Viral exanthems

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Purpose of review
Determining the viral cause of a rash presents significant diagnostic challenges. We review contemporary literature on viral exanthems and suggest a structured approach to aid diagnosis.

Recent findings
Strains responsible for, and the clinical presentation of, enteroviral infections have diverged from classic descriptions. The causative relationship between antibiotic administration and rash in Epstein–Barr virus infection has been recently questioned. Major measles virus outbreaks have recently occurred in Europe and the USA. The largest Ebola virus outbreak in West Africa has resulted in importation of the virus to other countries and secondary local transmission. Autochthonous transmission of Chikungunya virus has occurred in nonendemic areas, including Europe, the Caribbean and Americas. Zika virus has re-emerged in the Pacific with local transmission from imported cases. Climate change, global warming and spillover of zoonotic viruses are contributing to the emergence and spread of viral diseases.

Summary
Important clues to the diagnosis of viral exanthems include their distribution and morphology, geographic location and potential exposure to vector-borne or blood-borne viruses. Diagnosis is commonly made via serology, nucleic acid tests or, rarely, viral culture. Skin biopsy is not usually required. In general, viral exanthems are self-limiting and treatment is supportive.

Keywords
exanthem, Gianotti–Crosti syndrome, rash, viral infection, virus

INTRODUCTION

Exanthems commonly accompany viral infections, but may also be caused by other infectious and noninfectious aetiologies. Although exposure to viruses may occur at mucosal surfaces or abraded skin sites, the presence of a rash in viral infections is generally not due to viral replication *per se*, but a hypersensitivity reaction to the virus. Viral exanthems may or may not be pruritic, and may be the first symptom or develop during the course of infection. In addition, they can occur during primary infection or following reactivation of a latent virus.

The spectrum of viral causes of exanthems and enanthems (in which mucous membranes are also involved) has increased with emergence of novel viruses and advances in laboratory diagnostic methods. Although some exanthems and enanthems may be nonspecific, others can be pathognomonic [1]. Pattern recognition and knowledge of epidemiology is pivotal in differentiating the likely pathogen and predicting the natural course and public health importance of cases (Fig. 1). In the absence of a specific pattern, arthropod exposure, travel and vaccination history may provide clues to the differential diagnoses. However, atypical patterns of exanthems can occur in immunocompromised patients or following vaccination. Herein, we describe common causes of viral exanthems and outline an approach to guide further investigation and management.

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KEY POINTS

- Pathognomonic syndromes of HFMD, papular–purpuric 'gloves and socks' syndrome and Gianotti–Crosti syndrome are associated with recent changes in epidemiology and presentation.
- The role of HHVs in drug-associated rash is being redefined.
- Measles and rubella incidence is increasing.
- Arboviral transmission has expanded with increased travel and climate change.
- New viruses are emerging as pathogens, and the threat of old viruses that may re-emerge remains.

RASH SYNDROMES

Syndromic rashes in viral infections can generally involve hands, feet and mouth; 'gloves and socks'; and the face, limbs and buttocks with truncal sparing (Gianotti–Crosti syndrome).

Hand, foot and mouth disease

The enteroviruses have recently been reclassified (Table 1). Hand, foot and mouth disease (HFMD) is the commonest manifestation of human enterovirus infections (Table 2 [2–14]), which are a major cause of rash and fever [1,15▪▪] (Fig. 2 [16]).

Palmoplantar vesicular lesions and painful oral erosions (Fig. 2b) with the involvement of the

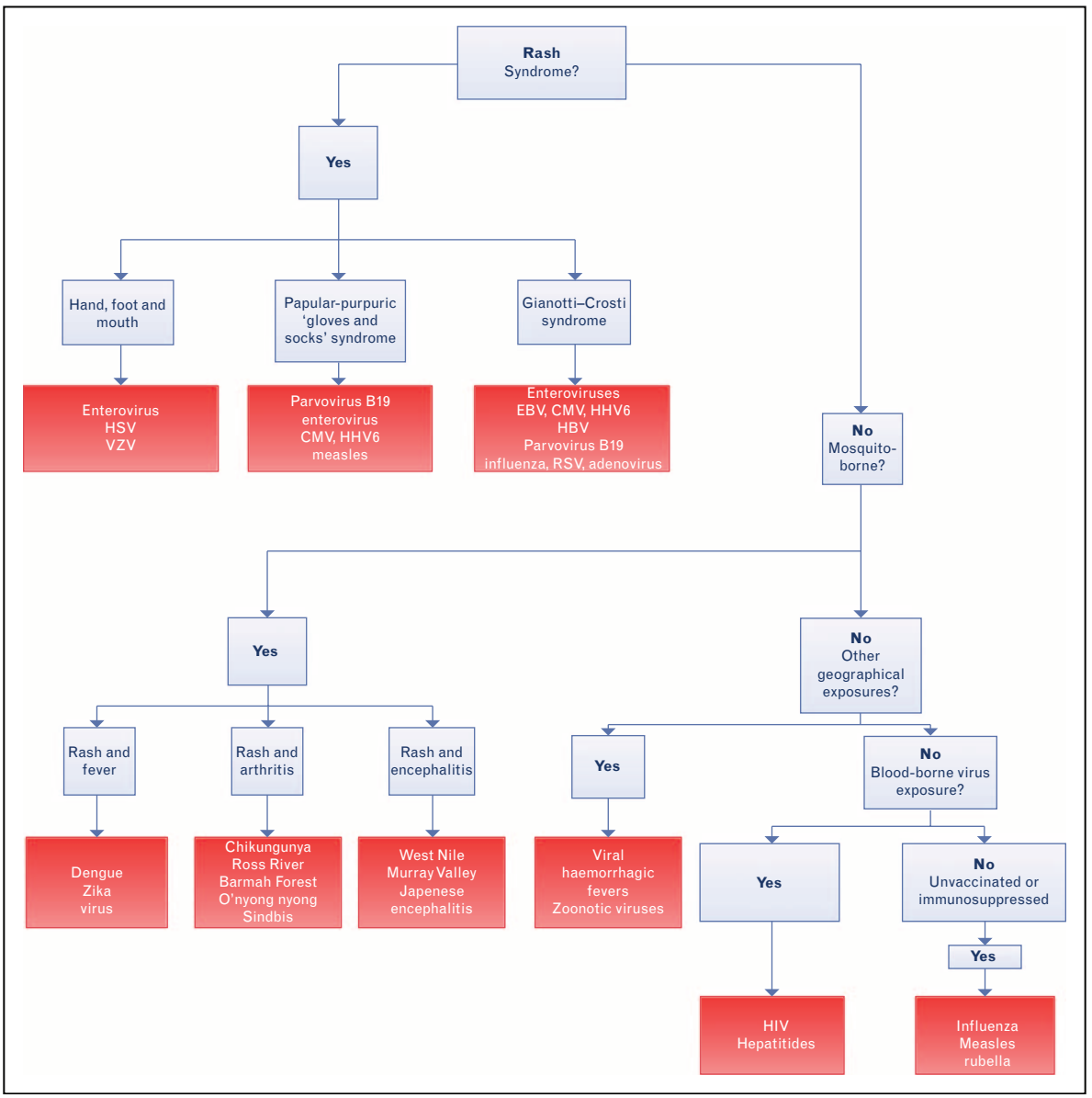

FIGURE 1. Flow chart of a practical clinical approach used to determine possible viral aetiologies of exanthems.

Table 1. Recent reclassification of enteroviruses[a]

Current species name	Former species name
Enterovirus A	Human enterovirus A
Enterovirus B	Human enterovirus B
Enterovirus C	Human enterovirus C
Enterovirus D	Human enterovirus D
Enterovirus E	Bovine enterovirus (group A)
Enterovirus F	Bovine enterovirus (group B)
Enterovirus G	Porcine enterovirus B
Enterovirus H	Simian enterovirus A
Enterovirus J	Unclassified simian viruses
Rhinovirus A	Human rhinovirus A
Rhinovirus B	Human rhinovirus B
Rhinovirus C	Human rhinovirus C

[a]Human enteroviruses are members of the family Picornaviridae. In 2013, more than 100 serotypes of human enteroviruses were reclassified into four species (enteroviruses-A, B, C, and D) based on genome organization, sequence similarity and biological properties (http://www.picornaviridae.com).

buttocks/perineum may be seen. Less commonly, onychomadesis (painless spontaneous nail shedding) occurs after HFMD [17–19]. A more fulminant progression of HFMD associated with enterovirus-A71 has been recently described, resulting in the death of 170 children in an outbreak in Vietnam in 2011 [1,20,21].

Coxsackie virus-A6 is increasingly recognized to cause HFMD with atypical presentations in children [2–6,22–24]. In addition to hand, foot and buttock involvement, rash may be present periorally, truncally or with a predilection for areas of active atopic dermatitis, termed 'eczema coxsackium'. Other reported morphologies include vesiculobullous eruption on the trunk, Gianotti–Crosti-like eruption, and petechial and purpuric eruptions [1,7▪▪,8,18–22,25–29]. Desquamation occurs in approximately 50% of cases, and rarely, a more severe form of infection occurs in the absence of rash [2–6,9,17,22–24].

In 2014, there has been a nationwide outbreak of enterovirus-D68 in the USA. Although respiratory illnesses are the predominant feature of enterovirus-D68 infections, rash may also be present [10,30].

Papular-purpuric 'gloves and socks' syndrome

Papular-purpuric 'gloves and socks' syndrome is most commonly associated with parvovirus B19 infection (Fig. 3). It is transmitted via respiratory droplets, blood products or *in utero*. The appearance of B19-specific immunoglobulin G coincides with onset of the rash, which is commonly pruritic [2,10]. Clinically, it can manifest as erythema infectiosum (Fig. 4), papular–purpuric 'gloves and socks' syndrome or purpuric exanthems. Unusual presentations include flagellate erythema [11,31]. Parvovirus is generally not infectious after the onset of the rash.

Gianotti–Crosti syndrome

Gianotti–Crosti syndrome commonly occurs in children and resolves over 3–4 weeks [12–14,32,33]. It was initially described in children with hepatitis B infection, but has subsequently been associated with many other viral and bacterial infections [1–14,34▪▪,35▪▪].

OTHER ENDEMIC VIRUSES – HUMAN HERPESVIRUSES

Human herpesvirus (HHV) can cause a variety of viral exanthems, including vesicular, maculopapular, morbilliform, urticarial, scarlatiniform or purpuric rashes. Distinct patterns and persistent reactivation of latent herpesviruses [Epstein–Barr virus (EBV), cytomegalovirus and HHV-6] have also been observed following drug-induced hypersensitivity syndrome/Stevens–Johnson syndrome [1,15▪▪,36▪].

Herpes simplex virus

Herpes simplex virus (HSV)-1 and 2 typically produce vesicular lesions in the oral-labial or genital regions, although primary infection may cause a maculopapular rash. Vesicles may involve single or multiple anatomical sites following autoinoculation or in disseminated disease. Eczema herpeticum in patients with atopic dermatitis, herpes gladiatorum in athletes and erythema multiforme are also associated with HSV infection.

Varicella zoster virus

Primary and secondary varicella zoster virus (VZV) infection produces a classical and easily recognizable rash that is diffuse and dermatomal, respectively. However, herpes zoster may manifest as dermatomal pain or encephalitis in the absence of a rash (zoster sine herpete) [16,37▪▪], making the diagnosis more challenging. VZV is now vaccine preventable.

Cytomegalovirus and Epstein–Barr virus

Acute cytomegalovirus infection does not generally cause an exanthema, although it was the proposed cause in 4% of patients presenting with atypical exanthems as determined by serology and polymerase chain reaction; EBV was identified in another 8% [1,17–19,38]. Acute EBV infection may be associated

Table 2. Clinical features and diagnostic methods of endemic and vaccine-preventable viral infections

Virus	Incubation period	Clinical features in addition to rash	Laboratory diagnosis	Comments
Enterovirus	3–10 days	Aseptic meningitis, encephalitis, acute flaccid paralysis, upper respiratory tract infection, myopericarditis	NAT: respiratory tract samples, CSF IFA: respiratory samples Viral culture: respiratory tract and stool samples	Typically involves children during the spring season in temperate climates. NAT is the test of choice and useful for phylogenetic and evolutionary studies.
Parvovirus B19	4–14 days	Arthropathy, transient aplastic crisis, hydropsfaetalis and intrauterine death, myocarditis [2–6]	Serology: parvovirus B19-specific immunoglobulin M NAT: blood, bone marrow, placenta, amniotic fluid, fetal tissue	Peak incidence occurs in winter and spring. Parvovirus B19 infects progenitor red blood cells causing anaemia. Immunoglobulin M is detectable at 2 weeks with the conclusion of viraemia. Immunoglobulin G appears around 1 week later with rash and arthralgia.
HSV	2–7 days	Hepatitis, disseminated disease in immunocompromised hosts	NAT: vesicular fluid, skin biopsy, respiratory samples, CSF IFA: vesicular fluid, skin biopsy, respiratory samples Viral culture: vesicular fluid, skin biopsy, respiratory samples	HSV1 is more common than HSV2. Serology is not generally useful. Immunoglobulin G may confirm prior exposure to HSV. NAT has a higher sensitivity than culture and immunofluorescence can provide rapid diagnosis. Viral culture is necessary to establish antiviral susceptibilities.
VZV	10–21 days	Herpes zoster ophthalmicus, acute retinal necrosis, herpes zoster oticus, aseptic meningitis, encephalitis, postherpetic neuralgia, stroke syndromes, granulomatous angiitis	NAT: vesicular fluid, CSF IFA: vesicular fluid, CSF Serology: VZV-specific immunoglobulin M	Varicella is highly contagious. Clinical findings are usually sufficient to make the diagnosis. NAT is highly specific. Serology is not generally useful. Immunoglobulin G may confirm prior exposure to VZV, most useful in establishing risk following contact in the antepartum period.
CMV	4–12 weeks	Mononucleosis syndrome, reactivation in critically unwell or immunocompromised hosts	Serology: CMV-specific immunoglobulin M NAT: qualitative assays in tissue specimens, quantitative assays in blood	CMV-specific immunoglobulin M is detectable within 2 weeks of exposure and falls over several months. It is also detectable during reactivation. Low-level CMV viraemia detected by NAT is usually not significant in the absence of end-organ CMV disease. Cross-reactivity with EBV.
EBV	4–8 weeks	Mononucleosis syndrome, splenic rupture, haemophagocytic lymphohistiocytosis, reactivation in immunocompromised hosts, post-transplant lymphoproliferative disorder, Burkitt's lymphoma, Hodgkin's lymphoma	Serology: EBV-specific VCA immunoglobulin M; EBNA immunoglobulin G; early antigen immunoglobulin G NAT: qualitative assays in tissue specimens, quantitative assays in blood	Monospot test for heterophile antibodies in diagnosing acute EBV is unreliable as it may also be positive with haematological malignancies, rubella, malaria, toxoplasmosis and babesiosis. EBV VCA immunoglobulin M has good specificity in the acute phase. In infants, it has a lower sensitivity, and looking for immunoglobulin G seroconversion is important. EBNA immunoglobulin G persists for life after infection, and antibodies to early antigen are generally positive for up to 2 years after the acute phase [1,7▪▪,8].
HHV-6	5–15 days	Encephalitis in immunocompetent hosts, reactivation in immunocompromised hosts	Serology NAT: qualitative and quantitative assays in blood	HHV-6 can integrate into host chromosomes, and in a small proportion of cases, transmitted vertically and found in all host nuclei [2–6,9].

Table 2 (*Continued*)

Virus	Incubation period	Clinical features in addition to rash	Laboratory diagnosis	Comments
HHV-8	Unknown	Kaposi's sarcoma, primary effusion lymphoma, Castleman's disease Reactivation in immunocompromised hosts	Serology NAT: blood, skin, lymph nodes, lungs, gastrointestinal tract	In the general adult population, seroprevalence of HHV-8 varies from <5% in the USA and western Europe to 60% in sub-Saharan Africa [10]. HHV-8 has also been detected by NAT in basal cell carcinoma, pemphigus vulgaris and foliaceus [10].
Measles virus	7–21 days	Prodrome of fever, malaise followed by conjunctivitis, coryza and cough; encephalitis, acute disseminated encephalomyelitis, subacute sclerosing panencephalitis	Serology: measles-specific immunoglobulin M IFA and NAT: in respiratory and/or urine specimens	Sensitivity of measles-specific immunoglobulin M is 67% if serum is collected <72 h after the onset of rash. Cross-reactivity from parvovirus B19, rubella and HHV-6. Blood collection difficult in young children. Sensitivity of IFA reported to be 46–54%.
Rubella	15–20 days	Five-day prodrome of fever, headache and upper respiratory tract symptoms; arthralgias involving the wrists, elbows and ankles lasting up to 3 weeks [11]; more severe complications include haemolytic anaemia, thrombocytopaenia, pericarditis, mypcarditis and encephalitis [12–14]	Serology: rubella-specific immunoglobulin M NAT: nasal, blood, urine or CSF Culture: nasal, blood, urine or CSF	Serum best collected 7–10 days after onset of the rash and repeated 2–3 weeks later. Acute rubella may be diagnosed by presence of rubella-specific immunoglobulin M, a four-fold rise in immunoglobulin G between acute and convalescent samples of less commonly, positive rubella culture from nasal, blood, urine or CSF specimens. Culture is useful for epidemiological purposes.

CMV, cytomegalovirus; CSF, cerebrospinal fluid; EBNA, Epstein–Barr virus nuclear antigen; EBV, Epstein–Barr virus; HHV, human herpesvirus; HSV, herpes simplex virus; IFA, immunofluorescence antigen detection; NAT, nucleic acid testing; VCA, viral capsid antigen; VZV, varicella zoster virus.

with a maculopapular rash lasting up to a week that begins on the trunk and arms before spreading to the forearms and face [7▪▪]. It may be associated with an enanthem.

The use of penicillin and subsequent development of rash has been recently challenged in a prospective study of 184 patients with acute EBV infection [39,40]. Most of the 103 patients who received antibiotics were prescribed amoxicillin, and the presence of rash in those given penicillin derivatives was not significantly different from those that were not exposed.

Human herpesvirus-6 and human herpesvirus-7

Roseola infantum is a febrile illness predominantly caused by HHV-6 and occasionally HHV-7. It typically occurs in early childhood and presents with a febrile illness followed by rose-pink macules and papules on the neck, proximal extremities, trunk and occasionally on the face. An enanthem may be present. Using serology, HHV-6 was the most common cause in a prospective study of rash and febrile illness amongst patients less than 40 years of age presenting to clinics or hospitals [41].

VACCINE-PREVENTABLE VIRAL INFECTIONS

Despite the availability of highly effective vaccines, reports of measles and rubella are increasing.

Measles

Measles incidence is rising, particularly in areas of low prevalence from imported cases where measles is endemic [42–44]. During 2011, more than 26 000 measles cases were reported in 36 European countries [45]. The USA has seen 20 outbreaks with 603 cases of measles in 2014 (until October 31) [46]. Following an influenza-like prodrome, Koplik spots usually precede a cephalocaudal morbilliform rash that appears 3–5 days after the onset of symptoms (Fig. 5).

Rubella

There have been recent rubella outbreaks in Japan, China, India and Tunisia [12,47▪,48,49]. A 5-day prodrome of fever, headache and upper respiratory tract symptoms is associated with cephalocaudal progression of a maculopapular rash (Fig. 6). Infected individuals should be quarantined until 4 days after the rash subsides.

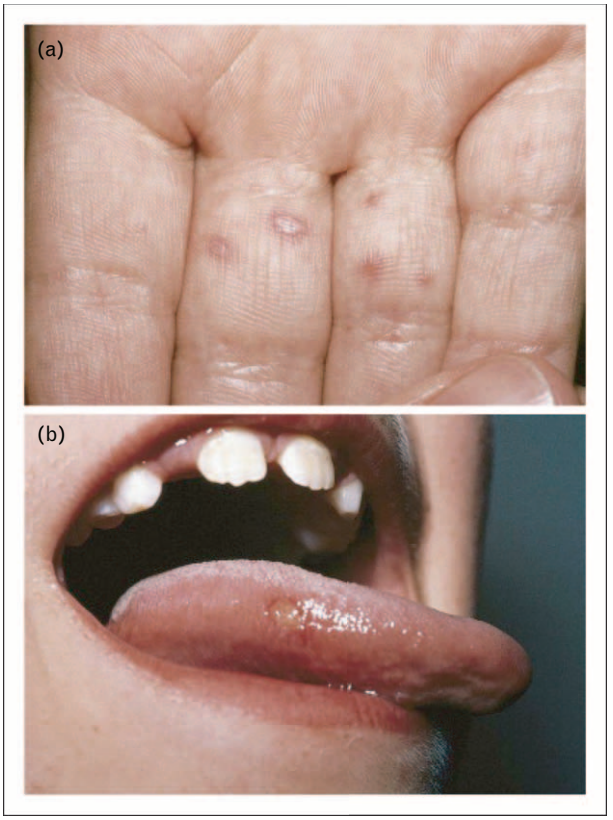

FIGURE 2. (a) Following a mild prodrome, the clinical hallmark of HFMD is a deep-seated vesicular eruption affecting the palmar and plantar surfaces. There are vesicles with surrounding erythema, located on the fingers [16]. (n) The lesions on the palms and soles can be associated with an erosive stomatitis, fever and malaise. There is painful erosion on the lateral aspect of the tongue [16]. CMV, cytomegalovirus; EBV, Epstein–Barr virus; HHV, human herpesvirus; RSV, respiratory syncytial virus; VZV, varicella zoster virus.

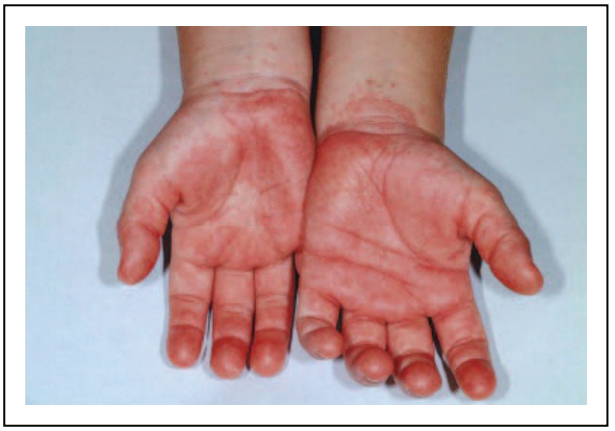

FIGURE 3. Papular–purpuric gloves and socks syndrome is seen in association with parvovirus B19 infection. Petechial purpura is seen on the palms in this patient, and such lesions are also seen on the soles of the feet [16].

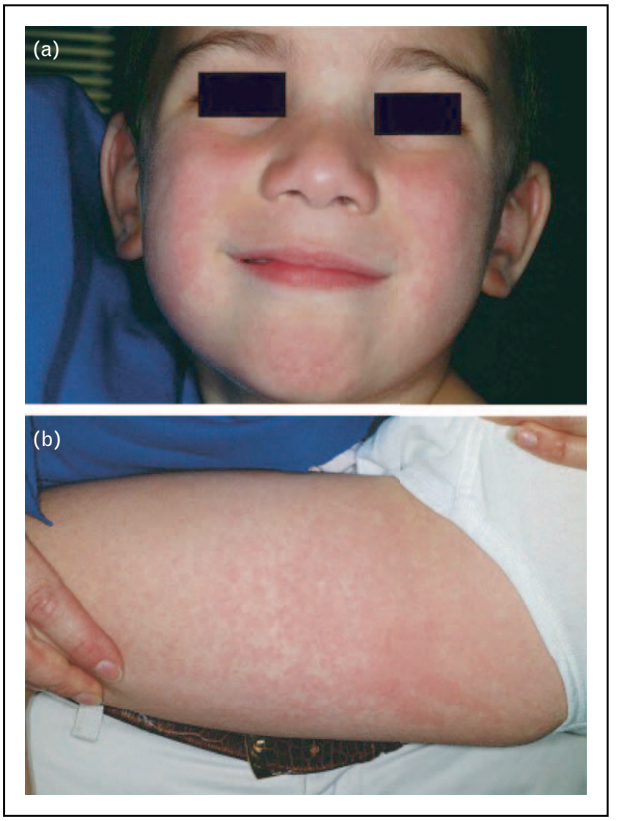

FIGURE 4. (a) Erythema infectiosum, also known as fifth disease and 'slapped cheek' syndrome has a mild prodrome with low-grade temperature, myalgias and headache 7–10 days before the onset of the exanthem. This picture shows bilateral erythema of the cheeks, likened to 'slapped cheeks', with circumoral sparing [16]. (b) Following the development of the facial rash, there is progression over 1–4 days to the trunk/limbs where a lacy/reticulated pattern is seen, as seen on the inner thigh of this patient. The rash lasts 1–3 weeks and is exacerbated by heat and sunlight exposure [16].

Influenza

Although rash is uncommon in influenza, cutaneous manifestations have been reported with influenza A (H1N1)pdm09, A/H7N9 and influenza B [50–53]. A confluent maculopapular rash that spares the face and palmoplantar surfaces has been observed in influenza A (H1N1)pdm09 infection [51]. Influenza should remain in the differential diagnosis of children with fever and rash, particularly in the presence of respiratory symptoms during the influenza season.

TROPICAL VIRUSES

With increased travel and population movements, imported viral infections with secondary local transmission are of great concern and outbreaks in susceptible populations may present containment issues.

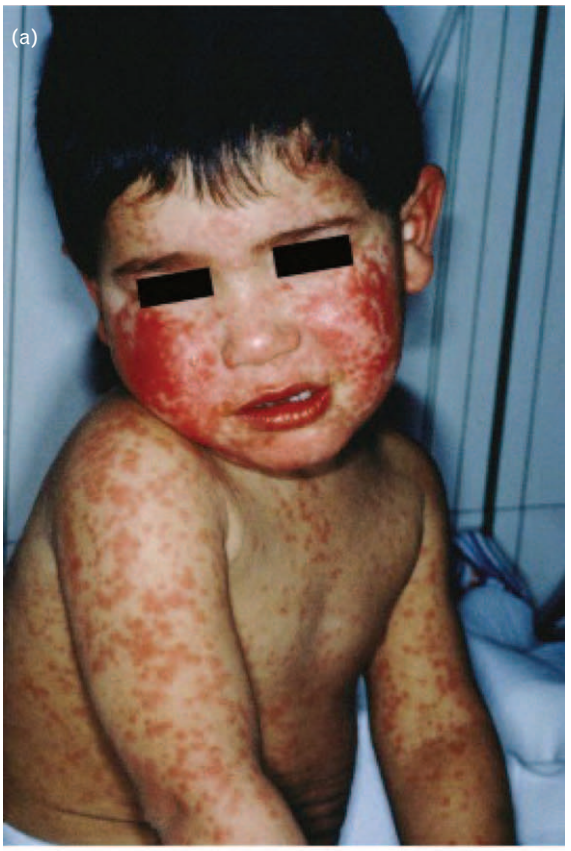

FIGURE 5. (a) The prodrome of measles consists of fever, cough, rhinoconjunctivitis and a diffuse morbilliform rash that progresses cephalocaudally [16,34▪▪]. (b) Koplik spots, which are grey–white papules on the buccal mucosa, are highly predictive of confirmed measles [16,54].

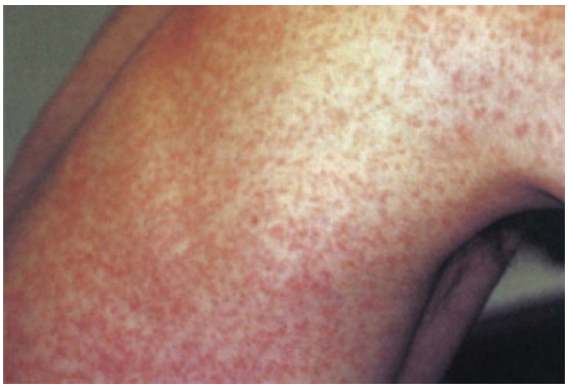

FIGURE 6. Rubella infection results in cephalocaudal progression of a nonspecific maculopapular rash. Petechial macules may be present on the soft palate (Forchheimer's spots) and tender lymphadenopathy, particularly in the head and neck region, may be present [16].

Arboviruses

Of the 754 recognized arboviruses, only Chikungunya, dengue, Japanese encephalitis and yellow fever viruses have evolved to primarily use humans as hosts. This implies that a large reservoir of other arboviruses in animals may affect humans. Table 3 details the clinical presentations, geographical distribution and diagnostic tests available.

Alphaviruses

Exanthems in alphavirus infections may appear anytime during the course of illness. Characteristic features include the cephalocaudal spread of rash in Barmah Forest virus (BFV) infection, and palmoplantar involvement in Ross River, Barmah Forest and Chikungunya virus.

Chikungunya virus

Chikungunya has spread to the Caribbean and Americas following large outbreaks in the Indian Ocean islands, Indian subcontinent and Europe [55–60]. The expansion of geographical areas of Chikungunya-competent vectors through climate change, and the spread of the virus into new vector species such as *Aedes albopictus* following importation from endemic areas have been responsible for the ongoing transmission of infection. Chikungunya virus rash is usually morbilliform, with or without acral and facial oedema, mucosal, genital and intertriginous ulceration. Vesiculobullous eruptions are more likely to occur in children.

Ross River and Barmah Forest virus

Ross River virus and BFV are endemic in Australia, with occasional outbreaks in the Pacific [11,61,62]. BFV is characterized by a rash in 90% of cases,

Table 3. Arboviruses divided into clinical presentation/syndrome, geographic region, clinical features and current diagnostic test availability

Arbovirus	Geographic distribution	Vector	Incubation period (days)	Clinical features	Laboratory diagnosis
Rash and arthritis					
Chikungunya	Africa, Indian Ocean, South and south-east Asia	*Aedes* spp.	1–12	Widespread nonpruritic and morbilliform rash with severe persistent arthritis of the small joints of the hands, lymphadenopathy	Serology: immunoglobulin M or seroconversion NAT (chikungunya displays the longest viraemia of the alphaviruses, virus may be detected by NAT for up to 6 days)
Ross River	Australia	*Aedes* spp. and *Culex* spp.	5–15	Epidemic polyarthritis and chronic arthralgia; glomerulonephritis Lymphadenopathy is rare	Serology: immunoglobulin M or seroconversion NAT early in course of infection (viraemia is as short as 3 days)
Barmah Forest	Australia	*Aedes* spp. and *Culex* spp.	5–15	More extensive rash than Ross River virus Epidemic polyarthritis, myalgia	Serology: immunoglobulin M or seroconversion NAT early in course of infection
Rash and fever					
Dengue	Asia, Central and South America	*Aedesaegypti* and, more recently, *Aedes albopictus*	4–7	Retro-orbital pain and headaches Faint macular rash that spares the palms and soles Haemorrhagic fever in secondary infections	Acute phase: nonstructural protein 1 (NS1) antigen or NAT Dengue-specific immunoglobulin M detectable ~5 days from symptom onset Viral culture
Zika	Africa, Asia and Polynesia	*Aedesaegypti* and other *Aedes* mosquitos	3–12	Similar to dengue	Serology: immunoglobulin M or seroconversion NAT PRNT can differentiate antibody specificity of Zika from dengue virus
Rash and encephalitis					
West Nile	Africa, Europe, Middle East, North and South America	*Culex pipiens*, *C. quinquefasciatus*, *C. tarsalis*	3–14	Rash, encephalitis	Serology: immunoglobulin M or seroconversion NAT
Murray Valley encephalitis	Australia	*C. annulirostris*	5–28	Encephalitis (most infections subclinical)	Serology: immunoglobulin M or seroconversion NAT
Japanese encephalitis	Japan, Russia, south-east Asia, India, Nepal, Papua New Guinea , and Northern Australia	*C. annulirostris*	6–16	Encephalitis (most infections subclinical)	Serology: immunoglobulin M or seroconversion NAT

NAT, nucleic acid testing; PRNT, plaque reduction neutralization test.

whereas Ross River virus infection is more commonly associated with arthritis. However, around 40% of patients develop a rash [11,62,63▪,64–66]. The rash seen in BFV infection appears with the onset of illness and has cephalocaudal spread. It may be maculopapular, purpuric or vesicular [62–64].

Flaviviruses

The flaviviruses are structurally similar and serology may be cross-reactive (Table 3).

Dengue and Zika virus

Dengue virus transmission overlaps with that of Chikungunya virus and coinfection can occur. A faint morbilliform or scarlatiniform rash with islands of sparing occurs in 50% of individuals. Minor haemorrhagic lesions can occur. The rash rarely persists beyond 2 weeks [67]. Although secondary dengue carries a greater risk of dengue haemorrhagic fever, severe dengue also occurs with primary infections and some strains appear to diminish in severity with subsequent infection [68▪▪,69–71]. Zika virus is a flavivirus with an indistinguishable presentation from dengue infection. Outbreaks of Zika, dengue and Chikungunya have increased in frequency in recent years, particularly in the Pacific [60,72,73].

West Nile virus

Cutaneous manifestations in West Nile virus occur in 25% of patients and nonspecific erythematous macular or papular eruptions affecting the extremities predominate [74].

Murray Valley and Japanese encephalitis

Murray Valley encephalitis was first recognized in the Australian states of Victoria and South Australia in 1951. First isolated in Japan, Japanese encephalitis virus is now the leading cause of viral encephalitis worldwide. Most infections are subclinical or mild, with fever and an erythematous macular and/or papular rash that is more pronounced on the extremities [62,75].

Filoviruses

The filoviruses responsible for viral haemorrhagic fevers include Ebola, Marburg and Lassa viruses. Ebola virus disease in West Africa has captured public attention with the largest recorded epidemic in 2014. Rash occurs in more than half of patients with Marburg virus infection after 4–5 days of symptom onset, but is uncommon in Ebola or Lassa virus infection. It develops over the upper limbs, face and trunk and resolves over days with desquamation and alopecia. It may be associated with enanthema involving the tonsils and palate with 'tapioca granules' on the soft palate with gingivitis, glossitis and fissuring [76–79].

HIV

In HIV infections, rash may be due to HIV *per se*, or from other infectious and noninfectious causes. HIV seroconversion illness may be associated with a generalized maculopapular rash, although this usually affects the palms and soles of the feet, with papules and nodules present on the trunk. Secondary syphilis should also be excluded. In HIV infection, HHV-8 can cause Kaposi's sarcoma, which may present as variegated macules, plaques or nodules. Multicentric Castleman's disease associated with HHV-8 infection can also result in a recurrent maculopapular rash of the limbs and trunk without mucosal involvement [69,80]. Other dermatoses in established HIV infection include papulo-pruritic eruptions, eosinophilic folliculitis, infective folliculitis, necrotizing vasculitis and drug reactions; skin biopsy is useful to differentiate these entities [81].

Hepatitides

Hepatitis B and C are uncommon causes of viral exanthema. Manifestations are summarized in Table 4 [35▪▪,82]. Treatment includes targeted antiviral therapy, and steroids and plasma exchange may have a role in the presence of serum sickness or vasculitis. Acute hepatitis E may also be associated with a rash [83].

Bioterrorism agents

Smallpox was last reported in Somalia in 1977, but has gained notoriety as a potential agent of bioterrorism. It is highly contagious and carries a 30% mortality rate in unvaccinated populations. Smallpox causes a characteristic maculopapular rash that progresses to raised fluid-filled blisters, pustules and pocks. Scabs appear 10–14 days after onset of rash and fall off, leaving areas of hypopigmentation. Scarring may persist lifelong. Unlike pocks from VZV, pocks from smallpox usually occur in the limbs with palmoplantar involvement and are in the same stage of development.

New zoonotic viruses

A recent report describes Sosuga virus as the cause in a wildlife biologist who developed fever and a

Table 4. Skin manifestations of hepatitides

	Hepatitis B	Hepatitis C
Virology	Hepadnaviridae	Flaviviridae
	Partially dsDNA virus	Positive-sense ssRNA virus
Transmission	Vertically, blood-borne or sexual exposure	Vertically, blood-borne, needle-stick or injecting drug use
Diagnosis	Serology	Serology
Skin manifestations in acute infection		
Serum sickness	Yes (10–20%)	Yes
	Fine erythematous, blanching, macular reticular rash over the trunks and limbs [27,72,73]. Resolves with the onset of jaundice after a few days to 4 weeks [35▪▪,82].	
Skin manifestation in nonacute infection		
Gianotti–Crosti syndrome	Yes (HBV > HCV)	Yes
Vasculitis	Small-vessel vasculitis	Small-vessel vasculitis
	Cryoglobulinaemic vasculitis	Cryoglobulinaemic vasculitis (HCV > HBV)
	Urticarial vasculitis	Urticarial vasculitis
	Polyartertitis nodosa (HBV > HCV)	Polyartertitis nodosa (HBV > HCV)
Urticaria	Yes	Yes
Porphyria cutanea tarda	Yes	Yes
Necrolytic acral erythema	Yes	Yes
Lichen planus	No	Yes
Sarcoidosis	Yes	Yes (HCV > HBV), with interferon or ribavirin therapy
Erythema multiforme	Yes	Yes
Erythema nodosum	Yes (HBV > HCV)	Yes

dsDNA, double-standed DNA; ssRNA, single-stranded RNA.

maculopapular exanthema after travel to South Sudan and Uganda [84▪]. This paramyxovirus is a rubella-like virus similar to others derived from fruit bats. Associated with an enanthem, the exanthema progressed to a petechial rash over sites of trauma or pressure. She recovered after 2 weeks.

DIAGNOSIS

Laboratory confirmation of viral exanthems is commonly made by virus-specific serology. The advantages of serology include its noninvasive nature and minimal sample degradation if transported and stored appropriately. Pathogen-specific immunoglobulin M is suggestive of an acute infection, but false-positive results can occur because of cross-reactivity with other viruses. Immunoglobulin G seroconversion (or a four-fold or greater rise in antibody titres between acute and convalescent sera) is regarded as definitive evidence of infection, but confirmation of infection may be delayed and a convalescent sera is not always collected. Measuring immunoglobulin G avidity to determine the maturity of the immunoglobulin G response may differentiate acute from previous infection. High immunoglobulin G avidity is indicative of previous infection, but low immunoglobulin G avidity is not necessarily suggestive of an acute infection as high avidity can take years to develop.

Where available, nucleic acid testing (NAT) on specimens including blood, fluid and tissues is generally the most sensitive and specific test, but specimen quality, storage and transport can affect the performance of NAT. Viraemia generally predates the onset of symptoms, but NAT of blood samples may be falsely negative if the period of viraemia is brief. In addition to qualitative assays, quantitative NAT, if available, can provide an assessment of disease progression and prognosis and guide treatment response. Antiviral resistance can also be detected using NAT. NAT is also useful for epidemiological purposes, which allows monitoring of phylogenetic secular trends and assay performance [34▪▪].

Immunofluorescence antigen detection is still used for the rapid diagnosis of HSV and VZV infections. Viral cultures are slow, time consuming, labour intensive and lack sensitivity, but remain the 'gold-standard' for diagnosis, which NAT assays are validated against.

Skin biopsies are not generally performed in viral exanthems as histological examination usually does not provide a definitive aetiological diagnosis. If the differential diagnosis includes a drug as the cause of the exanthem, then a skin biopsy should be performed as this may help elucidate the diagnosis. However, HHV infections have characteristic features

including multinucleation, nuclei enlargement, nucleoli and intranuclear inclusions. Immunohistochemistry using specific monoclonal antibodies may also identify specific viruses [85▪▪,86▪▪].

MANAGEMENT

The management of viral exanthems is largely supportive in the absence of specific antiviral therapy. Topical therapies such as steroid creams do not improve the natural history. Analgesia can be offered systemically, or via topical and viscous forms for painful enanthems and smaller areas of rash. Infection control measures remain an important strategy to limit further transmission of infection.

FIVE-YEAR OUTLOOK

Viral exanthems are becoming more common with declining vaccination rates, increasing population and vector movements and emerging novel viruses. Vector control remains pivotal in preventing arboviral infections, and we eagerly await outcomes of Ebola, Chikungunya, dengue, HCV and enterovirus-A71 vaccination trials. New immunosuppressive treatments have led to higher rates of reactivation of latent viruses, and clinicians should be alert to atypical presentations of established viruses.

CONCLUSION

We have outlined pathognomonic features of endemic viruses causing exanthems and key epidemiological clues that are important where rash morphology is nonspecific. Diagnosis is generally secured via serology or NAT. Prevention and control measures are crucial in management.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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