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Review Article

# Skin manifestation and diagnosis of febrile diseases by COVID-19 and other ribonucleic acid viruses: The diagnostic clues

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## Abstract

Many febrile diseases caused by ribonucleic acid virus infection demonstrate cutaneous manifestations with preceding prodromes. This review provides a flowchart highlighting the diagnostic clues of viral exanthem. Besides febrile prodromes, patients with chikungunya virus have severe arthralgias and macular hyperpigmentation on the noses. Coronavirus disease 2019 demonstrates unique acrocyanosis and pseudofrostbite besides erythematous rash and urticaria, suggesting abnormal coagulation. Dengue fever should be suspected when patients in the tropical region present with biphasic fever, headache, retroorbital pain, and centrifugal morbilliform rash. Dengue hemorrhagic fever, a potentially fatal complication, results from systemic vascular leakage. High-temperature fever and sudden-onset severe headache raise the possibility of Ebola virus infection. Patients with hand-foot-and-mouth disease may experience morbilliform or vesicular eruption, especially over the hands, feet, and oral mucosa. In acute human immunodeficiency virus infection, maculopapular eruptions often appear on the face and neck after prodromes. Primary human T-lymphotropic-III virus infection can induce widespread maculopapular or roseola-like exanthem, sparing the hands and feet. Cutaneous manifestations of rotavirus include generalized maculopapular rash, Sweet's syndrome, Henoch–Schonlein purpura, Gianotti–Crosti syndrome, and acute hemorrhagic edema. Rubella is usually suspected when low-grade fever and lymphadenopathy are accompanied by a discrete pinpoint-sized maculopapular rash, which spreads and diminishes faster than measles. Cough, coryza, and conjunctivitis followed by morbilliform eruptions and Koplik's spots are diagnostic of measles. Exanthem of Zika virus comprised of small pruritic papules that extend downwards. Laboratory testing is helpful in making a definitive diagnosis. Viral isolation, measurement of immunoglobulin M (IgM) or IgG, and/or reverse transcription polymerase chain reaction are useful diagnostic tools with favorable sensitivity and specificity.

**Key words:** Chikungunya fever; Chikungunya virus; coronavirus disease 2019; COVID-19; Dengue fever; Dengue hemorrhagic fever; Dengue virus; Ebola virus; exanthem; Hand-foot-and-mouth disease; HFMD; HIV; HTLV-III; Human immunodeficiency virus; Human T-lymphotropic virus-III; Measles; RNA virus; Rotavirus; Rubella; SARS-CoV-2; severe acute respiratory syndrome coronavirus 2; Zika virus

## Introduction

Viral exanthems are great imitators. Due to the universal vaccination in childhood, classic viral exanthems are becoming less common. However, recent outbreaks of measles reiterate the importance of our understanding of the cutaneous presentation of the viral exanthems.[1] Other than the classical viral infection, more novel viral infections with skin eruptions

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are emerging, and some of them are caused by ribonucleic acid (RNA) virus.

A novel febrile disease that presents with rashes is coronavirus disease 2019 (COVID-19), which caught global attention recently. Some RNA virus infections with rashes, including O'nyong'nyong virus, Mayaro virus, and Ross River virus, will not be discussed due to the rarity and endemic nature. These viruses belong to arthritogenic alphaviruses, similar to chikungunya virus, which will be discussed. Leishmania RNA virus can exacerbate the cutaneous manifestation of Leishmaniasis. However, this manuscript focuses on the skin manifestations caused by the RNA virus itself. Therefore, it is not included in the discussion.

Morbilliform rash is the prototype of viral exanthems, and "morbilliform eruption" literally means resembling the rashes of measles. It is characterized by generalized fine maculopapular erythematous eruptions that are usually symmetrically distributed. A morbilliform rash may be part of the symptoms and signs of many viral infections and drug eruptions. The cutaneous manifestations of other RNA viruses may simulate the classic viral exanthems but often show some additional features. Early recognition and differentiation of these viral exanthems are essential to direct further investigations and initiate treatment. In this review, we focus on febrile exanthems caused by RNA viruses, and we offer clues for the differential diagnosis and proper diagnostic testing in such cases.

## Chikungunya Virus

Chikungunya fever is a mosquito-borne single-stranded viral disease mainly affecting patients living or traveling to an endemic tropical area. The disease was first detected in 1952 in Tanzania.[2] Chikungunya means 'to walk bent over' in Tanzanian's language, which refers to the stooped posture caused by arthritic symptoms.[3] There were outbreaks across Asia, Latin America, and the United States in recent years. It is a febrile illness characterized by severe arthralgias, myalgias, headaches, photophobia, and skin rash.[3] The exanthem of chikungunya fever is observed in 30%–75% of patients and usually presents 2–5 days after the fever onset.[4] The most typical cutaneous manifestation is a morbilliform rash, occurring primarily over the face, trunk, and upper extremities.[5] Macular hyperpigmentation of the nose, face, or hands is the second-most characteristic cutaneous eruptions.[4] This peculiar nasal pigmentation is called "chik sign."[5] Other cutaneous manifestations include, in descending order, vesicles, and bullae, desquamation, toxic epidermal necrolysis-like, papular, urticarial, and purpuric lesions.[5] Oral mucosa involvements are found in the form of ulcerations, erosions, and cheilitis.[5] Nail findings in chikungunya infection demonstrate pigmentation, scattered leukonychia, and partial nail loss at a late stage.[6]

The characteristic histopathology findings of the morbilliform rashes in chikungunya fever are spongiosis, dermal edema, and perivascular lymphocytic infiltrate in the dermis.[5] Skin biopsies of the vesiculobullous lesions show intraepidermal or subepidermal bullae, with exocytosis of lymphocytes, perivascular lymphocytic infiltrate, acantholysis, necrotic keratinocytes, and occasional neutrophils.[7] The hyperpigmented lesions demonstrate increased basal pigmentation, pigmentary incontinence, and melanophages.[8]

Immunoglobulin (Ig) M antibody levels peak within three to 5 weeks after the initial manifestation and last for about 2 months.[4] Therefore, samples collected in the 1st week should include both serological tests and reverse transcription polymerase chain reaction (RT-PCR).[9] Chikungunya IgG antibodies are positive after the 1st week and persist for years.[4] Serial samples revealing 4-fold IgG antibody titer increase are suggestive of chikungunya infection, as in the Dengue virus, and Zika virus.[4]

## COVID-19

COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a single-stranded RNA virus. Clinical presentations of COVID-19 include fever, fatigue, dry cough, anorexia, dyspnea, rhinorrhea, ageusia, and anosmia.[10]

Recalcati analyzed 148 patients tested positive of SARS-CoV-2.[11] After excluding patients who had initiated new medication in the past 15 days, 18 out of 88 patients had cutaneous manifestations, including erythematous rash, widespread urticaria, and chickenpox-like vesicles. The time of viremia and skin manifestation may be different among diseases. There is no sufficient data to conclude the temporal relation between SARS-CoV-2 viremia and skin eruptions, but preliminary data showed that eight patients developed exanthem at the disease onset, and ten patients developed during hospitalization. Frostbite-like painful erythema, livedo, petechiae, and acrocyanosis have also been described.[12,13] The acro-ischemic lesions occur on the feet and hands of children and adolescents. These painful, well-demarcated, reddish-purple lesions may develop into bullae or blackish crusts, followed by self-healing within 2 weeks.[14]

Histopathological findings of patients with COVID-19 demonstrated perivascular infiltration of inflammatory cells, fibrinoid necrosis, and thrombus formation, which are similar to those of SARS.[15] Immunohistochemistry test of monoclonal antibody against nucleocapsid protein of SARS-CoV-2 and RNA polymerase showed positive staining at sweat glands,[15] indicating infection at cutaneous skin appendages. These findings may correlate with case reports of patients developing clinically significant coagulopathy, antiphospholipid antibodies, multiple infarcts, and even gangrene.[16] However, whether these vascular abnormalities represented direct cytopathic effects of the viruses or were the complication of disseminated coagulopathies due to secondary infections remained to be studied.

## Dengue Virus

Dengue fever is a mosquito-borne, single-stranded viral disease caused by any of the four serologic distinct RNA viruses that belong to the Flaviviridae family.[4] Although infection with one serotype produces lifelong immunity to that serotype, the protection to other types are transient.[17] Classic dengue fever consists of fever, headache, retroorbital eye pain, myalgia and arthralgia, and skin rash.[17] The peak of viremia occurred 2 days before the fever. Transient flushing erythema of the face, neck, and chest at the initial phase of febrile onset can be followed by a second rash in three to 6 days.[9] At this stage, the centrifugal morbilliform rash involves the face, abdomen, and extremities with sparing of the palms and sole.[17] When these individual lesions coalesce and form generalized erythema around the unaffected white area, they appear as "white islands in a sea of red"[9] [Figure 1a]. This faint morbilliform rash is observed in more than 50% of patients with dengue fever.[4] A fine macule over pressure areas, especially the palms and soles, may erupt before the onset of fever[18] [Figure 2]. Some patients develop mild hemorrhagic manifestations, including petechiae, purpura, or ecchymosis, particularly at sites of venipunctures[17] [Figure 1b]. The petechiae can be better demonstrated with tourniquet test, using pressure between systemic and diastolic pressure for 5 min. Oral mucosa involvement was rarely reported in the literature, but gingival bleeding may sometimes present.[19] In a report recruiting 45 patients from Southern Taiwan, 71% developed skin rashes, and these patients were younger, experienced more pruritus, and had more swollen palms/sole than those without exanthem.[20]

The disease may progress to life-threatening dengue hemorrhagic fever, which leads to noninfectious bleeding, thrombocytopenia, and leakage of plasma.[19] Dengue hemorrhagic fever and dengue shock syndrome are caused by systemic vascular leakage associated with secondary-type dengue antibody response, especially in children.[21] Dengue hemorrhagic fever is more often observed in dengue virus type 2 infections than those due to type 1 and 3.[21] The mortality rate of dengue hemorrhagic fever was reported to be 38.7% in southern Taiwan in 2015.[22]

Skin biopsy of dengue fever reveals swelling of the endothelial cells in small vessels of the papillary dermis, transendothelial cell diapedesis of neutrophils, extravasation of erythrocytes, and perivascular mononuclear cells infiltration.[23]

Clinical test methods for dengue fever include virus isolation, direct detection of viral RNA, detection of the secreted NS1 protein, or measurement of virus-specific IgM (≥4 days after fever onset).[24] Virus isolation is definitive, but requires days to weeks to perform.[24]

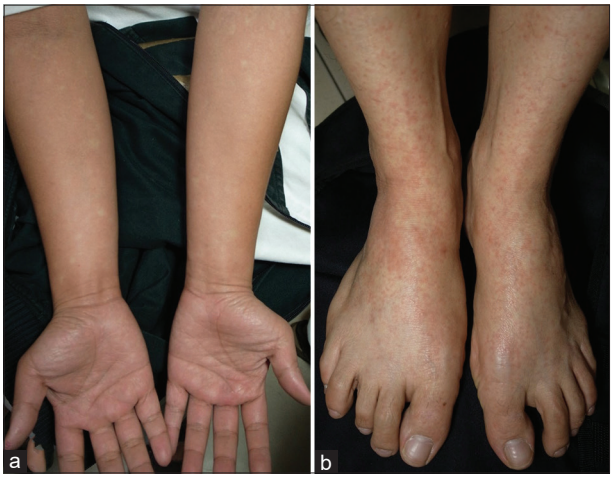


**Figure 1:** (a) Morbilliform eruptions coalesce and form generalized erythema around the unaffected white area, showing a "white islands in a sea of red" appearance suggestive of dengue fever. (b) Petechiae over the extremities, one of the mild hemorrhagic manifestations of dengue fever, may be seen in some patients

## Ebola Virus

*Zaire ebolavirus*, also known as the Ebola virus, is a filovirus with single-stranded RNA genomes belonging to the Filoviridae family.[25] Fruit bats are the likely reservoir, and human infection occurs through contact with infected animals or by person-to-person contact.[26] High-temperature fever with abrupt onset, severe headache, myalgia, arthralgia, generalized fatigue, abdominal pain, diarrhea, and vomiting are the characteristic manifestations of Ebola virus infection.[26] Muscle and joint pain are almost always present. The headache located primarily in the occipital region and may spread to the frontal or parietal area.[26] The skin rash of Ebola virus infection is often a nonpruritic, dark-red, maculopapular eruption with fine scaling that appears between day four and six of disease, which is described as "ghost-like" appearance.[25,26] The rash initially appears on the upper arms and upper legs, and gradually spread in a centripetal fashion.[25] At this stage, nervous system involvement, petechiae, melena, hematemesis, hematuria,

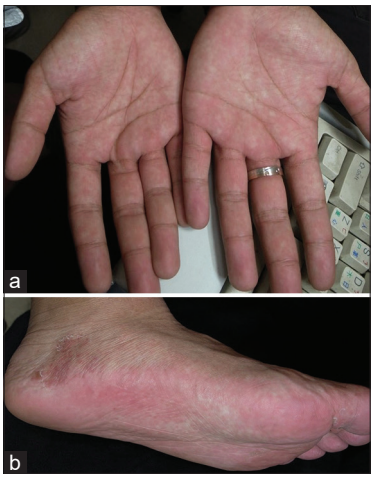


**Figure 2:** Some patients with Dengue fever present with erythematous macules over pressure areas, especially the palms (a) and soles (b)

hemoptysis, and hemorrhage may also be found.[25] The rash becomes generalized and dusky in about 8 days, and then the erythema clears with desquamation.[25]

Biopsy of the skin eruptions shows minimal nonspecific alterations with various degrees of dermal edema, focal hemorrhage, and endothelial cell swelling and necrosis.[26]

Ebola virus can be detected by serum IgM and IgG using the enzyme-linked immunosorbent assay (ELISA) technique; however, primary infection-induced antibodies only become detectable approximately 3 weeks later.[27] Therefore, the diagnosis relies on the detection of Ebola viral proteins or RNA sequences using RT-PCR techniques.[28] Both tests are suitable for emergent diagnosis, as virus levels in the serum increase rapidly within the first few days of infection.[28] Specific immunohistochemical assays can be performed on formalin-fixed skin specimens to diagnose Ebola virus infection.[29]

## Hand-Foot-and-Mouth Disease

Hand-foot-and-mouth disease (HFMD) is a self-limiting febrile illness with acral/oral involvement. It is commonly observed among young children and infants, but adults can also be affected.[30] Typical HFMD presents as fever along with morbilliform or vesicular eruptions limited to the hands, feet, and oral mucosa[9] [Figure 3]. Lesions can also present in other sites, including the buttocks, extremities, and torso.[30] The rash usually onsets in 3–6 days.[30]

The causative virus of HFMD belongs to the nonpolio enterovirus genus (single-stranded).[9] Classic HFMD is most commonly caused by coxsackievirus-A16 and enterovirus 71.[30] Coxsackievirus-A6 has been recognized as the leading cause of atypical HFMD, which is associated with generalized vesiculobullous eruptions that may ulcerate, prominent perioral involvement, and onychomadesis.[31] Echovirus can also cause HFMD, and sometimes induce complications such as aseptic meningitis or encephalitis.[9]

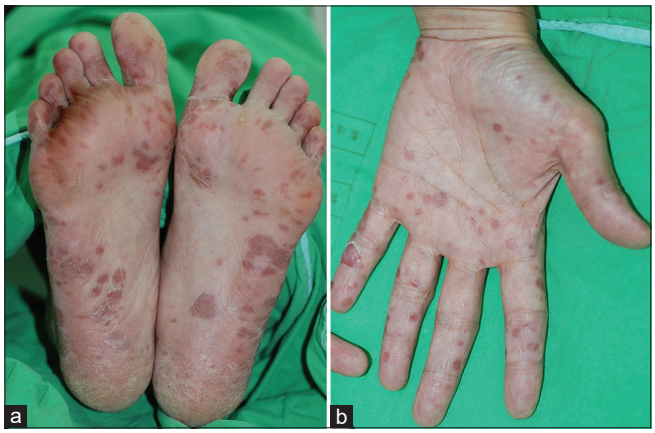


**Figure 3:** A 42-year-old woman presented with variously-sized, erythematous macules on the soles (a) and palms (b) following contact with a child with HFMD. Fever and sore throat developed one week before the exanthem

Distinctive histologic features were found in the biopsies of adult patients with HFMD. Spongiosis, neutrophilic exocytosis, massive keratinocyte necrosis, and ballooning were present in the upper epidermis, with vacuolization of basal cells, necrotic cells in follicles and sweat glands.[32] Cytotoxic T cells with strong granulysin expression comprised the main component of inflammatory infiltration.[32] Despite some similar histopathological findings, the number of neutrophils is significantly more numerous and necrosis is more extensive in the upper part of the epidermis in HFMD when compared to erythema multiforme.[33]

Enterovirus 71-IgM-capture ELISA was reported to reach 97.7% sensitivity and 93.3% specificity, with most specimens taken within a week after the onset of symptoms.[34] A novel method to detect enterovirus 71 infections with IgA in the saliva is promising, as it demonstrated similar sensitivity and specificity compared to detecting IgM in the serum.[35] Besides, the former is less invasive and shows a higher sensitivity in detecting secondary infections.[35] Although the IgM anti-coxsackievirus-A16 assay demonstrated favorable sensitivity and specificity, RT-PCR is often a better diagnostic tool for coxsackievirus-A6.[36] RT-PCR can help the rapid diagnosis of enterovirus, coxsackievirus, or echovirus infection. The use of RT-PCR has been associated with reduced duration of empirical antimicrobial therapy and length of hospital stay.[36]

## Human Immunodeficiency Virus

Human immunodeficiency virus (HIV) is a member of the genus Lentivirus, which transmits as a single-stranded enveloped RNA virus and reverse transcribes into double-stranded DNA upon entry into the target cell. Manifestations of primary HIV infection include fever, lymphadenopathy, pharyngitis, myalgia, arthralgia, headache, gastrointestinal, and central nervous system symptoms.[37] Approximately 77% of patients experience primary skin eruptions after HIV infection.[37] Acute infection with HIV can cause 5-10 mm-sized, well-defined, round to oval, erythematous maculopapular eruptions most often on the face and neck, although the palms and soles, and extremities can be involved.[37] Sometimes a hemorrhagic or necrotic center can be observed. Oral lesions are usually present, ranging from erythema to ulcers.[37] Along with dull-red and violaceous maculopapular lesions and enanthem, acute genitocrural intertrigo has been reported as an early cutaneous feature for HIV infection.[38] The skin manifestation initiates 3 days after the fever and usually lasts approximately 1 week before gradually resolves.[9]

The exanthem of acute HIV infection cannot be diagnosed specifically through histopathological examination, but a characteristic histopathological picture may suggest the diagnosis in an appropriate clinical context.[39] Similar to other maculopapular eruptions due to viral infections, histopathology features of maculopapular rash in the acute phase of HIV infection are sparse perivascular infiltration of lymphocytes

and histiocytes in the upper dermis.[40] The skin biopsy of an acutely infected patient shows interface dermatitis and diffuse vacuolization of the basal cell layer.[40]

Although a variety of laboratory investigations are available for HIV infection, a particular test should be chosen based on understanding the timeline of virological and serological events as well as the difference between laboratory-based and point-of-care tests.[41] According to the diagnostic algorithm proposed by Hurt *et al*.,[41] HIV-1/2 Ag/Ab combination immunoassays (p24/IgM/IgG sensitive) in combination with an IgG sensitive HIV-1/2 antibody differentiation supplemental assay is favored in most clinical scenarios. The median window period is 17.8 days for HIV p24/IgM/IgG sensitive laboratory tests, and 23.1 days for IgM/IgG sensitive laboratory tests.[41]

## Human T-Lymphotropic Virus

Primary infection with the human T-lymphotropic virus (HTLV)-III, a single-stranded RNA virus, was documented to present as fever, rigors, arthralgias and myalgias, abdominal cramps, and diarrhea. Cutaneous manifestations include maculopapular rash and urticaria.[42] Lindskov *et al*. described patients with HTLV-III with roseola-like rash on the face, trunk, and extremities, sparing the hands and feet.[43] The estimated incubation period was four to 6 weeks, while the symptoms lasted 2–3 weeks.[42] Seroconversion occurred 8–12 weeks after exposure.[42] In some cases, Western blotting was able to detect HTLV-III antibodies earlier.[44]

## Measles (Rubeola)

Measles virus, a single-stranded member of the Paramyxoviridae family, usually causes stepwise fever, malaise, and weight loss, accompanied by cough, coryza, and conjunctivitis, known as the "3C". Morbilliform rash is the prototype of viral exanthems, and "morbilliform eruption" literally means resembling the rashes of measles. A morbilliform rash may be part of the symptoms and signs of many viral infections and drug eruptions. The characteristic exanthem of measles consists of erythematous, 2–10 mm-sized macular lesions and 1-3 mm-sized papules with healthy-looking intervening skin. The maculopapular rash may become confluent 4 days later.[45] The exanthem of measles usually develops three to 5 days after prodromal symptoms, which is consistent with the surge of the level of measles RNA.[46] Characteristic erythematous macules and papules develop on the face and spread cephalocaudally, which heals with hyperpigmentation after 5–7 days.[45] The rashes of measles are usually only mildly itchy or not itchy at all. Koplik's spots [Figure 4] are the pathognomonic sign of measles during the prodromal period, appearing in more than 70% of patients.[9] They appear as bluish-white plaques about 2-4 mm in size on an erythematous base on the buccal mucosa, typically molar and pre-molar areas, but may also occur on the lips, gingiva, conjunctival folds or vaginal mucosa.[47] Patchy erythema with tiny white specks (grains of salt) appearance became evident when the lesions increase in numbers. Koplik's spots usually resolve by the peak of the exanthem.[45]

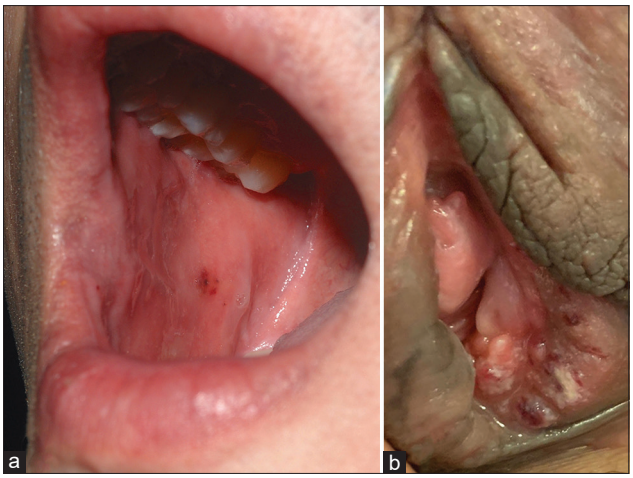


**Figure 4:** (a) White arrows indicate white plaques on an erythematous base on the right buccal mucosa, showing a characteristic "grains of salt" appearance of measles. (b) A case of reverse transcription polymerase chain reaction confirmed measles virus infection presented with Koplik's spots on the vaginal mucosa

The histopathological features of cutaneous lesions in measles are quite distinctive. It is composed of multinucleated keratinocytes, individual and clustered necrotic keratinocytes in the epidermis.[48] Pronounced folliculosebaceous and acrosyringeal involvement are usually found.[48] The histopathological findings of Koplick spots show multinucleated T-lymphocytes, also known as Warthin–Finkeldey cells, and neutrophils.[49] Warthin–Finkeldey cells [Figure 5] are grape-like clusters of dozens of small nuclei, surrounded by a small amount of eosinophilic or basophilic cytoplasm.[49] The nuclei often resemble those of lymphocytes. The cells rarely contain inclusion bodies. Warthin–Finkeldey giant cells are not specific for measles but are associated with reactive lymphatic proliferation.[50]

Measles is usually diagnosed clinically based on characteristic mucocutaneous findings. If necessary, a blood test can be performed to confirm the diagnosis. Serologic examinations are highly sensitive and specific for measles. Both IgM and IgG antibodies are produced during the primary immune response and can be detected in the serum within a few days after rash onset.[51] The sensitivity of ELISA for measles IgM can reach 90% at 3 days post rash onset.[51] In the serum, IgM antibody levels peak in 7–10 days and then decline rapidly, being barely detectable after 6–8 weeks.[51] IgG antibody levels increase in the beginning 4 weeks and remain detectable persistently.[51] Serum IgA and secretory IgA antibodies are also produced. The measles virus can also be isolated from blood, urine, and nasopharynx.[51]

## Rotavirus

Rotavirus belongs to the Reoviridae family, with a genome consisting of eleven double-stranded RNA.[52] The incubation

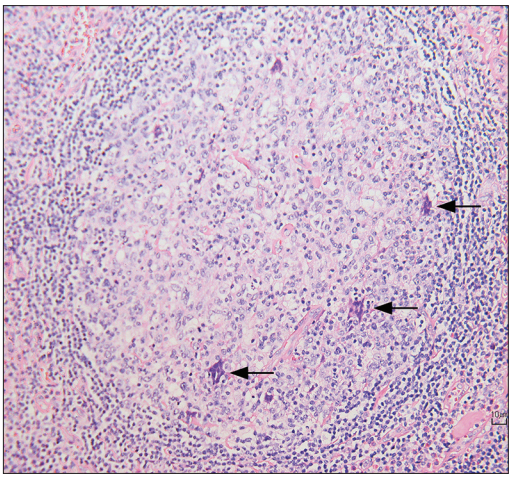

**Figure 5:** Black arrows point out the multinucleated T-lymphocytes, also known as Warthin–Finkeldey cells, which consists of grape-like clusters of dozens of small nuclei, surrounded by a small amount of eosinophilic or basophilic cytoplasm

period for rotavirus infections is usually <48 h.[52] The characteristic symptoms of rotavirus gastroenteritis are vomiting, abdominal pain, and low-grade fever, followed by watery, foul-smelling diarrhea for 4–8 days.[52,53] A generalized erythematous maculopapular exanthem has been reported to be associated with rotavirus infection.[52] Other cutaneous manifestations include Sweet's syndrome,[54] Henoch–Schonlein purpura,[53] Gianotti–Crosti syndrome,[52] and acute hemorrhagic edema.[52] Rotavirus antigen has been identified in the patient's serum 3–7 days after disease onset, but at present, routine diagnostic testing is based primarily on stool specimens.[55] ELISA tests are widely used to screen for rotavirus infection, while RT-PCR is an alternative.

## Rubella (German Measles)

Rubella virus, a single-stranded virus, belongs to the Togaviridae family. Patients with rubella may manifest with a prodrome of low-grade fever and lymphadenopathy. The postauricular, posterior cervical, and suboccipital lymph nodes are often involved. The rubella exanthem [Figure 6] is often the first clinical sign of infection.[45] The nonpruritic rubelliform rash consists of discrete, rose-pink, pinpoint-sized maculopapules which first appears on the face, then spreads downward and becomes generalized within about 24 h. The rash then fades in the same fashion as it spreads, lasting at most 3 days.[45] Hence, rubella is nicknamed "three days measles". Although the distributions of measles and rubella exanthem are similar, the spread of rubella is much more rapid. Besides, the rash of rubella is usually fainter and less infiltrated than the exanthem of measles.[9] Furthermore, the rash seen in rubella does not darken or coalesce but rather evolves rapidly and become delicate, flaky desquamation with only rare postinflammatory hyperpigmentation.[9] Forchheimer spots and nonexudative conjunctivitis may develop in 20% of patients.[45] Forchheimer spots consist of pinpoint petechiae or red macules on the soft palate.[45]

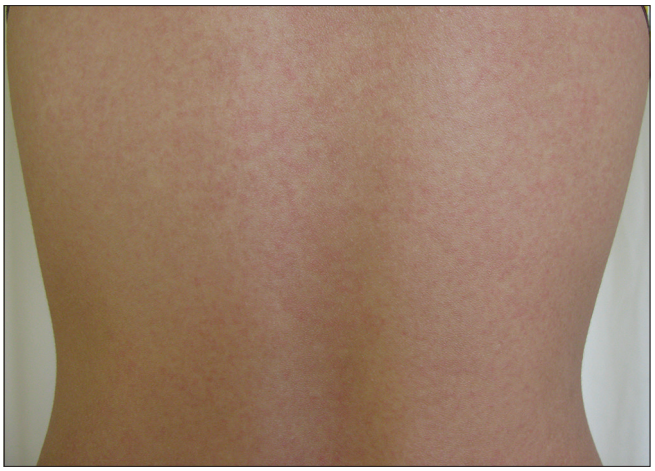

**Figure 6:** A 21-year-old woman with rubella complained of general malaise, cough, rhinorrhea, sore throat, injected conjunctiva with minimal discharge, and myalgia, followed by rashes spreading cephalocaudally. Discrete, rose-pink, pinpoint-sized maculopapules distributed on the back. Note that the rash of rubella is usually fainter and less infiltrated than measles

Histopathological examination of rubella reveals distinctive features compared to measles. While the latter shows interface dermatitis, inflammatory cell infiltration in rubella is restricted to the perivascular area.[56]

The most common diagnostic method for rubella infection is the serologic investigation.[9] The level of IgM antibodies should be measured, as the presence of IgG may result from earlier vaccination. In a previous report comparing different assays for the detection of anti-rubella IgM antibodies, the sensitivity and specificity can reach up to 96.5% and 100%, respectively.[57] However, samples taken in <7 days after the rash onset showed a suboptimal detection rate of rubella.[58] Depending on the clinical scenario and the laboratory medicine department, RT-PCR can be performed for the diagnosis of rubella virus infection in selected cases and the prenatal diagnosis of congenital rubella syndrome.[9] The virus can be demonstrated in the skin with and without eruptions.[59]

## Zika Virus

Zika virus is a single-stranded RNA flavivirus, which is primarily transmitted through mosquitoes.[4] Approximately 80% of patients with acute infection of the Zika virus are asymptomatic, while others experience mild fever, muscle and joint pains, nonpurulent conjunctivitis, headache, retroorbital pain, and vomiting.[9] Fever is often low-grade or even absent, making skin rashes the hallmark clue for clinicians to suspect Zika virus infection. Skin manifestation is observed in 90% of febrile patients with Zika virus, initiating in one to 4 days after extracutaneous symptoms, and usually lasts 6 days.[4] Pruritic morbilliform eruptions predominantly appear on the trunk and extremities and palms and soles.[4,9] Despite being described as maculopapular in character, the skin lesions are distinctly comprised of small papules.[60] The skin involvement

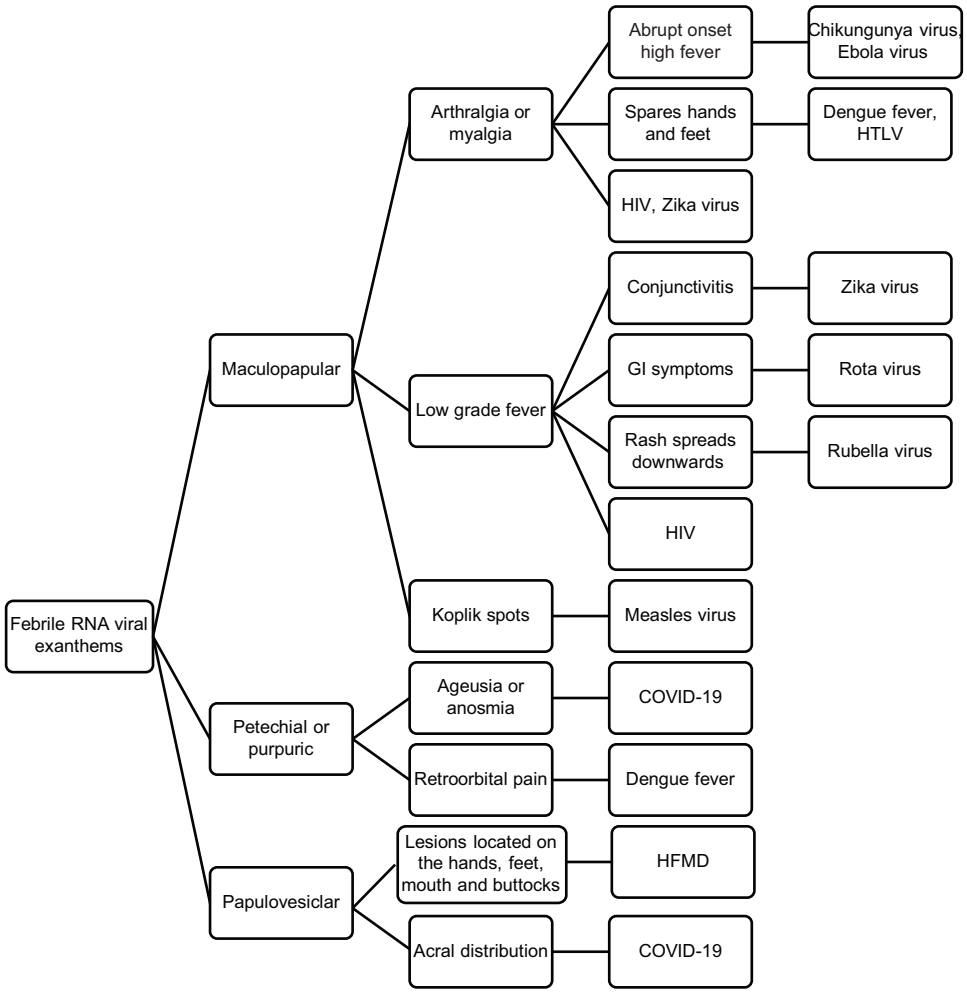


**Figure 7:** Diagnostic clues of characteristic presentations of febrile diseases caused by RNA viruses. COVID-19: Coronavirus disease 2019, GI: Gastrointestinal, HFMD: Hand-foot-and-mouth disease, HIV: Human immunodeficiency virus, HTLV: Human T-lymphotropic virus

typically begins on the face and extends downward to the trunk and extremities.[60]

Mild hemorrhagic manifestations, including petechiae on the palate and gingival bleeding, may be observed in some cases.[60] These symptoms last 2–3 days and usually heals with desquamation within 1 week.[60] Vertical transmission of the virus may be teratogenic to the fetal nervous system.[4] Affected pregnant women who conceive babies with adverse congenital outcomes, such as fetal death, craniofacial disproportion, microcephaly, and macular atrophy, are four times more likely to have a history of a rash during pregnancy.[61]

Histopathological findings are nonspecific and may vary according to the biopsied lesions.[62] Classic maculopapular eruptions showed a nonspecific mild to moderate lymphocytic dermal infiltrate, often perivascular and superficial.[62]

A diagnosis of Zika virus infection can be made through virus isolation from an appropriate specimen, detection of viral RNA by RT-PCR or nucleic acid amplification tests (<14 days after symptom onset), or the detection of IgM (≥14 days after onset of symptoms).[63] When diagnostic testing is performed with RT-PCR, urine instead of serum can be a better specimen due to a higher load of viruses and a longer duration for detection.[64]

## Conclusion

Summary of the information of the Centers for Disease Control and Prevention[55,65] and this review is provided in Table 1. A flowchart [Figure 7] with diagnostic clues summarizes the characteristic findings of febrile diseases caused by RNA viruses. Cutaneous manifestations can be categorized into maculopapular, petechial or purpuric, and papulovesicular exanthems. Characteristics of fever, prodromal symptoms, and distribution of the rashes can further distinguish diseases from others. Serologic and virological tests are recommended before making a definitive diagnosis. The outbreak of novel viruses, for instance, COVID-19, warrants further investigations for their dermatological presentation.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

**Table 1: Summary of the symptoms and diagnostic tools for febrile diseases caused by ribonucleic acid viruses**

| Virus | Incubation period | Prodrome | Exanthems | Recovery | Complications | Lab tests |
|---|---|---|---|---|---|---|
| Chikungunya virus | 3-7 days | Sudden onset high fever, severe joint pains, headaches, and photophobia | - Occurs 2-5 days after prodrome<br>- Morbilliform rash, occurring primarily over the face, trunk, and upper extremities<br>- Macular hyperpigmentation of the nose, face, or hands<br>- Chik sign | 7-10 days | Myocarditis, uveitis, retinitis, hepatitis, acute renal disease, and neurologic disease | Viral culture or RT-PCR of serum (first week after onset); 4-fold rise in IgG; Positive serologic test for IgM |
| COVID-19 | 2-14 days | Fever, fatigue, dry cough, anorexia, dyspnea, rhinorrhea, ageusia, and anosmia | - Erythematous rash, widespread urticaria, and chickenpox-like vesicles<br>- Frostbite-like painful erythema, livedo, petechial, and acrocyanosis | 2 weeks | Pneumonia, organ failure, and death | RT-PCR |
| Dengue virus | 5-7 days | Fever typically lasts 2-7 days and can be biphasic; Severe headache, retroorbital pain, muscle, joint, and bone pain | - Transient flushing erythema of the face, neck, and chest at the initial phase of febrile onset<br>- 3-6 days later, centrifugal morbilliform rash involves the face, abdomen, extremities with sparing of the palms and sole; "white islands in a sea of red" | 24-48 h after defervescence | Dengue hemorrhagic fever, dengue shock syndrome | RT-PCR or detection of NS1 antigen (≤7 days after fever onset); Positive serologic test for IgM (≥4 days after fever onset) |
| Ebola virus | 8-10 days | Fever, abrupt onset, severe headache, myalgia, arthralgia, generalized fatigue, abdominal pain, diarrhea and vomiting | - Occurs 4-6 days after prodrome; Nonspecific maculopapular rash with fine scaling<br>- Begins from upper arms and upper legs, and gradually sprea | 2 weeks | Blurry vision, eye pain, hearing problems, hemorrhagic symptoms, death | Skin biopsy with immunohistochemistry assay; Detection of IgM or IgG with ELISA; detection of ebola viral proteins or RT-PCR |
| HFMD | 3-6 days | Fever and malaise, followed by sore throat | - Occurs 3-6 days after prodrome<br>- Morbilliform or vesicular eruption limited to the hands, feet, and oral mucosa | 1 week | Enterovirus 71 rarely cause central nervous system disease or death | RT-PCR of vesicle fluid, throat or buccal swabs, or stool |
| HIV | 10 days | Fever, arthralgia, myalgia, malaise, lymphadenopathy, oral ulcers, pharyngitis, and weight loss | Occurs 3 days after prodrome; 5-10 mm-sized, well-defined, round to oval, erythematous maculopapular eruptions most often on the face and neck | 1 week | Opportunistic infections, neuropsychiatric disease, retinopathy, cardiomyopathy, pulmonary hypertension, enteropathy, nephropathy, lipodystrophy | Detection of anti-HIV antibodies, HIV p24 antigen, or HIV-1 RNA |
| HTLV-III | 4-6 weeks | Fever, rigors, arthralgias and myalgias, abdominal cramps, and diarrhea | - Maculopapular rash and urticaria<br>- Roseola-like rash on the face, trunk, and extremities, sparing the hands and feet | 2-3 weeks | Impairment of the immune system may result in tuberculosis, crusted scabies, and strongyloidiasis | ELISA is frequently used for screening; Western blotting is normally used for confirmatory |

*Contd...*

**Table 1: Contd...**

| Virus | Incubation period | Prodrome | Exanthems | Recovery | Complications | Lab tests |
|---|---|---|---|---|---|---|
| Measles | 10-12 days | Stepwise increase in fever, weight loss (Meunier's sign); Cough, coryza, conjunctivitis; Koplik's spots | - Occurs 2-4 days after prodrome<br>- Persists 5-6 days<br>- Prototype of "morbilliform eruption"<br>- Nonitchy erythematous, 2-10 mm-sized macular lesions and 1-3 mm sized papules with healthy-looking intervening skin<br>- Begins on the face and behind the ears, then spreads to the entire trunk and extremities in 24-36 hours (palms and soles rarely involved) | 1-3 weeks | Diarrhea, otitis media, pneumonia | Virus isolation from urine, nasopharynx, blood, throat; Significant rise in IgG; Positive serologic test for IgM |
| Rotavirus | 1-3 days | Low-grade fever, vomiting, abdominal pain, and watery, foul-smelling diarrhea | - Generalized erythematous maculopapular exanthem<br>- Other cutaneous manifestations include Sweet's syndrome, Henoch-Schonlein purpura, Gianotti-Crosti syndrome, and acute hemorrhagic edema | 3-7 days | Severe diarrhea, dehydration, electrolyte imbalance, metabolic acidosis | Detection of rotavirus antigen<br>By immunoassays or RT-PCR on stool specimens |
| Rubella | 14 days | Low-grade fever, malaise, lymphadenopathy, and upper respiratory symptoms | - Occurs 14-17 days after exposure<br>- Lasting at most three days; Discrete, rose-pink, pinpoint-sized maculopapules first appears on the face, then spreads downward and becomes generalized within about 24 h | 1 week | Arthralgia or arthritis (especially adult female) | Virus isolation from nasopharynx, urine; Significant rise in IgG; Positive serologic test for IgM |
| Zika virus | 3-12 days | Mild fever, muscle and joint pains, nonpurulent conjunctivitis, headache, retroorbital pain, and vomiting | - Occurs 1-4 days after prodrome<br>- Pruritic morbilliform rash begins on the face and extends downward to the trunk and extremities<br>- Skin lesions are distinctly comprised of small papules | 1 week | Guillain-Barré syndrome, encephalopathy, meningoencephalitis, myelitis, uveitis, and severe thrombocytopenia; severe teratogenic effects on the fetal nervous system | RT-PCR (<14 days after symptom onset); Positive serologic test for IgM (≥14 days after onset of symptoms) |

COVID-19: Coronavirus disease 2019, ELISA: Enzyme-linked immunosorbent assay, HFMD: Hand-foot-and-mouth disease, HIV: Human immunodeficiency virus, HTLV: Human T-lymphotropic virus, Ig: immunoglobulin, RNA: Ribonucleic acid, RT-PCR: Reverse transcription polymerase chain reaction, IgM: Immunoglobulin M, IgG: Immunoglobulin G

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