REVIEW

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Future MICROBIOLOGY

Contemporary infectious exanthems: an update

Francesco Drago[1], Giulia Ciccarese*[,1], Giulia Gasparini[1], Ludovica Cogorno[1], Sanja Javor[1], Antonio Toniolo[2] & Francesco Broccolo[3]

An exanthem is a skin rash that may be associated with mucous membrane eruption, fever or other symptoms. It may develop as manifestation of an infectious disease or as adverse reaction to drugs. Beside the 'classical exanthems' commonly occurring in childhood, other exanthems, defined as 'atypical' for the different morphology and causal agents, may occur. Among the atypical exanthems with infectious etiology, viral, bacterial, parasitic and helminth infections are implicated. We describe herein etiology and epidemiology of the atypical exanthems caused by infectious agents. In case of exanthem, to make a correct etiological diagnosis is crucial for both the patient and community concerning issues such as time off school, immunizations and risk in pregnancy and immunocompromised individuals.

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KEYWORDS
• bacteria • diagnosis • exanthem • parasite • skin eruption • skin infection • skin rash • virus

An exanthem is defined as any eruptive skin rash that may be associated with lesions of the mucous membranes (enanthem), fever or systemic symptoms. It may be the manifestation of an infectious disease or an adverse reaction to drugs and is among the most frequent reasons for consultation of a dermatologist [1]. Beside the 'classic exanthems' **(Table 1)** [2], other exanthems with different morphology and caused by different infectious/toxic agents may occur. These skin rashes have been defined as 'atypical exanthems' [1,3]. Other authors [4,5] distinguished the so-called 'paraviral exanthems' as the skin diseases suspected to be caused by viruses, but with a single virus–exanthem relationship not universally accepted. However, we prefer the term 'atypical' for defining the exanthems that are different from the classic ones, because there are many skin rashes, like the sixth disease, that may have more than a single well-demonstrated virus as causal agent. Therefore, accepting the definition 'paraviral,' the exanthem list should become too much long.

Etiological diagnosis of atypical exanthems is difficult but important for both the patient and community concerning issues such as time off school, immunizations and risk for pregnant women and immunocompromised patients. Among the infectious exanthems, viral, bacterial, parasitic and helminths infections are implicated. Distinguishing viral exanthems from other life-threatening bacterial and rickettsial diseases with similar cutaneous manifestations may be crucial. Although the pathogenesis is little known, skin manifestation can result by the direct inoculation of the infectious agent into the cutaneous surface or by dissemination from a distant site. Alternatively, it may result from an immune response between the virus and antibody or cell-mediated response to virus in the skin **(Table 2)** [6].

[1]DISSAL Department of Dermatology, IRCCS AOU San Martino-IST, Largo Rosanna Benzi, 10, 16132 Genoa, Italy
[2]Laboratory of Medical Microbiology, Department of Biotechnology & Life Sciences, University of Insubria, Varese, Italy
[3]Laboratory of Molecular Microbiology & Virology, School of Medicine, University of Milano-Bicocca, 20900 Monza, Italy
*Author for correspondence: Tel.: +39 010 555 5750; Fax +39 010 555 6509; giuliaciccarese@libero.it

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Table Features of the six classic exanthems and of atypical measles.

Disease	Infectious agent	Average incubation time	Appearance and distribution of rash	Other features
Measles	Measles virus (paramyxovirus)	14 days	Red, raised papules (sometimes confluent) on the face and neck spreading to trunk and limbs	Prodromes with fever, cough and coryza; fever rises when rash appears; koplik's spot: white lesions on a red granular appearance mucosal surface
Atypical measles	Measles virus (paramyxovirus)	14 days	Urticarial/maculopapular/heamorragic lesions on the face and neck spreading to trunk and upper extremities, sparing the lower extremities	Modified type of measles that occurs with mild symptoms in adolescents/adults who have been immunized previously with killed measles vaccine and subsequently exposed to wild-type measles
Rubella	Rubella virus	17 days	Pink macules and papules on the whole body surface	Suboccipital lymphadenopathy; few or no constitutional symptoms in children
Varicella (chickenpox)	Varicella zoster virus	16 days	Successive crops of lesions that are simultaneously present in various stages of morphogenesis (macules, papules, vesicles and crusts). The exanthem begins on the trunk spreading on the neck, face and limbs	Prodromes with malaise and fever
Scarlet fever (streptococcal disease)	Streptococcus β emoliticus (group A) and its exotoxins	1–5 days	Scarlet papules on the whole body surface except inside of elbows and around mouth; hyperpigmentation in skin creases	Chills, fever, sore throat; strawberry tongue; desquamation after rash
Fifth disease (erythema infectiosum)	Parvovirus B 19	7 days	Slapped cheek appearance; maculopapular rash with a typical reticular pattern	Mild fever, headache, chills, malaise
Roseola infantum (exanthema subitum, sixth disease)	Human herpes virus 6B or 7	9 days	Pink/erythematous macules and papules primarily on the neck and trunk	High fever and lymphadenopathy: fever drops as rash appears (opposite of measles)

As classic exanthems are well known to clinicians, we summarized their main features **(Table 1)** [2] and describe etiology and epidemiology of the atypical exanthems caused by viral, bacterial, parasitic and helminthic infections.

Viral exanthems

• Eczema herpeticum or Kaposi's varicelliform eruption

Eczema herpeticum is a rare, potentially fatal condition usually caused by widespread dissemination of HSV-1 primary infection in a patient with pre-existing skin diseases, mostly atopic dermatitis, and presents as vesiculopustules on the trunk associated with fever and lymphadenopathy. These lesions progress to painful hemorrhagic, crusted erosions. Disease duration is about 2 weeks and lesions heal without scarring within 2–6 weeks. Eczema herpeticum is due to humoral and cellular immunity dysfunction: patients affected by diseases with skin barrier damage or immunodeficiencies are the most susceptible. Complications are due to bacterial infection (that can lead to sepsis) and to viremia with involvement of other organs [7,8].

• Varicella zoster virus

Shingles

Reactivation of varicella zoster virus (VZV) after the primary infection (chickenpox) produces a classic unilateral dermatomal rash, generally limited to the skin area innervated by a single spinal/cranial sensory ganglion, with erythematous maculopapular lesions that quickly develop into vesicles and crusts. Burning pain, itching and paresthesias are often associated but herpes zoster may manifests as dermatomal pain or encephalitis without rash (zoster sine herpete), making the diagnosis more challenging [9].

• Cytomegalovirus

Cytomegalovirus (CMV) is a very common, usually unapparent, worldwide infection [10] that is transmitted from person to person via close contact with an individual excreting the virus. CMV can also be transmitted through oral/vaginal

Table 2. Pathogenesis of the infectious exanthems: blood-borne dissemination of the infectious agent.

Location	Histology	Clinical expression	Pathophysiology
Dermal capillary endothelium	Damage to vessel; endothelial swelling; perivascular edema; hemorrhage; visualization of organism by electron microscopy	Macules, papules; petechiae	Direct effect of the virus/infectious agent; immune response between infectious agent and antibodies or cell-mediated response to it
Dermis	Edema; cellular infiltration; hemorrhage; visualization of organism by electron microscopy	Papules; urticaria; purpura; vesicles	Direct effect of the virus/infectious agent; immune response between infectious agent and antibodies or cell-mediated response to it; histamine release
Epidermis	Visualization of organism by electron microscopy; cytopathic effects induced by viruses (inclusions, ballooning, vacuolation, necrosis)	Papules; vesicles; ulcer	Direct effect of the infectious agent

secretions, urine, semen, placenta, breast milk, blood transfusions and organ transplantation. Primary infection is followed by lifelong virus carriage with intermittent shedding in secretions. When symptoms appear they resemble infectious mononucleosis with fever and lymphadenopathy. In a third of cases, there is a follicular, maculopapular eruption, often affecting the legs **(Figure 1)** and lasting up to 2 days. Also urticarial and scarlatiniform eruption may occur. Small vessel lymphocytic vasculitis [11], Gianotti-Crosti syndrome (GCS) [12] and acute generalized exanthematous pustolosis (AGEP) [13] are other manifestations of CMV infection in immunocompetent patients. In immunosuppressed patients, a widespread papular/purpuric eruption with vesicobullous or pustular lesions and indurated pigmented nodules/plaques may appear. Sharply demarcated ulceration may occur, mostly around genitalia, perineum, buttocks and thighs. Keratotic skin lesions and mucosal/skin ulcerations have been reported in AIDS patients [10].

- **EBV**

EBV is a ubiquitous herpesvirus spread in childhood by contact with saliva. In all populations, the great majority of people are infected by middle age [14]. Skin lesions occur in 2–3% of patients with acute infectious mononucleosis. A faint morbilliform eruption lasting 24–48 h or a maculopapular rash occurring 7–10 days following ampicillin treatment are the most common manifestations, probably reflecting an enhanced reaction to drugs or their metabolites during the viral infection. Moreover, EBV infection has been related to GCS and unilateral laterothoracic exanthem in children [14], maculopapular atypical exanthems [1,3], AGEP [12], palmar eruption, erythema multiforme, urticaria vasculitis [1], drug reaction with eosinophilia and systemic symptoms (DRESS) [15] and genital ulcers in adults [1]. Eyelid and widespread petechiae, periorbital edema and maculopapular enanthem can also be noted [1]. Rarely, skin lesions are the presenting sign of the disease [16]. EBV-related skin diseases in immunodepressed patients include oral hairy leukoplakia and lymphoproliferative disorders [14].

- **Human herpesvirus 6 & 7**

Commonly spread by saliva, human herpesvirus (HHV)-6 and HHV-7 usually causes a subclinical infection that persists lifelong (90% of adults

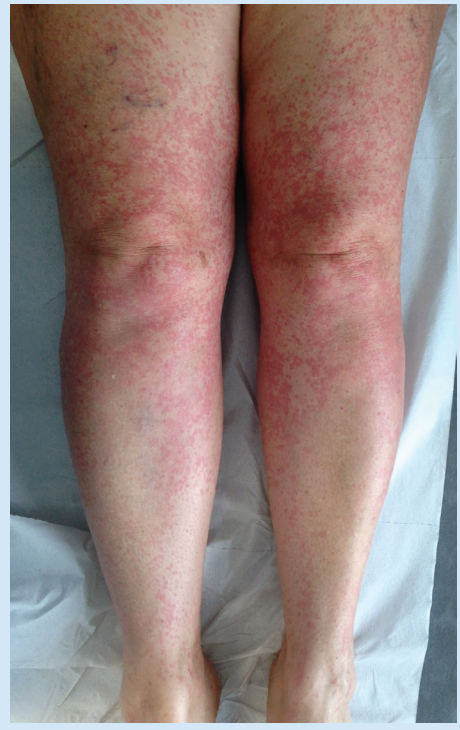

Figure 1. Maculopapular eruption affecting the legs due to cytomegalovirus infection.

are seropositive). These viruses may cause exanthem subitum, the most common exanthematic fever in children under the age of 3 years, and are implicated in different cutaneous manifestations during their systemic reactivation [17]. Pityriasis rosea (PR) is an acute, self-limiting exanthematous disease associated to the endogenous systemic reactivation of HHV-6 and/or HHV-7. Although some authors have not been able to demonstrate this relationship [18,19], recent studies established a role for systemic active HHV-6 and HHV-7 infection in the pathogenesis of PR, based on the detection of HHV-6 and HHV-7 DNA in plasma and their mRNA expression and specific antigens in skin lesions. In addition, herpesvirus virions in various stages of morphogenesis were detected by electron microscopy in skin lesions and in the supernatant of cocultured peripheral blood mononuclear cells from PR patients. The cytopathic effect and syncytia formation observed in peripheral blood mononuclear cell cultures from PR patients, HHV-6 and HHV-7 mRNA expression and antigens found in lesional skin are additional evidence of productive infection. Remarkably, HHV-6 and HHV-7 plasma viremia, a marker of systemic active infection, has been related to the presence of constitutional symptoms. On the basis of these studies, the association between HHV-6/7 and PR is considered definitive [20–24]. PR typically begins with a single, erythematous scaly plaque, followed by a secondary eruption consisting of smaller papulosquamous lesions on the cleavage lines of the trunk **(Figure 2)**. Duration may vary from 2 to 10 weeks and constitutional symptoms may precede or accompany the eruption [23,24]. Maculopapular-petechial atypical PR may occur [1,3,24]. HHV-6 reactivation has been described 2–3 weeks after organ transplantation, causing fever and maculopapular eruptions resembling acute graft-versus-host disease [25]. HHV-6/7 reactivation has also been reported in DRESS **(Figure 3)** [26,27]. DRESS is a life-threatening multiorgan adverse drug reactions characterized by maculopapular rashes developing >3 weeks after starting with a limited number of drugs, prolonged clinical symptoms after discontinuation of the causative drug, fever (>38°C), liver abnormalities (ALT >100 U/l), leukocyte abnormalities (at least one between leukocytosis [>11 × 109/l], atypical lymphocytosis [>5%], eosinophilia [>1.5 × 109/l]), lymphadenopathy, HHV-6 reactivation [27]. Papular-purpuric gloves and socks syndrome [28] and GCS [29] have also been associated with HHV-6 infection.

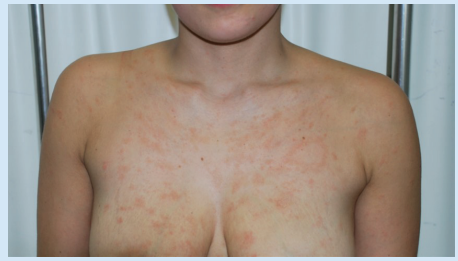

Figure 2. Pityriasis rosea: single, erythematous scaly plaque, followed by a secondary eruption consisting of smaller papulosquamous lesions on the cleavage lines of the trunk.

• Human herpesvirus 8

HHV-8 seroprevalence greatly varies between geographic regions. Transmission mainly occurs through saliva or genital secretions. HHV-8 is etiologically associated with Kaposi's sarcoma (KS) and other proliferative diseases. Primary infection may be associated with a febrile maculopapular rash (median duration of 6 days) [30].

Erythematous rash has been described in an immunocompetent patient who had recurrent HHV-8 infection associated with a relapsing systemic inflammatory syndrome characterized by fever, lymphadenopathy, splenomegaly, edema and arthrosynovitis [31].

• Parvovirus B19 (B19V)

B19V is a DNA virus transmitted via the respiratory tract [32]. Seroprevalence increases with age up to 85% in adults. B19V infection differently manifests in different age groups and 20–50% of infections are asymptomatic. Erythema infectiousum (fifth disease) is the most common manifestation in children, whereas arthralgias and arthritis with or without rash are more common in adults [32,33]. A unique syndrome of pruritic erythema and edema with petechiae affecting hands and feet, called papular-purpuric gloves and socks syndrome, is often associated with florid B19V [34]. Sporadic association of this syndrome with other viruses (VZV, EBV, CMV, HHV-6/7, Coxsackie, hepatitis B virus and rubella) has been reported [35]. Moreover, B19V related maculopapular purpuric eruption involving trunk and limbs or inguinal folds and buttocks in a 'baboon-like' fashion have been recognized. Palms and soles are usually spared

and when the eruptions have a reticulated appearance **(Figure 4)** they resemble erythema infectiousum [33].

• Enteroviruses

Enteroviruses includes Polioviruses 1, 2 and 3, Coxsackieviruses (A1–24 and B1–6), Echoviruses 1–34 and Enteroviruses 68–71. They inhabit the human alimentary tract and leave the host through throat secretions and feces; infection of the new host is acquired through oral cavity. Enteroviruses are the leading cause of exanthems in children, especially during summer and fall [1,3]. The incidence of exanthem is inversely related to age (more frequent in childhood) and there is marked variation in the clinical expression of the infection: the same virus may cause a different pattern of exanthem during the same epidemic and even in the same patient. Neurologic symptoms may develop simultaneously. Enteroviruses may determine maculopapular rash or hand–foot–mouth syndrome, often associated with systemic symptoms [1,3,36–37].

Coxsackieviruses, mainly A16, cause the hand–foot–mouth disease, that begins with low-grade fever and malaise. The presenting complaint is sore throat due to papulovesicular lesions that quickly erode and form shallow ulcerations **(Figure 5)**. Shortly thereafter, peripheral vesicular lesions occurred on hands, feet and sometimes buttocks and genitalia with resolution in a week. Children are most frequently affected whereas adults may have an unapparent or aborted syndrome, the only visible manifestations occurring within the mouth, mistaken for aphthous stomatitis or HSV infection. Other oropharyngeal involvement without skin lesions caused by group A Coxsackievirus are herpangina [6] and acute lymphonodular pharyngitis [38]. Herpangina is characterized by fever, sore throat, vomiting and backache. Papulovesicular lesions occur in the soft palate and tonsils, progress to shallow ulcers and heal in a few days. Also group B Coxsackieviruses, Echoviruses, other Enteroviruses and Adenoviruses have been implicated. Acute lymphonodular pharyngitis presents with tiny nodules in the soft palate and tonsils which resolve without ulceration.

Coxsackieviruses can also cause diffuse maculopapular (mainly A9 and B5) or vesicular (mainly Coxsackieviruses A4, A9, A12) exanthems [1,3] associated with fever and, rarely, with more severe manifestations (meningitis, pneumonia, hepatitis). Eruptions due to coxsackie A4 and A9 begins on the face and trunk and occasionally spread centrifugally. A9 may also involve palms and soles [6,36]. The maculopapular eruption can progress, in case of A4 infection, becoming vesicular and may occur in crops with yellowish opaque vesicles. The lesions may mimic bug bites, but are no itchy. Conversely, in A9 vesicular exanthems, vesicles are clear resembling chickenpox. Coxsackie A9 may cause outbreaks of infection presenting with maculopapular exanthem and pneumonia [6,36]. Coxsackievirus A6 has been associated to a diffuse papular eruption extended over the whole body, with some papules evolving into vesiculobullous lesions and onychomadesis [37].

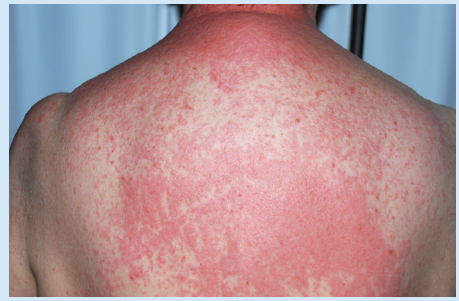

Figure 3. Maculopapular eruption of the trunk in drug reaction with eosinophilia and systemic symptoms associated with HHV-6 reactivation.

Coxsackievirus B4 and A9 have also been related to AGEP (see under specific paragraph). Coxsackievirus B2 and B3 infection cause vesicular rash and/or transient macular rash [6,38–39]. Coxsackievirus B6 may cause an eruption resembling papular-purpuric gloves and socks

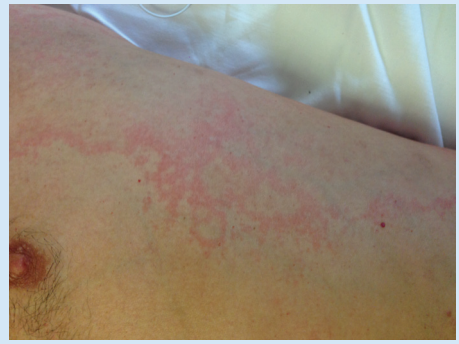

Figure 4. Parvovirus B19 infection: skin eruption have a reticulated appearance.

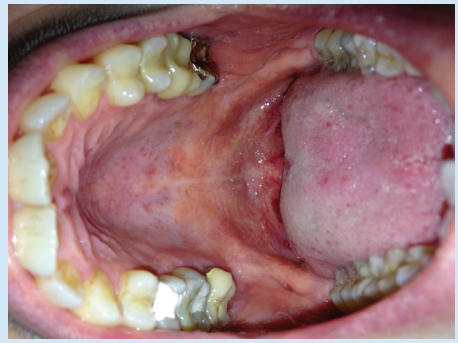

Figure 5. Enanthem in Coxsackievirus infection: papulovesicular lesions of the palate that quickly erode and form shallow ulcerations.

syndrome [40].

Echoviruses determined diffuse erythematous macular/maculopapular **(Figure 6)**/petechial rashes that may be associated with fever and/or meningitis starting on the face and upper trunk and spreading to the extremities. Echovirus 9 is the type most frequently found with fever, petechial eruption and signs of neurologic involvement that can mimic meningococcal meningitis or rickettsial disease. It can also cause erythematous macular localized eruptions **(Figure 7)** [41]. Echovirus 3 infection have been associated with petechial rash and meningitis [6]. Echovirus 11 infection can cause fever, pharyngitis, coryza and lymph nodes enlargement together with maculopapular/vesicular/urticarial rash. Skin lesions can be generalized or sparse and discrete, limited to extremities or to face and trunk [42]. Boston exanthem is a maculopapular/vesicular eruption involving face and trunk preceded by high fever caused by Echovirus 16 [43]. Enteroviruses, especially 25 and 32, have been associated with eruptive pseudoangiomatosis, a rare spontaneously regressing exanthem characterized by asymptomatic small, shiny red papules of angioma-like appearance surrounded by a characteristic pale halo. The lesions, often precede in children by fever, headache, vomiting, diarrhea or respiratory prodromal symptoms, involve checks and limbs with sudden onset resolving within a few days [44]. Echovirus 11 and 30 have also been linked with AGEP [13].

• Adenoviruses & other respiratory viruses

Adenoviruses, including 51 serotypes, inhabit the tonsils and leave the infected host through throat secretions. They are overlooked as cause of eruptions that develop during a respiratory/ocular infection. An exanthem associated with these infections occur primarily in children and occasionally in adults, during winter/spring. It manifests as a maculopapular [45] or vesicular exanthem beginning 1–2 days after the onset of fever and respiratory symptoms and characterized by centrifugal spread from the face toward the trunk and extremities [1,3], resolving in 3–5 days. A petechial exanthem has also been described with adenovirus type 7 [46]. AGEP is another disease linked to adenovirus [14]. Exanthems have been described, especially in children, in association with other viruses responsible for respiratory illnesses (rhinoviruses, influenza A/B viruses, respiratory syncytial virus, parainfluenza viruses). They are more common than we though and usually mild and not very remarkable [36]. Moreover, co-infection with EBV/CMV and other respiratory agents may cause maculopapular rash and palatal petechiae [46] making it difficult to assign the cause of the rash.

Exanthem is uncommon during influenza viruses infection (2–8% of patients), more frequent in children than adults [47]. It may be localized (face and hands) or generalized and described as macular/maculopapular, papular, petechial, itchy or not [47,48]. Respiratory infections lead to increased susceptibility to subsequent bacterial superinfection treated with antibiotics making difficult to distinguish between rash due to infection and allergic drug reaction. An erythematous macular rash due to respiratory syncytial virus might account for the so-called second attacks of measles or rubella [49].

• Rotavirus

Rotavirus infection is the most common cause of diarrhea in children worldwide. It may be accompanied by fever and vomiting followed by diarrhea and abdominal pain. An erythematous macular/maculopapular unnoticed exanthems lasting a few days may be present [1,3].

• GCS

Initially described in association with hepatitis, GCS has now been linked to numerous etiologies: EBV, CMV, PVB19, Coxsackieviruses, influenza A virus and vaccinations. Worldwide, with the advent of hepatitis B virus immunization, EBV is the most common cause of this exanthem. GCS primarily affects children (2–6 years of age) presenting as a papular/vesicular eruption,

little or not itchy, that typically affects the extensor surfaces of upper/lower extremities, buttocks and face with truncal sparing. It may be accompanied by fever, hepatosplenomegaly and lymphadenopathy. GCS is self-limiting lasting for 3–5 weeks [12].

• Eruptive hypomelanosis

Zawar *et al.* [50] recently described a novel exanthem in nine Asian children presented with eruptions of hypopigmented macules following coryzal symptoms. The lesions were extrafacial, symmetric, of very similar sizes and were of acute onset without any personal or family history of atopic diathesis. Eruptive hypomelanosis has been related to a viral infection because of a prodromal coryzal phase 1–2 weeks preceding the lesions, the eruptive nature with one or more successive eruptions of lesions, the fairly uniform sizes of lesions and spontaneous resolution without action intervention. However, detection of viral DNA (respiratory viruses or other viruses) by PCR in the plasma, peripheral blood mononuclear cells and lesional biopsy specimens have not yet fully investigated. Moreover, acute and convalescent sera should be tested in parallel to detect rises of the IgG titers against a panel of viruses [50].

• Superimposed lateralized exanthem

Also known as 'asymmetrical periflexural exanthema of childhood,' superimposed lateralized exanthem is prevalent in childhood but several cases have been reported in adults. The eruption begins unilaterally, near the axilla or groin, with erythematous, maculopapular, slightly pruritic lesions that spread centrifugally and may become bilateral and scaly. The lesions usually resolve in 5 weeks with fine desquamation. The hypothesis explaining the unilateral preponderance is an increased responsiveness of a polygenic predisposed body side to various infectious agent: adenovirus, parainfluenza virus, PVB19, HHV-6/7 and EBV. Some of these viruses provide particular features to the exanthem, for example, PVB19 may be responsible for a purpuric pattern. An asymmetrical presentation may also be observed in PR [51] and some superimposed lateralized exanthem may be considered as atypical PR.

• AGEP

AGEP is a rare acute febrile eruption often associated with leucocytosis, characterized by small non follicular sterile pustules arising over an edematous erythema. It affects mainly the upper trunk, folds and face resolving within 2 weeks with widespread desquamation. AGEP is usually drug induced but it may also be secondary to viral (enteroviruses, adenoviruses, CMV, EBV, hepatitis B virus) or bacterial (Chlamydia and mycoplasma) infections [13,52].

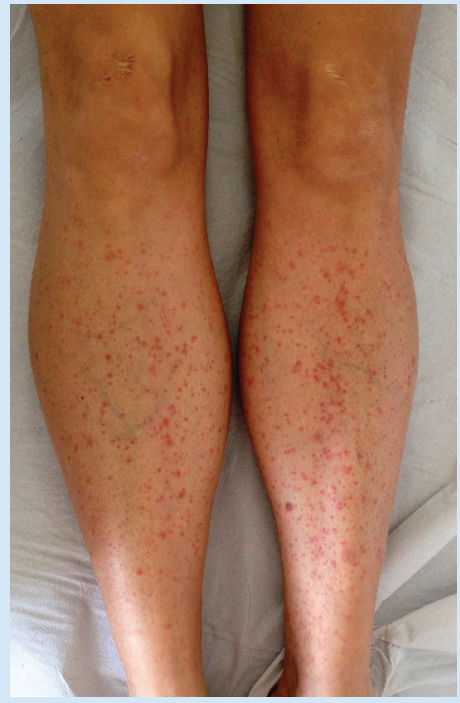

Figure 6. Maculopapular exanthem in Echovirus infection.

• Hepatitis B & C virus exanthems

These viruses, whose transmission may be vertical, blood-borne or through sexual exposure, are uncommon causes of exanthems. Skin manifestations in acute infections include fine erythematous, macular reticular rash over trunk and limbs that resolves with the onset of jaundice

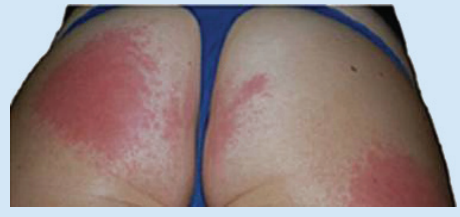

Figure 7. Erythematous macular localized eruptions in Echovirus infection.

Table 3. Arbovirus exanthems.

Virus	Geographical distribution	Presenting symptoms	Timing from symptoms to rash	Exanthem features	Patients with exanthem
Dengue fever	Central/South America, sub-Saharan Africa, Asia	Fever, chills, headache, vomiting, myalgia/arthralgia	3–5 days	Maculopapular eruption with islands of sparing; possible petechiae and purpura	83%
Dengue hemorrhagic fever	Central/South America, sub-Saharan Africa, South Central/Southeast Asia	High fever, vomiting, nausea	2–3 days	Petechiae and purpura	100%
West Nile fever	Widespread	Fever, headache, photophobia, myalgia, arthralgia	3–12 days	Macular/maculopapular rash on extremities and trunk;	20%
Rift Valley fever	Southeastern/western/ northern Africa, Madagascar, Yemen	Fever, myalgia, dizziness, headache, mood swings, tachycardia	2–4 days	Petechial rash and/or a petechial enanthema, involving mouth and/or throat	1%
Sandfly fever	Mediterranean Africa and Europe, Central Africa and Central Asia	Fever, chills, headache, myalgia, possible abdominal pain, diarrhea	Concomitant	Flushing erythema on face and neck; rarely subsequent macular rash	Frequent but no clear reference in the literature
Chikungunya fever	Sub-Saharian Africa, India, Southeastern Asia	Biphasic fever, headache, myalgia, phtophobia, vomiting	4–5 days	Maculopapular rash on extremities and trunk	40–50%
O'nyong-nyong fever	Uganda, Tanzania, Kenya	Fever and polyarthralgia	2–4 days	Maculopapular exanthem on trunk and extremities	70%
Mayaro fever	Brazil, Colombia	Fever, chills, headache, arthralgia	5 days	Maculopapular rash on trunk and limbs, possible petechial manifestation	24–67%
Ross river fever	Australia, Nuova Guinea	Mild fever, myalgia, arthralgia	5 days	Maculopapular rash on trunk and limbs	50–60%
Barmah Forest virus infection	Australia	Fever, lethargy, arthralgia	2–5 days	Maculopapular/vesicular/ purpuric eruption on trunk, limbs and face	70%
Sindbis virus	Africa, Asia, northern Europe	Fever, myalgia, arthralgia	2–10 days	Itchy papular rash on trunk and limbs	96%
Colorado tick fever	USA, Canada, Mexico	Biphasic fever, headache, myalgia, ocular disorders	4 days	Evanescent macular rash on trunk and limbs	5–15%
Zika virus	Africa, southeast Asia	Fever, headache, fatigue, aphthous ulcers, arthralgyas	Concomitant	Maculopapular on trunk	80%

after a few days to 4 weeks [53]. Hepatitis B virus infection has also been associated with AGEP [13].

• HIV

HIV transmission can occur through blood transfusions, organ transplantation, transplacentally and mostly through heterosexual/homosexual relationships. Cutaneous eruptions may be due to HIV *per se* or from other infectious and noninfectious causes. HIV seroconversion illness may be associated with a nonpruritic generalized maculopapular rash involving trunk, hands and feet sometimes associated with painful oral/genital erosions. Moreover, in HIV-patients, HHV-8 can cause KS, which manifests as angiomatous macules, plaques or nodules. Multicentric Castleman's disease associated with HHV-8 infection can also result in a recurrent maculopapular rash on limbs and trunk [54].

• Arboviruses & tropical fevers

Arboviruses are transmitted to humans by arthropods and maintained in nature by biological cycles involving a susceptible vertebrate host reservoir and hematophagous arthropods vectors. Arboviruses generally have an enzootic cycle and

only accidentally infect humans. However, for dengue virus or sandfly fever virus, humans are the natural vertebrate host. In these cases infections are endemic or epidemic if the arthropod vector is abundant. In arboviruses infections, more than half of the patients present a skin rash. The exanthem type varies according to the arbovirus and usually develops 1–12 days after the onset of fever, headache, conjunctival injection and arthromyalgias **(Table 3)** [55–59]. Nowadays, chikungunya virus and Zika virus are emerging pathogens that are spreading widely in different parts of the world. In chikungunya infection, a maculopapular rash of the trunk and extremities may be seen in more than 50% of the patients, sometimes associated with oral ulcers. The rash may evolve into petechiae, urticaria, xerosis or hypermelanosis and gradually fades in about 1 week. Some of the symptoms and signs of chikungunya infection are almost indistinguishable from those of dengue infection [60,61]. In Zika virus infection a diffuse maculopapular rash may be observed in up to 98% of the patient also in association with conjunctivitis and edema of hands and feet lasting only a few days [62–64]. Clinicians should include these exanthems in the differential diagnosis of patients who presented with fever, polyarthralgia and skin rash, especially if there is a recent history of travels to and from epidemic areas (Americas and India for chikungunya; Brasil for Zika virus).

• Viral hemorrhagic fevers

In viral hemorrhagic fevers skin and mucous membranes are the first sites where hemorrhagic manifestations are visible. Petechial/purpuric eruptions, ecchymosis, enanthem and mucosal bleeding are common features that occur usually 1 week after the onset of symptoms (fever, chills, myalgia, vomiting). Depending on the type of fever, there may be peculiar cutaneous manifestations that can orient in the diagnostic process. Dermatological signs may be helpful for a prompt diagnosis in febrile patients returning from endemic areas (South America or Africa) **(Table 4)** [65,66].

Bacterial exanthems

• Scarlet fever

Scarlet fever has been described in **Table 1**.

Toxic shock syndromes

Toxic shock syndromes (TSSs) are life-threatening illnesses caused by *Streptococcus pyogenes* (group A) or *Staphylococcus aureus* infection. Their virulence is mainly due to the production of circulating toxins, which often function as superantigens in causing clinical manifestations, morbidity and mortality associated with these diseases. The initial infectious outbreak may be localized in the skin, soft tissues, vagina or a surgical wound. The hallmarks of TSSs are high fever, myalgia, vomiting, diarrhea, headache and nonfocal neurologic abnormalities accompanying a macular erythroderma followed by desquamation, hypotension and multiple-organ involvement. Erythema and edema of palms and soles and scarlatiniform flexural accentuation of the rash are frequently observed. Petechial hemorrhages, mucous membranes hyperemia and strawberry tongue are often noted. Disseminated intravascular coagulation may supervene. TSSs usually complicate the use of absorbent tampons, barrier contraceptives, surgical and postpartum wound infections, burns, cutaneous lesions, osteomyelitis and arthritis [67].

• Rickettsial exanthems

Rickettsioses are worldwide-distributed zoonoses caused by obligate intracellular Gram-negative bacteria which have marked tropism for endothelial cells of small vessels. Rickettsiae are transmitted by arthropods to vertebrates via salivary secretions or feces. Rickettsial diseases vary in severity from self-limited mild illnesses to fulminating life-threatening infections and their main symptoms are fever, headache and cutaneous eruptions [68]. Cutaneous eruptions occur in almost 100% of the rickettsiosis.

Rocky Mountain spotted fever, widespread in all American countries, is caused by *Rickettsia rickettsii*, transmitted to humans by the bite of infected ticks.

It is considered the most severe rickettsiosis, since it can be lethal even in healthy people. After the incubation period (5–10 days), patients complain of fever, chills, conjunctival injection, myalgias and headache followed, 3 days after onset, by a macular rash starting on the wrists **(Figure 8)** [69] and ankles as small, not itchy pink lesions that become maculopapular with extension to extremities, buttocks, face and trunk. In a few days, petechial/purpuric lesions supervene which may coalesce to form large hemorrhagic areas. Up to 10% of the patients have no rash (Rocky Mountain 'spotless' fever). Eschars may be present. The disease recover in 2–3 weeks but in untreated cases fatality is high (20–50%) [68].

Table 4. Viral hemorrhagic fevers.

Virus type	Disease	Geographical distribution	Presenting symptoms	Exanthem features and associated signs/symptoms
Lassa virus	Lassa fever	West Africa	Fever, chills, headache	Disseminated nonpalpable petechiae and purpura; conjunctivitis, oral ulcers, pharyngitis, facial edema
Junin virus	Argentine hemorrhagic fever	Argentina	Fever, myalgia	Erythema of the face and trunk; conjunctival inection; petechiae on the trunk; petechial enanthem
Machupo virus	Bolivian hemorrhagic fever	Bolivia	Fever, headache, arthralgia	Diffuse petechiae, mucosal bleeding
Guanarito virus	Venezuelan hemorrhagic fever	Venezuela	Fever, headache, myalgia, arthralgia	Diffuse petechiae, mucosal bleeding
Sabià virus	Brazilian hemorrhagic fever	Brazil	Fever, headache, myalgia, arthralgia	Diffuse petechiae, mucosal bleeding
Hantaviruses: Hantaan, Seoul, Dobrava-Belgrade, Saaremaa	Hantavirus syndrome (renal syndrome)	Eastern Asia; western and central Europe but Seoul virus worldwide	Fever, myalgia, nausea, vomiting, conjuntival irritation	Erythematous-petechial rash on face, neck, shoulders, chest
Crimean-Congo virus	Crimean-Congo hemorrhagic fever	Africa, the Balkans, the Middle East and Asian countries	Fever, myalgia, dizziness, stiffness, vomiting, agitation followed by sleepiness, depression	Petechiae that widen into large ecchymosis, petechial enanthem
Marburg virus	Marburg hemorrhagic fever	Africa	Fever, myalgia, severe prostration	Maculopapular rash and petechial enanthem
Ebola virus	Ebola virus disease	West and central Africa	Fever, myalgia, sore throat; subsequently gastrointestinal signs	Maculopapular rash, petechiae, purpura, ecchymosis; oral-throat fissured lesions, gengival bleeding
Dengue virus	Dengue fever	Southeastern Asia, Africa, Mediterranean Europe	Fever, conjuntival injection, arthromyalgias	Maculopapular rash with petechiae during defervescence (favorable evolution)
Dengue virus	Dengue hemorrhagic fever	Central Asia, Central/South America	Fever, conjuntival injection, arthromyalgias	Maculopapular rash with petechiae during defervescence; hypotension, tachycardia, cyanosis
Omsk hemorrhagic disease virus	Omsk hemorrhagic disease	Siberia	Fever, myalgia, occipital rigidity, loss of taste, decrease in hearing	Petechial rash and petechial enanthem
Kyasanur forest virus	Kyasanur forest hemorrhagic fever	India, Saudi Arabia	Severe headache, mental disturbance, tremors, rigidity, photophobia	Suffusion of the conjuntiva, petechial hemorrhages on the mucous membranes, bleeding from nose, mouth

Epidemic typhus is caused by *Rickettsia prowazekii*, transmitted worldwide by body louses and by flying squirrel in the USA. The incubation period lasts 10–14 days and the exanthem occurs 5–7 days after appearance of systemic symptoms (fever, myalgias and sensory impairment). It has a centrifugal distribution, starting on the trunk and spreading to the extremities without palmoplantar and face involvement. The early rash consists of pink macules which fades when you press on it. Later, the rash becomes maculopapular and does not fade. The disease is fatal in 10–30% of patients. After some years from acute infection, *R. prowazekii* can reactivate and cause a recurrent form of epidemic typhus known as Brill–Zinsser disease: adipose tissue has recently been discovered in humans as reservoir for Rickettsiae [68].

Murine typhus is an acute febrile illness diffuse in tropical/subtropical regions caused by *Rickettsia Typhi* and *Rickettsia felis* transmitted by the fleas of rodents. The incubation time is 7–14 days. Signs/symptoms include fever, rash and arthralgia. The rash is macular/maculopapular, nonpruritic, starting on the trunk and spreading peripherally [68].

Mediterranean spotted fever, Rickettsialpox and Tsutsugamushi are acute febrile illness presenting with or without rash. The most common sign of infection is the inoculation eschar.

Mediterranean spotted fever, the most frequent rickettsiosis in Europe, is caused by *R. conorii*, transmitted by the brown dog tick. Sometimes conjunctivitis might represent the eye-inoculation site occurring after the manipulation of crushed infected ticks. After an incubation period of 5–7 days, the onset of fever (39–40°C) is accompanied by conjunctival injection, headache, photophobia and arthralgias. With the onset of fever, a small ulcer (tache noire) appears at the site of the tick bite: it has a necrotic center surrounded by erythematous skin and is associated with regional lymphnodes enlargement. On the 4th day of fever, a maculopapular/petechial exanthem appears on the forearms and extends to the body, involving face, palms and soles [68]. A vesicopustular rash has also been described [70]. Fever lasts into the 2nd week and the rash fades slowly.

Rickettsialpox, widespread worldwide, is caused by *Rickettsia akari* transmitted by the bite of the house-mouse mite. A papulovesicular lesion, 24–48 h after the bit, is the first manifestation evolving later in a crusted, ulcerated papule (eschar) with a red halo associated with regional lymphadenopathy. After a few days, fever, chills, photophobia, headache and myalgia begin followed by 2–3 days by a papulovesicular eruption on face, trunk and extremities and by a vesicular enanthem.

The vesicles can develop in pustules that later crust and resolve in a week. Rickettsialpox can resemble chickenpox but in chickenpox the vesicles are larger and surrounded by erythema in a 'dewdrop on a rose petal' fashion. Unlike chickenpox, the Tzank test does not show multinucleated giant cells and fever precedes the eruption.

Scrub typhus is caused by Orientia Tsutsugamushi (formerly *Rickettsia Tsutsugamushi*), following the bite of infected mite vectors. One to 2 weeks after the bite fever, chills, conjunctival injection, headache, myalgia, diarrhea and generalized lymphadenopathy suddenly start and an eschar develops at the bite site. A centrifugal maculopapular eruption primarily involving the trunk and extending to arms and legs may occur, fading within a few days [68].

• Anaplasma & erlichia

Anaplasma phagocytophilum and *Ehrlichia chaffeensis* are the etiologic causes of anaplasmosis and herlichiosis, tick-borne diseases that are widespread in the USA. Accompanying fever, headache, myalgias, arthralgias, vomiting and cough, a rash is present in less than 10% of Anaplasmosis and in 30% of Erlichiosis. The rash is maculopapular or petechial involving the trunk and sparing palms and soles [71].

• Syphilitic roseola

Secondary syphilis is the stage in which generalized manifestations occur on the skin and mucous membranes. Patients may complain of constitutional symptoms but the majority of them have only skin rash and generalized lymphadenopathy. Eruptions develop in 80–95% of cases, occurring within 3 months from initial infection and may mimic other exanthems. A fading symmetrical, pink or coppery-red, nonitching macular eruption (roseola syphilitica) that follows on the back the lines of cleavage may pass unnoticed and maculopapules may be the first sign of the diseases **(Figure 9)**. The lesions have a scaly surface with a squamous ring (Biet's collarette). Palms and soles may be involved with more pronounced papulosquamous lesions. Vesicular and pustular lesions are rare. Papules may coalesce into gray patch with erosions covered by macerated scales on the oral mucosa, tongue or tonsillae [72].

• Neisseria meningitidis

The skin lesions associated with meningococcemia and meningococcal meningitis, occurring in 40–90% of cases, result from damage of small dermal blood vessels. Transient erythematous macular/maculopapular eruptions involving any part of the body are seen but a purpuric eruptions on trunk and limbs is typical.

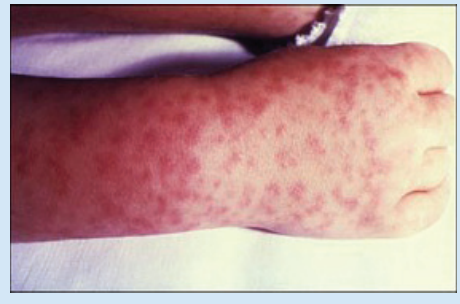

Figure 8. Macular rash starting on the wrists in Rocky Mountain spotted fever.
Adapted with permission from the CDC [69].

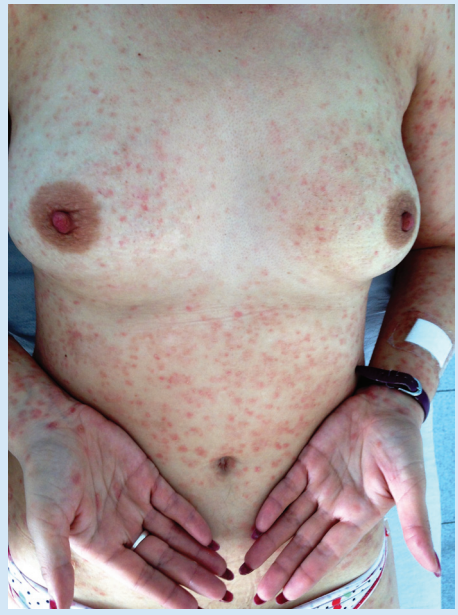

Figure 9. Symmetrical, pink/erythematous, nonitching macular eruption (roseola syphilitica).

The petechiae may also affect the mucous membranes (meningococcal conjunctivitis) and have a subungual location. Similar lesions can be caused in other bacterial meningitis due to *Streptococcus pneumoniae*, hemophilus influenza and listeria monocytogenes [73]. Meningococcemia may be in differential diagnosis with enteroviral infections in the presence of a patient, especially a child, with fever, headache, petechial exanthem and neck stiffness. Furthermore, no child with a rash confined to the distribution of the superior vena cava (petechiae above the nipple line) had meningococcal infection. In adults with bacterial meningitis rash is present in 26% but almost all had at least two of the four following symptoms: fever, headache, neck stiffness and changes in mental status [74].

- ***Neisseria gonorrhea***

Neisseria gonorrhea is a Gram-negative diplococcus that cause gonorrhea and occasionally disseminated infections. However most patients with septic gonococcal infection have no symptoms indicating a sexually transmitted disease [75]. Bacteremic dissemination is regularly associated with arthralgia and skin lesions (arthritis-dermatitis syndrome), occurs in 1–3% of the patients and usually develops within 2–3 weeks from the primary infection. *Neisseria gonorrhea* spread from a primary site, such as endocervix, urethra, pharynx or rectum, and disseminate to the blood to infect any organs. Patients may present with rash, fever, arthralgias, migratory polyarthritis, septic arthritis, tenosynovitis; meningitis, endocarditis or osteomyelitis are rare. The skin lesions, present in 60% of the patients, are few in number (<20 lesions) but are a crucial diagnostic sign. There may be violaceous macular/maculopapular/vesicular lesions with a dusky red halo evolving into pustules and bullae that may become hemorrhagic or necrotic. Purpuric lesions and subcutaneous painful nodules may be present. Urticarial lesions and erythema multiforme has also been reported. The lesions, which predominate on the trunk and limbs including fingers, palms and soles, may be in various stages of evolution resolving over a few days without scars [75].

- ***Staphylococcus aureus***

Staphylococcus aureus from pyodermas, soft tissue infections or medical devices can invade lymphatic and blood vessels resulting in dissemination of the infection at distant sites. In acute *S. aureus* endocarditis and bacteremia, skin and mucous membranes lesions occur in the majority of patients and provide a clue to the diagnosis. Petechial eruption occurring in crops affects mainly the extremities (including palms and soles) and oral mucous membranes and conjunctivae. These eruptions as well as splinter hemorrhages (subungueal hemorrhages), Osler's nodules (erythematous, painful nodules over the limbs, palms, soles and on the pads of the fingers and toes) and Janeway lesions (erythematous macules/papules on palms and soles) are common in bacteremia and endocarditis due to streptococci, enterococci and gonococci [76]. These eruptions can be the overture of hemorrhagic infarction and necrosis of the skin due to disseminated intravascular coagulation. In focal infections, erythematous macular/maculopapular eruptions are described [1].

- **Enterobacteriaceae**

Enterobacteriaceae is a family of Gram-negative bacteria that are residents of the GI tract including *Escherichia*, *Klebsiella*, *Salmonella*, *Shigella*, *Proteus*, *Enterobacter* and *Yersinia*. They may cause sepsis, lower respiratory tract infections, endocarditis and infections of CNS, skin and soft tissues, urinary tract, joints, bones and eyes.

Escherichia coli cause maculopapular [1,3] and localized macular exanthems during urinary infections and perinephric abscess.

Klebsiella pneumoniae may colonize the skin, pharynx or GI tract. The hands of hospital personnel can spread rapidly the infection leading to nosocomial outbreaks. The spectrum of clinical syndromes includes pneumonia, bacteremia, urinary tract infections, cholecystitis, diarrhea, wound infections, osteomyelitis and meningitis. Skin eruptions caused by Gram-negative bacteria is uncommon in newborns but *Klebsiella* may cause maculopapular exanthems arising during septicemia [77].

Salmonella typhi can cause the so-called 'rose spots,' pink maculopapules which arise in crops of 10–20 lesions on the anterior trunk, fading in a few days [78].

Shigella species cause bacillary dysentery and, mainly in children and immunocompromised patients, also extragastrointestinal complications (septicaemia, neurologic involvement). Rose spots, resembling salmonella infections, have been described [79].

Yersinia enterocolitica and *Yersinia pseudotuberculosis* are zoonosis acquired by ingestion of contaminated food/water which occur worldwide. *Yersinia enterocolitica* is a common cause of diarrheal disease and mesenteric adenitis that clinically mimics appendicitis, whereas *Y. pseudotuberculosis* most commonly causes mesenteric adenitis. Both species can cause pharyngitis, septicemia, focal infections in multiple organs, postinfectious erythema nodosum and reactive arthritis. During yersiniosis a scarlet fever-like illness and maculopapular, papulovesicular, erythema multiforme-like eruptions have been described [80].

• Other bacteria (miscellanea)

Maculopapular eruptions involving mainly the trunk may be caused by *Chlamydia psittaci* and *trachomatis*, *Arcanobacterium hemoliticum, Streptococcus pyogenes* [1], *Streptococcus dysagalactiae* [81], *Borrelia burgdorferi* and *Haemophilus influenzae* [1]. *Mycoplasma pneumoniae* is a common cause of community acquired pneumonia which may be responsible for mucocutaneous lesions associated with systemic infection [82]. Prodromal symptoms (cough and fever) usually precede the skin eruption with vesico-bullae followed by maculopapular lesions [36]. An acral distribution of the exanthem is frequent. Oral lesions often accompany the cutaneous eruptions and in a third of patients are not associated with skin involvement.

Disseminated pruritic papules and pustules (hot tub folliculitis) may arise on the trunk and limbs immersed in community heated wading pool, swimming pools, whirlpool, hot tubes or after-diving suit dressing contaminated by *Pseudomonas aeruginosa* **(Figure 10)**. In addition, painful erythematous nodules may develop on the soles immersed in contaminated wading pool [83].

Bartonella henselae and *Bartonella Quintana* are Gram-negative bacteria which cause bacillary angiomatosis, vascular purple papules or bleed nodules arising on the trunk and limbs, occurring most commonly in immunocompromised patients. Papules and nodules can group in indurated plaques resembling pyogenic granuloma or KS. Subcutaneous nodules and visceral lesions may occur. The patient may complain of chills, headache, fever and anorexia and the lesions may be few or hundreds [84]. *Brucella* species cause a zoonotic infection which is endemic in Mediterranean countries. Skin involvement is rare but disseminated macular rash on the trunk and extremities have been described [85].

Legionella pneumophila is a Gram-negative bacillus, that may cause pneumonia in adults. The term Legionnaires' disease is given to the severe pneumonia and systemic infections presenting with fever, headache, nausea, diarrhea, abdominal pain and myalgias, caused by *Legionella*. *Legionella* species affect susceptible patients as a result of age (patients <1 year or elderly), underlying debilitating conditions or immunosuppression. During pneumonia, maculopapular eruption and pretibial erythema have been described [86].

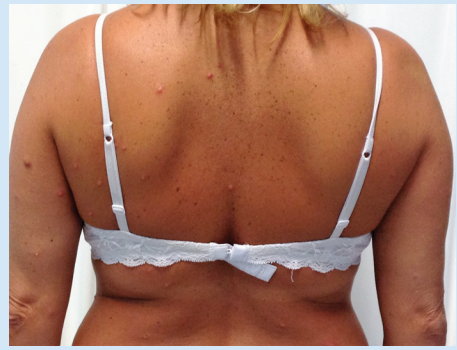

Figure 10. Disseminated pruritic papules and pustules (hot tub folliculitis) on the trunk in Pseudomonas infection.

Table 5. Common infectious agents causing exanthems and enanthems: morphology of the skin and mucosal lesions.

Agent	Disease	Exanthem morphology	Enanthem morphology
Viruses			
Herpes simplex virus 1/2	Herpes labialis/genitalis	Grouped vesicular lesions in orolabial or genital areas evolvinging to erosions	
Herpes simplex virus 1	Eczema herpeticum	Vesiculopustules on the upper part of the body evolving to painful hemorrhagic, crusted erosions.	
Varicella zoster virus	Shingles	Unilateral erythematous maculopapular lesions that quickly develop into grouped vesicles and crusts	
Citomegalovirus	Mononucleosis; atypical exanthems; GCS	MP, U pattern in immunocompetent; P, PE, VB, PU in immunosuppressed	MPP
Epstein–Barr virus	Mononucleosis; atypical exanthems; GCS; APEC; AGEP	MP; U; PE	MP
Human herpes virus 6 and 7	Pityriasis rosea; atypical exanthems; DRESS; GCS; APEC	M; MP; MPP	M; MP; MPP
Human herpes virus 8	Atypical exanthems	MP	MP
Parvovirus B 19	Fifth disease; atypical exanthems; GCS	M; MPP	M; MPP
Coxackieviruses	HFM; atypical exanthems; AGEP; GCS	EV; MP	EV; MP
Echoviruses	HFM; atypical exanthems; AGEP	M; MP; MPP; U	EV; MP
Enteroviruses	HFM; atypical exanthems; AGEP	EV; MP	EV
Adenoviruses and other respiratory viruses	Atypical exanthems; AGEP; GCS; APEC	M; MP; EV; PE	MP; MPP
Rotavirus	Atypical exanthems	M; MP	
Hepatitis B and C viruses	Atypical exanthems; AGEP	M	
Human immunodeficiency virus	Seroconversion illness	MP	M; MP
Arboviruses	Atypical exanthems	MP; MPP	MP; MPP
Viruses responsible for hemorrhagic fevers	Atypical exanthems	MPP; PE	MPP; PE
Bacteria			
Streptococcus pyogenes; *Staphylococcus aureus*	Atypical exanthems; TSS	M; MP; MPP	MP
Rickettsia rickettsii	Rocky Mountain spotted fever	M; MP; MPP	
Rickettsia prowazekii	Epidemic typhus	M; MP	
Rickettsia typhi and *Rickettsia felis*	Murine Typhus	M; MP	
Rickettsia conorii	Mediterranean spotted fever	MP; MPP; VP	
Rickettsia akari	Rickettsialpox	PV	V
Rickettsia tsutsugamushi	Scrub typhus	MP	
Anaplasma phagocytophilum and *Ehrlichia chaffeensis*	Anaplasmosis and Erlichiosis	MP; MPP	PE
Treponema pallidum	Secondary syphilis	M; MP	P
Neisseria meningitidis	Atypical exanthem	M; MP; PE	PE
Neisseria gonorrhea	Atypical exanthem	M; MP; V; PU; PE; U	
Staphilococcus aureus	Atypical exanthems	M; MP; PE	PE
Escherichia coli	Atypical exanthems	MP	
Klebsiella pneumoniae	Atypical exanthems	MP	
Salmonella typhi	Atypical exanthems	MP	
Shigella species	Atypical exanthems	MP	
Yersinia enterocolitica and *Y. pseudotuberculosis*	Atypical exanthems	MP; PV	

AGEP: Acute generalized exanthematous pustolosis; APEC: Asymmetric periflexural exanthem of childhood; EV: Erythematovesicular; GCS: Gianotti Crosti syndrome; M: Macular; MP: Maculopapular; MPP: Maculopapular with petechiae; P: Papular; PE: Petechial; PU: Pustular; TSS: Toxic shock syndrome; U: Urticarial; V: Vesicular; VB: Vesicobullous; VP: Vesicopustular.

Table 5. Common infectious agents causing exanthems and enanthems: morphology of the skin and mucosal lesions (cont.).

Agent	Disease	Exanthem morphology	Enanthem morphology
Bacteria			
Chlamydia psittaci, *C. trachomatis*, *Arcanobacterium hemoliticum*, *Streptococcus pyogenes*, *Streptococcus dysagalactiae*, *Borrelia burgdorferi* and *Haemophilus influenzae*	Atypical exanthems	MP	
Chlamydia pneumoniae; *Mycoplasma pneumoniae*	Atypical exanthems	VB; MP	M
Pseudomonas aeruginosa	Atypical exanthems	P; PU	
Bartonella henselae and *B. quintana*	Atypical exanthems	P	
Brucella species	Atypical exanthems	M	
Legionella pneumophila	Atypical exanthems	MP	
Francisella tularensis	Tularemia	MP; MPP	
Listeria monocytogenes	Listeriosis	MP; PV	
Acinetobacter baumanii	Atypical exanthems	MP	
Fusobacterium necrophorum	Atypical exanthems	MP	
Parasites			
Toxoplasma gondii	Atypical exanthems	MP; P; PV; PE	
Plasmodium vivax	Atypical exanthems	MP; U	
Plasmodium falciparum	Atypical exanthems	M; PE	
Helminths			
Enterobius vermicularis	Atypical exanthems	M	
Ascaris lumbricoides	Atypical exanthems	U	
Toxocara canis; *Toxocara cati*	Atypical exanthems	MP; V	
Schistosomes	Atypical exanthems	M; PV; PU; U; PE	
Trichinella spiralis	Atypical exanthems	MP; U	

AGEP: Acute generalized exanthematous pustolosis; APEC: Asymmetric periflexural exanthem of childhood; EV: Erythematovesicular; GCS: Gianotti Crosti syndrome; M: Macular; MP: Maculopapular; MPP: Maculopapular with petechiae; P: Papular; PE: Petechial; PU: Pustular; TSS: Toxic shock syndrome; U: Urticarial; V: Vesicular; VB: Vesicobullous; VP: Vesicopustular.

Francisella tularensis is a Gram-negative, pleomorphic bacillus which causes tularemia, a reemerging disease worldwide. Francisella resides in more than 100 species of animals and the infection usually follows contact with infected animals or their bite. Tularemia can be divided in systemic form (without indication of the inoculation site) and the most common ulceroglandular form (primary lesions on the hands with regional lymphadenitis). Multiple organs may be involved and dissemination of the infection may occur. The onset of any of the forms is sudden with fever, chills, headache and arthromyalgias. A painful papule appears at the site of inoculation that become an ulcer cover by an eschar associated to regional lymph-nodes enlargement. From 6 to 30% of all forms of tularemia are accompanied by generalized maculopapular/petechial exanthems [87].

Listeria monocytogenes is a Gram-positive bacterium acquired by contaminated food, contaminated soil or inhalation of the bacterium. In immunocompetent adults the infection cause a mild illness with nonspecific symptoms (fever, nausea, vomiting and diarrhea). In immunocompromised patients, it may cause CNS involvement, endocarditis, pneumonia, osteomyelitis and arthritis. In pregnancy, the infection may lead to fetal transplacental infection. Neonatal listeriosis may be presents as early or late onset listeriosis. Early onset listeriosis may result in stillborn, premature birth or sepsis, pulmonary, hepatic, gastrointestinal or neurologic involvement. The newborn may present dark red papular, pustular/petechial skin eruption on trunk and legs or a generalized maculopapular exanthem that is the clue for listeria neonatal infection [88]. Late onset meningitis and septicemia are acquired through vaginal transmission. Neonatal late-onset and adult listeriosis cutaneous eruptions have rarely been described. Direct inoculation of listeria

Table 6. Clinical features and diagnostic methods of viral exanthems.

Virus	Incubation period	Clinical features in addition to rash	Laboratory diagnosis	Comments on diagnosis
Enterovirus	3–10 days	Aseptic meningitis, encephalitis, acute flaccid paralysis, upper respiratory tract infection, myopericarditis	NAT: respiratory tract samples, CSF, blood IFA: respiratory samples Serology: detection of Neutralizing Antibodies	NAT: routine qualitative assays have poor clinical sensitivity
Parvovirus B19	4–14 days	Arthropathy, hydropsfetalis and intrauternine death myopericarditis	Serology: Parvovirus B19-specific IgM NAT: blood, bone marrow, placenta, amniotic fluid, fetal tissue	IgM is detectable at 2 weeks with the conclusion of the viremia. IgG appears around 1 week later with rash
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	Serology is not generally useful. IgG 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 syndrome	NAT: vescicular fluid, CSF IFA: vesicular fluid, CSF Serology: VZV-specific IgM	Varicella is highly contagious. Clinical findings are usually sufficient to make the diagnosis NAT is highly specific Serology is not generally useful IgG may confirm prior exposure to VZV, most useful in establishing risk following contact in the antepartum period
EBV	4–8 weeks		Serology: EBV-specific VCA IgM; EBNA IgG; early antigen IgG NAT: qualitative assays in tissue specimens, quantitative assays in blood	EBV VCA IgM has good specificity in the acute phase. In infants, it has a lower sensitivity, and looking for IgG seroconversion is important. EBNA IgG persists for life after infection, and antibodies to early antigen are generally positive for up to 2 years after the acute phase
CMV	4–12 weeks	Mononucleosis syndrome, reactivation in critically unwell or immunocompromised hosts	Serology: CMV-specific IgM NAT: qualitative assays in tissue specimens, quantitative assays in blood	CMV-specific IgM is detectable within 2 weeks of exposure and falls over several months. It is also detectable during reactivation. Low-level CMV viremia detected by NAT is usually not significant in the absence of end organ CMV disease
HHV-6	5–15 days	Encephalitis and probably multiple slcerosis 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
HHV-8	Unknown	KS, primary effusion lymphoma, Castleman's disease Reactivation in immunocompromised hosts	Serology NAT: qualitative and quantitative assays in blood plasma, skin, lymph nodes, lungs, GI tract	HHV-8 Plasma viremia is a marker of active AIDS-KS disease
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 IgM IFA and NAT: in respiratory and/or urine specimens	Sensitivity of measles-specific IgM is 67% if serum is collected <72 h after the onset of rash. Cross-reactivity from parvovirus B19, rubella and HHV-6 Sensitivity of IFA reported to be 46–54%

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; KS: Kaposi's sarcoma; NAT: Nucleic acid testing; VCA: Viral capsid antigen; VZV: Varicella zoster virus.

Table 6. Clinical features and diagnostic methods of viral exanthems (cont.).

Virus	Incubation period	Clinical features in addition to rash	Laboratory diagnosis	Comments on diagnosis
Rubella	15–20 days	5 days prodrome of fever, headache and upper respiratory tract symptoms; arthralgias involving the wrists, elbows and ankles lasting up to 3 weeks; more severe complications include hemolytic anemia, thrombocytopenia, pericarditis, myocarditis and encephalitis	Serology: rubella-specific IgM NAT: 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 IgM, a fourfold rise in IgG between acute and convalescent

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; KS: Kaposi's sarcoma; NAT: Nucleic acid testing; VCA: Viral capsid antigen; VZV: Varicella zoster virus.

in the skin of veterinarians who have exposure to animal products of conception or gardeners may hesitate in nonpainful, nonpruritic, papulopustular or papulovesicular eruptions that are usually self-limited and resolve without antibiotic treatment [88].

Acinetobacter species are highly resistant, opportunistic, pleomorphic aerobic Gram-negative bacteria commonly isolated from the hospital environment and hospitalized patients, capable of causing infection in immunocompromised patients. Among Acinetobacter species, *Acinetobacter baumanii* accounts for the most of the infections and may involve any organ, including skin and soft tissues; disseminated infection may occur causing abscess formations. A diffuse maculopapular rash with petechiae involving trunk, limbs, palms and soles has been reported in early prosthetic valve endocarditis [89].

Fusobacterium necrophorum is an anaerobic Gram-negative bacterium causing acute pharyngotonsillitis that may lead to peritonsillar cellulitis with thrombophlebitis of the internal jugular vein. A nonpruritic painful maculopapular rash on the extremities has been described during this infection [90].

Parasitic exanthems

Toxoplasma gondii is acquired by ingestion of contaminated food/water or in utero. Cutaneous toxoplasmosis occurs as congenital or acquired infection (including acute and reactivated forms). In toxoplasma infection, cutaneous involvement occurs in less than 10% of immunocompetent patients, but the frequency may be greater in immunocompromised hosts. In acquired infections, cutaneous lesions may be maculopapular, papulopustular, vesicular, nodular, purpuric or lichenoid. In congenital infections, skin lesions are usually hemorrhagic/necrotic papules on the trunk [1,3,91].

During malaria caused by *Plasmodium vivax* and *Plasmodium falciparum* petechiae and purpura have been reported [92,93]. More specifically, maculopapular skin eruptions and urticarial lesions occur in malaria by *Plasmodium vivax* [92]. Asymptomatic reticulate erythema with petechiae involving upper and lower limbs has been associated with malaria by *P. falciparum* [93].

Helminths exanthems

Rare cases of exanthems related to helminths have been described. Transmission occurs by ingestion of contaminated food (especially fruits/vegetables) with mature eggs of the worm. A macular exanthem has been described during *Enterobius vermicularis* infection whereas *Ascaris lumbricoides* can cause urticarial lesions, both associated with pruritus [1,94]. *Strongyloides stercoralis* infection may cause a characteristic thumbprint periumbilical purpura due to larvae transmigration across the vascular endothelium into the dermis with red cells extravasation [94]. Toxocariasis is an infection caused by the ingestion of larvae of the dog roundworm *Toxocara canis* or the cat roundworm *Toxocara cati*. It may presents with pruritic eosinophilic folliculitis diffuse over face, trunk and upper extremities and a widespread erythematous, maculopapular/vesicular eruption involving abdomen, thighs, upper arms and palms [95]. Cercarial or schistosome dermatitis is an acute eruption caused by an immunologic reaction to the cercarial stage

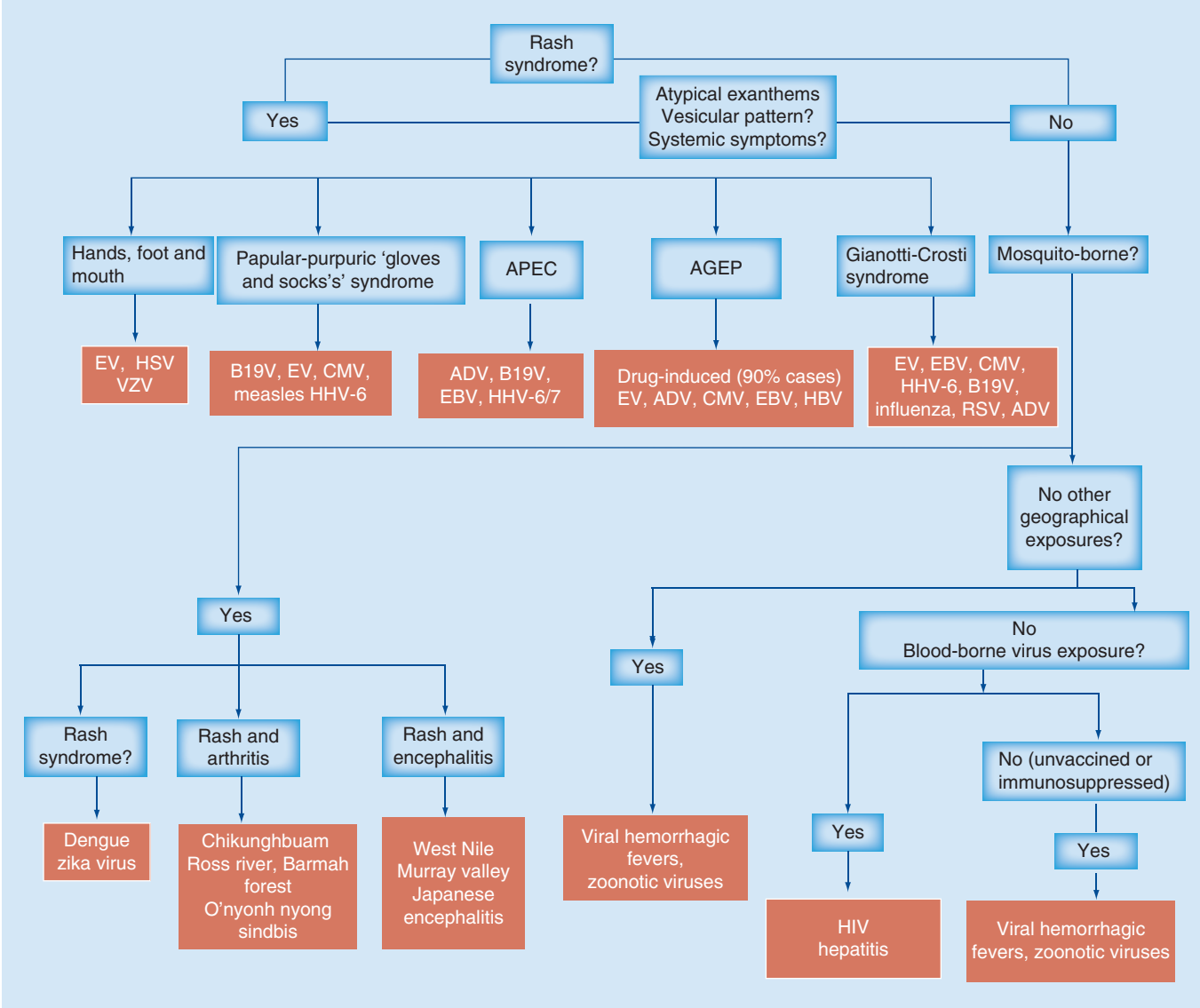

Figure 11. Flow chart of a preclinical approach used to determine possible viral etiologies of exanthems.
AGEP: Acute generalized exanthematous pustolosis; APEC: Asymmetric periflexural exanthem of childhood; B19V: Parvovirus B19; CMV: Cytomegalovirus; EBV: Epstein–Barr virus; EV: Erythematovesicular; HHV: Human herpesvirus; HSV: Herpes simplex virus; VZV: Varicella zoster virus.

of nonhuman schistosomes, whose hosts are birds and small mammals. Schistosomes which cause invasive disease in humans may cause a similar skin eruption soon after exposure to the helminth. On re-exposure after sensitization, the rash may begin sooner and be more severe. A pruritic, erythematous macular eruption develops and may progress to papulovesicular/pustular/urticarial lesions. Petechiae and purpura may be present. The rash spares area of the body covered by clothing [96]. Patients affected by Trichinosis, caused by *Trichinella spiralis*, may present periorbital edema, conjunctival hemorrhages, splinter hemorrhages of the fingernails and maculopapular/urticarial eruption on the limbs. In 10% of them, bilateral asymptomatic hand swelling and macular erythema of the palms occur and resolve with desquamation [97].

• Diagnosis

In two of our previous studies, we found a relationship between morphological pattern of the exanthem and etiology [1,3]: the erythematous-vesicular pattern was primarily related to viral infections and the urticarial pattern with parasitic infections. The maculopapular pattern was

EXECUTIVE SUMMARY

Atypical exanthems

- An exanthem is defined as any eruptive skin rash that may be associated with lesions of the mucous membranes (enanthem), fever or systemic symptoms.
- Beside the 'classic exanthems,' other exanthems with different morphology and caused by different infectious/toxic agents may occur ('atypical exanthems'). Among the atypical exanthems with infectious etiology, viral, bacterial, parasitic and helminths infections are implicated.

Viruses

- Many viral infections are responsible for atypical exanthems. The main correlations between virus and type of exanthem are listed below. Herpes simplex virus (HSV)-1 and 2 are related to eczema herpeticum; varicella zoster virus to shingles; cytomegalovirus and Epstein–Barr virus to maculopapular exanthems; Human herpesvirus (HHV) 6 and HHV-7 to Pityriasis rosea; HHV-8 to Kaposi's sarcoma; B19V to maculopapular/purpuric eruptions; enteroviruses to hand-foot-mouth syndrome and maculopapular or papulo/vesicular eruptions; respiratory viruses and rotavirus to mild maculopapular exanthems; hepatitis B virus and hepatitis C virus to macular reticular rashes; HIV to generalized maculopapular rash; arboviruses with maculopapular/petechial exanthems. Viral exanthems are often associated with enanthem.

Bacteria

- Many bacterial infections are responsible for atypical exanthems. The main correlations between bacterium and type of exanthem are listed below. *Streptococcus pyogenes* (group A) and *Staphylococcus aureus* may be related to the macular erythroderma of the toxic shock syndrome; Rickettsiae to maculopapular exanthems that often become petechial/purpuric; *Anaplasma phagocytophilum* and *Ehrlichia chaffeensis* to maculopapular or petechial exanthem; secondary syphilis is associated with a symmetrical, pink or coppery-red macular eruption; *Neisseria meningitidis* and gonorrhea with erythematous macular/maculopapular eruptions; Enterobacteriaceae may cause maculopapular rashes. Many other bacteria (*Chlamydia psittaci* and *trachomatis*, *Arcanobacterium hemoliticum*, *Streptococcus pyogenes*, *Streptococcus dysagalactiae*, *Borrelia burgdorferi*, *Haemophilus influenzae* and others) may be related to skin eruptions with different morphology (maculopapular/vesicular/pustular exanthems).

Parasites

- Toxoplasma gondii may be associated, in acquired infections, with maculopapular, papulopustular, vesicular, nodular, purpuric or lichenoid eruptions. In congenital infections, skin lesions are usually hemorrhagic/necrotic papules. *Plasmodium vivax* and *Plasmodium falciparum* may cause petechial/purpuric skin eruptions..

Helminths

- Rare cases of exanthems related to helminths have been described. A macular exanthem has been described during *Enterobius vermicularis* infection, whereas *Ascaris lumbricoides* can cause urticarial lesions. *Toxocara canis* or *Toxocara cati* may be associated with a widespread erythematous, maculopapular/vesicular eruption.

Relationship between morphological pattern of the exanthem & etiology

- The erythematous-vesicular pattern was primarily related to viral infections and the urticarial pattern with parasitic infections. The maculopapular pattern was almost evenly distributed among the various etiologies, although the color was duskier in drug-related exanthems. Enanthems were most often infectious in nature, especially viral.

Laboratory diagnosis

- Specific serology is not sufficient by itself to identify an active infection. The detection of pathogen-specific IgM reveals a viral reactivation or a primary infection. IgG seroconversion is considered evidence of infection: at least a four-times difference in IgG titers in two consequential samples (collected in the acute and convalescent phases) of the same patient may be helpful. Nested PCR techniques can be used to detect the viral DNA in plasma or serum, a well-known marker of active viral replication and active infection. Although culture tests are slow and have low sensitivity, they remain the gold standard for diagnosis of infections for which molecular methods, such as nested PCR, are validated against.

EXECUTIVE SUMMARY (CONT.)

Importance of the diagnosis

- Etiological diagnosis of the atypical exanthems especially the infectious ones, remains difficult but crucial for both the patient and community concerning issues such as time off school, immunizations and risk for pregnant women and immunocompromised patients.

almost evenly distributed among the various etiologies, although the color was duskier in drug-related exanthems **(Table 5)**. Enanthems were most often infectious in nature, especially viral. Regarding seasonality, viral infections resulted more prevalent during spring/summer whereas bacterial infections during fall/winter [1,3].

Laboratory examinations may help in identifying the causative infectious agent.

Specific serology is not sufficient by itself to identify an active infection. The detection of pathogen-specific IgM reveals a viral reactivation or a primary infection but one has to remember that cross-reactivity with other infectious agents may give false-positive results. IgG seroconversion is considered evidence of infection: at least a four-times difference in IgG titers in two consequential samples (collected in the acute and convalescent phases) of the same patient may be helpful. To differentiate acute from previous infection, it is useful to determine the maturity of the IgG response through the measurement of IgG avidity. High IgG avidity points out a past or recurrent infection whereas low IgG avidity indicates a recent primary infection, even if only one serum sample is available [98,99].

Nested PCR techniques can be used to detect the viral DNA in plasma or serum, a well-known marker of active viral replication and active infection [7,18,36,100].

Antigen detection by immunofluorescence is used for the diagnosis of HSV and VZV infections. Although culture tests are slow and have low sensitivity, they remain the gold standard for diagnosis of infections for which molecular methods, such as nested PCR, are validated against **(Table 6)**.

Histological examination usually does not provide a conclusive etiological diagnosis in infectious exanthems. Conversely, if the differential diagnosis includes a reaction to a drug, then a skin biopsy should be promptly performed, especially in life-threatening conditions such as DRESS syndrome [26,27], since it may help to elucidate the diagnosis. Immunohistochemistry with specific monoclonal antibodies is helpful to detect specific antigens belonging to virus/bacteria/parasites [101].

Conclusion

Understanding the etiology of atypical exanthems, especially the infectious ones, remains difficult but crucial for patient and community concerning issues such as time off school, immunizations, risk for pregnant women and immunocompromised patients. However, the morphological patterns, seasonal occurrence, presence of enanthem and systemic symptoms may offer the physician important clues to make a quick etiological diagnosis **(Figure 11)**, which, if confirmed by tests, ensures timely and appropriate treatment.

Future perspective

In case of viral exanthems, the management is mainly supportive because of the lack of specific antiviral therapies. Nowadays, viral exanthems are becoming more common due to the decline of vaccination rates, the increase of the global population, the vector movements and the emerging novel viruses. Moreover, new immunosuppressive therapies have led to higher rates of reactivation of latent viruses. Clinicians should be alert and trained to recognize atypical presentations of established viruses and other infectious agents. Measures of infection control remain the main strategy to limit further transmission of infections.

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