rash develops. Fever has typical biphasic pattern as it may
subside after 2-7 days, only to reappear after 1-2 days. The critical phase starts at defervescence, associated by some warning signs like intense abdominal pain, persistent vomiting, mucosal bleeding, clinical fluid accumulation, lethargy, and tender hepatomegaly. This is followed by second phase which is associated with a generalized morbilliform maculopapular rash sparing the palms and soles. The progression to the next phase of severe dengue is determined by the extent of plasma leakage. Severe dengue is defined by one or more of the following: (a) shock from plasma leakage; (b) severe bleeding; and (c) severe organ impairment. (Ranjit and Kissoon 2011)

Chikungunya fever: It is associated with high temperature with rigors, intense joint pain, headache, myalgia, and rash. The arthritis is polyarticular, migratory involving small joints and may persist for long duration. The rash appears 4-8 days after fever and arthritis. It is itchy, transient, maculopapular, spread over trunk, and extremities. (Krishnamoorthy, Harichandrakumar et al. 2009)

Herpes simplex types 1 and 2: Fever blisters are usual presentation of recurrent HSV-1 infection, primarily seen over lips, nose, chin, cheek, or oral mucosa. The lesions are in the form of single or grouped vesicles varying from 2 to 10 mm, on a mildly erythematous base.
Occasionally, erythema multiforme or Steven-Johnson Syndrome may be seen. (Bale 1999)

**Infectious mononucleosis:** Fever is accompanied by pharyngeal inflammation, generalized lymphadenopathy, and hepatosplenomegaly are associated with a maculopapular rash. The rash may develop into erythema multiforme or urticaria. The exanthem arises 3-13% of cases and increases to 50% if treated with ampicillin or amoxicillin. (Ebell 2004)

**HHV6 and HHV7:** HHV6 infection is characterised by a sudden high fever lasting for 3-5 days. Following decrease in fever, discrete macular or maculopapular rash erupt, known as exanthem subitum (ES), over neck and trunk which begins to disappear in a few hours. Febrile convulsions appear as complication in 10% children. Lesions are distributed along the lines of cleavage and have a ring of scales surrounding them. (Wananukul, Nopponpunth et al. 2003)

**Erythema infectiousum:** It is caused by Parvovirus B19 characterised by a homogenous erythema over the cheeks giving an appearance of typical "slapped cheek" associated with a reticulate maculourticarial exanthem over the proximal extremities and occasionally over distal extremities and trunk. There is repeated fading of rash and recurrence triggered by local irritants, high temperature, and emotional stress. Oral erosions, vesicles, lip edema, and petechiae over hard palate, pharynx, and tongue may also appear. (Tuccio, Zanelli et al. 2014)

**Enteroviruses:** They are responsible for a large number of exanthems of which HFM disease is most common.

**Staphylococcal infections:** It’s manifestation in children range from furuncles, carbuncles, folliculitis, bullous impetigo to Staphylococcal toxic shock syndrome (TSS) and Staphylococcal scalded skin syndrome (SSSS) (which are associated with high temperatures). TSS is an acute multisystem disease manifests as 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. By 7-10 days symptoms resolve with desquamation of palms and soles. Predominantly children under 5 years age at risk of SSSS which is characterized by scarlatiniform erythema changing into a wrinkled paper appearance with peeling of large sheets of epidermis. Healing takes place by 10-15 days without scarring. (Chi, Wang et al. 2006)

**Scarlet fever:** It is caused by Group A streptococcus (GAS). (Baseii, Hodgson et al. 2017) It manifests as rash and strawberry tongue appearing 1-2 days after an upper respiratory tract infection. The rash spreads throughout the body, sparing the palms and soles, with characteristic circum-oral pallor. The rash is characterized by confluent, erythematous, blanching, fine macules, resembling a sunburn, and sandpaper-like papules. In skin folds, such as the axilla, antecubital fossa, and buttock creases, an erythematous, non-blanching linear eruption (Pastia lines) may develop. Petechiae on the palate may occur, as well as erythematous, swollen papillae with a white coating on the tongue (white strawberry tongue). Red strawberry tongue occurs after desquamation of the white coating. After several weeks, the rash fades and is followed by desquamation of the skin, especially on the face, in skin-folds, and on the hands and feet, potentially lasting four to six weeks.

- White strawberry tongue followed in another two days by Red strawberry tongue
- Desquamation of the rash
Another complication of prior GAS infection is nonsuppurative erythema marginatum which is one of the major diagnostic criteria of acute Rheumatic Fever. The rash characterized by erythematous, serpiginous, macular, nonpruritic lesions with central pallor, primarily occurring over trunk and extremities, sparing the face. (Feeney, Dowse et al. 2005) Enterococcal and viridans group of streptococci are known causes of bacterial endocarditis, with rash characterized by petechiae, splinter hemorrhages, Osler's nodes, and Janeway's spots. (Sarkar, Mishra et al. 2012)

**Meningococcemia**: It is manifested as fever with petechiae, occasionally with transient lesions resembling a viral maculopapular rash. The petechiae are present on trunk and extremities are elevated with a "smudged" appearance. In fulminant meningococcemia, gangrenous hemorrhagic areas similar to purpura fulminans appear which are associated with adrenal hemorrhage, hypotension, multiorgan failure.

**Leptospirosis**: Fever has 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). The second phase occurs after a short period characterized by a transient (<24 hours) rash in 10% of cases which may be urticarial, petechial-purpurial or desquamating type. (Karande, Bhatt et al. 2003)

**Yersinia enterocolitica**: Reactive complications such as erythema nodosum, arthritis, and uveitis may develop. Yersinia pestis is responsible for causing septicemic plague which is
characterised by generalized erythema, petechiae and purpura. (Abdel-Haq, Asmar et al. 2000)

**Borrelia infections**: It is characterized by fever with rash. Erythema migrans, an annular rash, is typical of Lyme disease. 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.

**Rickettsial fevers**: 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 erythematous rim at site of vector bite.

**Drug eruptions**: These are commonly seen as morbilliform and exanthematous lesions. The knowledge of characteristic presentation may aid the establishment of the causative drug and the most appropriate treatment.

1. Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome: It is also referred to as drug-induced hypersensitivity syndrome. Commonly caused by anticonvulsants, is characterized by the triad of fever, skin eruption, and internal organ involvement. (Cacoub, Musee et al. 2011)

2. Acute generalized exanthematous pustulosis (AGEP): characterized by acute-onset fever associated with generalized scarlatiniform erythema and many small, sterile, non-follicular pustules. Antibiotics are the common cause, others being mercury exposure or UV radiation.

3. Steven-Johnson syndrome (SJS): It is characterized by serious mucocutaneous eruptions with systemic symptoms manifested as flat, atypical target lesions, epidermal detachment comprising less than 10% of the total body surface area (BSA) and involvement of two or more mucosal sites.

4. Toxic Epidermal Necrolysis is a fatal condition manifested 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. The causative agents are anticonvulsants (especially carbamazepine and phenytoin) and other drugs include NSAIDs and antibiotics like sulphonamides, penicillins, and fluoroquinolones. (Oodiuk-Gad, Chung et al. 2015), (Paulmann and Mockenhaupt 2017)

5. Serum sickness: Antibiotics are commonly responsible for serum sickness.

6. Leucocytoclastic vasculitis: It is characterized by blanching erythematous macules, transformed later to palpable purpura, may be associated with fever, myalgias, arthritis, and abdominal pain. The onset is usually 7-21 days after the onset of drug therapy. (Sarkar, Mishra et al. 2012)

**Collagen vascular diseases:**

CVDs generally present with insidious onset, low-grade, indolent fever with nonspecific constitutional symptoms like fatigue, anorexia, and weight loss. However in sjCA and KD high spiky fever is seen.

**Evaluation and diagnosis of fever with rash in children**

A child with fever and with rash is often a diagnostic challenge for health care professionals. A detailed 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 elicited. The typical morphological features and distribution of the rash along with a characteristic cluster of systemic features may provide a clue to the physicians. A thorough physical examination involves meticulous examination of rash and salient features of systemic involvement.

**Age of child**

The probable cause of fever with rash can be predicted by the age of the child. Infants and children below 3 years of age are more vulnerable to viral rashes like measles, ES, EBV. The age of occurrence of varicella, rubella, and EI extends from 3 to 10 years of age. Most of the cases of KD and SSSS are children below 5 years of age. SLE, JD, RF, PAN, and WG affect older children above 6-7 years while HSP occurs 2-8 years. Dengue and chikungunya affect all ages.

**Upper respiratory tract infection prodrome**

Generally prodrome of upper respiratory infection characterized by malaise, fever, catarrhal symptoms, and sore throat preceding the rash usually indicative of viral exanthems like measles, rubella, ES, EI, varicella, coxsackievirus, EBV, and adenoviral infection. In most cases virological confirmation becomes unnecessary.

**Gradual onset fever**

Collagen vascular disease like SLE, JD, PAN, and WG are characterized by insidious onset fever, relatively higher age of presentation, and characteristic distribution of rash. Typical clinical features, a positive antinuclear antibody (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.

**Diseases mimicking viral exanthems**

Kawasaki Disease is often mis-diagnosed as viral infections due to common features and it 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, edema over hands and feet with desquamation, and a raised ESR, differentiate KD from the infections.

Sometimes it becomes difficult to differentiate between scarlet fever and KD as both are associated with scarlatiniform rash and strawberry tongue. Positive response to antistreptococcal antibiotics within 24-48 hours would go in favor of scarlet fever.

It is quite challenging to differentiate from viral exanthems form drug-induced eruptions. Viral exanthems are associated with the prodromal features whereas the latter may or may not be associated with fever and the rash is likely to be urticarial, intensely erythematous and pruritic. Scarlet fever and KD involving skin and mucous membrane may resemble SJS however it may be differentiated from Scarlet fever and KD by its typical erythematous macules with central necrosis resulting in vesicles, bullae, and denuded areas.
Drugs also trigger TEN which 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 intake of drugs and appearance or worsening of rash which is pruritic nature, and presence of eosinophilia in blood are suggestive of drug-induced rash. Diagnosis of drug eruption can be confirmed by biopsy that reveals eosinophils in morbilliform eruptions.

**Circulatory failure**

There are certain conditions which are potentially fatal may be associated with shock caused by Dengue and chikungunya. 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. Progressive leukopenia and a positive tourniquet test are the earliest markers of probable dengue. Before clinical signs of plasma leakage appear, careful monitoring for warning signs can detect onset of critical phase. Severe dengue must be differentiated from similar features of malaria, leptospirosis, and meningococcal or other bacterial shock. Generally tender hepatomegaly and splenomegaly is suggestive of malaria and lymphadenopathy would indicate leptospirosis. Dengue may have also hepatomegaly. Diagnosis should be confirmed by blood counts, blood culture for meningococcemia, peripheral smear and rapid antigen tests for malaria, serological tests for dengue, chikungunya, and leptospira.

**Conclusion**

The list of causes of fever with rash in children is quite exhaustive. A stepwise approach involving detailed history taking, studying the morphological type of lesion, and finally interpreting the findings in the background of appropriate clinical milieu will help diagnosis and management of the disorders.

Fever with characteristic rash identification helps in appropriate treatment. Serious illnesses can be diagnosed by identification of the characteristic rash. Early diagnosis and treatment helps in prevention of occurrence of complications.

**References**


Dear Doctor,

It gives me immense pleasure to present to you this QMR issue by eminent pediatrician Dr. N. K. Agrawal, from Patna.

Fever with rash is common illness experience in childhood which is responsible for lot of anxiety among parents. Generally fever with rash is benign viral exanthems without much clinical significance. In most case reassurance and supportive therapy is all that is needed. However, a health care professional should be aware of signs and symptoms of the serious illnesses which may be associated with complications resulting in substantial morbidity and mortality.

In this issue an attempt has been made to provide an overview of the etiology, pathology, clinical presentation and management of fever with rash in the pediatric patients.

As always, I hope you enjoy reading this QMR issue. Please do get in touch if you have any feedback, or think you might have a story for us.

With best regards,

Dr. Balaji More
Vice President - Medical