

# Febrile Illness with Skin Rashes

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Skin rashes that appear during febrile illnesses are in fact caused by various infectious diseases. Since infectious exanthematous diseases range from mild infections that disappear naturally to severe infectious diseases, focus on and basic knowledge of these diseases is very important. But, these include non-infectious diseases, so that comprehensive knowledge of these other diseases is required. Usually, early diagnostic testing for a febrile illness with a rash is inefficient. For clinical diagnosis of diseases accompanied by skin rash and fever, a complete history must be taken, including recent travel, contact with animals, medications, and exposure to forests and other natural environments. In addition, time of onset of symptoms and the characteristics of the rash itself (morphology, location, distribution) could be helpful in the clinical diagnosis. It is also critical to understand the patient's history of specific underlying diseases. However, diagnostic basic tests could be helpful in diagnosis if they are repeated and the clinical course is monitored. Generally, skin rashes are nonspecific and self-limited. Therefore, it could be clinically meaningful as a characteristic diagnostic finding in a very small subset of specific diseases.

**Key Words:** Febrile illness; Skin rash; Infectious disease; Non-infectious disease

## Introduction

When patients with febrile illnesses also develop a rash, they tend to visit the hospital with serious disease in mind. Many rashes that appear during febrile illnesses are in fact caused by various infectious diseases. Since infectious exanthematous diseases range from mild infections that disappear naturally to severe infectious diseases, focus on and basic knowledge of these diseases is required. Although the appearance of the rash is essential for diagnosis of some diseases, rashes are generally non-specific findings, and play supportive roles in the differential diagnosis of other diseases. These include

non-infectious diseases, so that comprehensive knowledge of these other diseases is required for clinical diagnosis of a febrile illness with a rash. A skin rash is a symptom that appears during the course of a systemic or localized disease, and therefore could be clinically meaningful as a characteristic diagnostic finding in a very small subset of specific diseases. However, rashes are generally nonspecific and have complementary significance in differential diagnosis when combined with antecedent and concurrent symptoms, medication and allergy history, or social and environmental background, as well as the characteristics of the rash itself, such as morphology, location, and distribution [1].

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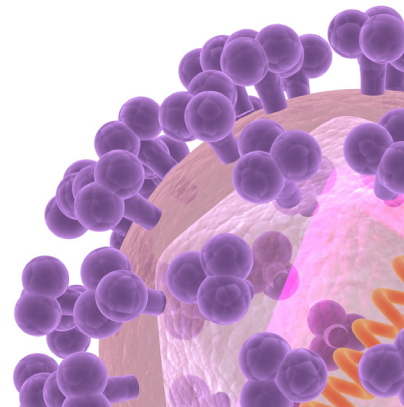
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Febrile rashes are classified into maculopapular rash, generalized diffuse erythema, and vesicular, pustular, nodular, petechial, and purpuric rashes, depending on characteristic morphology, distribution, and accompanying symptoms. They are also classified as systemic or localized, depending on distribution, and symmetric or asymmetric [2]. However, these are not specific to the diagnosis and are unrelated to the severity of the disease. Rashes are also divided into infectious and non-infectious skin rashes, depending on causation, and into acute and chronic rashes according to occurrence pattern [1, 3, 4].

## Diagnostic approach

Understanding the etiology of atypical exanthems remains difficult and often the routine procedures do not allow a definitive diagnosis to be achieved. For clinical diagnosis of diseases accompanied by a rash and fever, a complete history must be taken, including recent travel, contact with animals, medications, and exposure to forests and other natural environments. In addition, time of onset of symptoms could be helpful in the clinical diagnosis. It is also critical to understand the patient's history of specific diseases, including cardiovascular, sexually-transmitted, and immunodeficiency diseases; in particular, an evaluation of immune status is needed [5]. In recent time, with increased travel and population movements, imported infections with secondary local transmission are of great concern and outbreaks in susceptible populations may present containment issues. In this aspect, imported viral infections such as arboviral infections (Chikungunya, dengue, Japanese encephalitis and yellow fever viruses) and new zoonotic viral infection (Sosuga virus) and should be considered through the recent travel history [6].

The location, pattern, and rate of emergence, as well as accompanying pruritus, association between the rash and fever, and the morphological classification, all play supporting roles

in the diagnosis [2]. In addition, the morphology of the primary skin lesions associated with the rash (Table 1), and the distribution, morphology, and arrangement of secondary lesions, must be monitored. Especially, morphological patterns, seasonal occurrence, and the presence of enanthem can help physicians make a quicker etiological diagnosis, which, if confirmed by tests, ensures timely and appropriate treatment while avoiding unnecessary therapy. In fact, knowledge of exanthem morphologies, season and historical data combined with selective laboratory testing should lead to appropriate management of these patients and their families. Several researches concerned with the basis of morphology, the associated symptoms and laboratory results, they concluded that a good correspondence between morphology and etiology was found, and their morphology and their association with pruritus or constitutional symptoms proved to be important diagnostic clues; The erythematous-vesicular pattern was exclusive to viral infections. The erythematous-pustular and papular patterns were found only in drug-related cases and in some undiagnosed cases. In contrast, the macular and maculopapular patterns were almost evenly distributed among the various etiologies, although their color was dusky in the drug-related exanthems. Severe pruritus was associated with drug-related exanthems [7, 8]. Furthermore, examination is necessary for lymphatic enlargement, abnormal oral, genital, and conjunctival findings, enlargement of the liver, presence or absence of tender areas, stiff neck, and neurologic findings [5, 9].

When fever accompanies a rash in children, it is usually caused by viral infections. Although viral exanthems are usually associated with benign, self-limited diseases, in some cases correct diagnosis of an exanthem may be required for proper treatment, monitoring, and initiation of preventive measures for contacts. Furthermore, Fever, sore throat, vomit, diarrhea, fatigue, irritability, anorexia, conjunctivitis, cough, and insomnia all significantly indicated viral infections.

In the majority of cases, early diagnostic testing for a febrile

**Table 1.** Common primary skin lesions

Lesion type	Description
Macule	Circumscribed area of change in normal color, with no skin elevation or depression; may be any size
Papule	Solid, raised lesion up to 0.5 cm in greatest diameter
Nodule	Similar to papule but located deeper in the dermis or subcutaneous tissue
Plaque	Elevation of skin occupying a relatively large area in relation to height
Pustule	Circumscribed elevation of skin containing purulent fluid of variant character
Vesicle	Circumscribed, elevated, fluid containing lesion less than 0.5 cm in diameter
Bulla	Same as vesicle, except lesion is more than 0.5 cm in greatest diameter

illness with a rash is inefficient. In other words, although a diagnosis may be initially attempted from testing of whole blood, inflammatory markers, common clinical chemistries, liver and renal functions, and blood and urine cultures, early diagnostic testing is problematic. However, these basic tests could be helpful in diagnosis if they are repeated and the clinical course is monitored. In fact, reactive lymphocytosis and eosinophilia findings from basic blood tests in patients with fever and a rash suggest the possibility of viral exanthema and hypersensitivity reaction, respectively.

On the other hand, Gram staining and culture can be performed using tissue fluid in vesicular and pustular diseases, and the Tzanck test can be performed by scraping skin lesions when herpes infections are suspected. If there is constant pruritus, it is possible to make a diagnosis with a skin biopsy, which is actually used for specific diagnosis of diseases including systemic lupus erythema (SLE), herpetic infectious diseases, erythema multiforme, allergic vasculitis, secondary syphilis, and dermal fungal infections. But, skin biopsies are rarely helpful even when graft versus host disease is considered. Serologic tests can be helpful in the diagnosis of rheumatic diseases, lupus, and some viral infectious diseases [9].

## Maculopapular rashes

This is the most common type of rash in a viral infection, but can also occur with immune-mediated diseases, drug rashes, and systemic bacterial infections. Systemic rashes mostly appear centrally rather than peripherally. Representative viral diseases include measles, rubella, first year baby rashes, and infectious erythema. In contrast, among bacterial infections, scarlet fever shows a typical systemic rash. Systemic rashes are also found in other bacterial infections, including leptospirosis, mycoplasma infection, and disseminated gonococcal infection. In addition, systemic rashes are found in tinea versicolor, a fungal infection caused by *Pityrosporum orbiculare*. These rashes can also be found regionally in rickettsial infections like tsutsugamushi fever. Erythema multiforme is the most representative disease with a peripheral maculopapular rash, and is mostly seen in 20-30 year olds. In addition, such rashes can occur in sexually-transmitted infections like secondary syphilis and condylomata.

**Measles rashes:** Measles is a representative infectious disease with a skin rash. The rash starts from behind the ears and progresses to the face, followed by the neck, torso, and extremities over the course of 2-3 days. The disease shows a

characteristic course in that the fever disappears when the rash stops evolving. Measles appears as a diffuse macular rash at the outset, followed by a rash with a papular morphology, and gradually develops into a morbilliform, or typical systemic maculopapular rash. The rash starts to disappear from the face, and residual brown skin pigmentation may appear in areas where the rash has faded. Disappearance of the rash may be accompanied by dry desquamation. In addition, Koplik spots (enanthem) appear either 12 h before or within 24 h of rash appearance [10].

**Rubella:** The rash in rubella, like measles, also progresses from the face to the body. However, progression is complete within a few hours, which is much faster than measles, and the rash has a lighter color. Although it is not easy to differentiate the rash from measles within 24 h of onset, the rash fades within 2-4 days, which is faster than measles, with no residual skin pigmentation after fading of the rash. However, desquamation can be seen, as in measles. Although lymph node enlargement may be seen behind the ears or below the occiput in rubella, this finding is nonspecific, and is not essential for diagnosis. Since rubelliform rashes occur during the evolution of various viral diseases, rubella can be diagnosed only by the overall clinical course [4, 10].

**Exanthem subitum (three-day fever, 6th disease):** Exanthem subitum is a typical infectious systemic maculopapular rash that is caused by human herpesvirus 6 [11]. The rash shows a unique progression, in that fever lasts for about 3 days, and the rash appears as soon as the fever ends; it then spreads to the neck, the face, and the extremities within 24 h, and disappears after 1-2 days. Rashes in this disease, unlike those of measles and rubella, are indistinct in the face and the extremities, and show papular or macular features that are light rose in color.

**Erythema infectiosum:** This is an exanthematous disease that is caused by human parvovirus B19 [12], and is characterized by an erythematous or elevated rash, as if the patient had been struck on both cheeks; it gradually evolves to a papular rash after appearance of a macular rash at the margins of the extremities and on the buttocks. These rashes persist for a while, and then start to fade from the middle of the 6th day, take on an appearance like lace, and disappear on the 7th-9th day after the first appearance of the rash. However, sometimes the rash may recur after a few weeks. Infectious erythema, unlike measles, rubella, and roseola, does not occur in infants, but mostly in school-aged children.

**Enteroviral infection:** Rashes caused by enteroviruses show highly diverse patterns, including maculopapular petechiae

and urticaria; since progression of the rashes varies, they are not clinically specific. However, these diseases may be considered when a rash appears in a clinical context; it should be noted that ECHO virus (particularly type 9) can frequently cause petechial rashes [4].

**Acute infectious mononucleosis:** When pediatric patients with this disease receive  $\beta$ -lactam antibiotics, especially semi-synthetic penicillin-derivatives, 50-100% will develop speckled or maculopapular rashes that spread systemically and last 2-7 days. In these cases, the rashes clearly appear on the torso and proximal extremities. These pediatric patients have fever for several days, but the rashes could provide complementary diagnostic information when there are clinical findings of infectious mononucleosis, including pharyngitis, lymphadenitis, and enlargement of the liver or spleen [10].

**Gianotti-Crosti syndrome:** This is an exanthematous disease that is associated with hepatitis B or other viral infections, although the etiology is unclear [13]. A systemic rash occurs in association with fever and lymph node enlargement. The rashes are mostly papular, showing a characteristic concentration over the face and extensor musculature of the extremities, and last for 3-4 weeks.

**Papular-purpuric gloves and socks syndrome;** Symmetric erythematous skin eruptions and edema of the hands and feet progress to petechial and purpuric macules and papules that are followed by fine desquamation. And there is a sharp demarcation at the wrists and ankles. Rarely, this eruption may extend to nonacral sites and the eruption may be painful or pruritic [14]. **Papular-purpuric gloves and socks syndrome (PPGSS)** is caused by parvovirus B19 [15], and may be developed by trimethoprim-sulfamethoxazole. PPGSS occurs most commonly in adolescents and young adults during the spring and summer. PPGSS is unlike 5th disease (erythema infectiosum) where skin signs develop after clearance of viremia and in the presence of rising antibody titers. PPGSS spontaneously resolves in 1-2 weeks without any known late sequel [14].

**Pityriasis rosea;** Pityriasis rosea (PR) is an acute self-limited disorder affecting primarily children and young adults, and developed typically in the spring and autumn. There are many factors that are suggestive of a viral etiology by seasonal clustering, prodromal features, increased erythrocyte sedimentation rate, and biopsy findings of dyskeratotic cells and multinucleated giant cells in the epidermis. However, no definite association of a known pathogenic virus has been established [16]. In recent time, HHV-6 and HHV-7 may play a part in some patients with PR, but other causative agents may exist. The exanthem in PR consists of discrete oval salmon-colored

papules and macules that may become confluent. The eruption often begins with a single herald patch, a week or more before the other smaller lesions. Topical steroids, emollients, and antihistamines may be used for the pruritus, which may be intense [17].

**Unilateral laterothoracic exanthem (asymmetric perilesional exanthem of childhood);** *Unilateral Laterothoracic Exanthem (ULE)* shows a unilateral eruption, either eczematous or scarlatiniform, localized to an axilla, and concomitant symptoms such as fever, sore throat, conjunctivitis, rhinopharyngitis or diarrhea may be developed. The eruption does not always remain unilateral and can involve the lower extremities [18]. The ULE rash has erythematous macules or papules that form morbilliform, scarlatiniform, or eczematous patterns which begins unilaterally in the axilla or groin, spreads centrifugally, and usually resolves spontaneously by 4 weeks. The causative pathogen of this eruption remains unknown, in spite of a continued, active search for an infectious etiology. However, an infectious etiology is suspected because of a seasonal pattern and the presence of prodromal symptoms. The majority of cases occur in children during winter and spring, and show self limited course [19].

**Eruptive pseudoangiomatosis;** Hemangioma-like exanthem cases in children described small erythematous papules with central pinpoint vascular supply and surrounding avascular halo [20]. Direct pressure resulted in complete blanching, and lesions were transient. Dilated capillaries with plump endothelial cells without vascular proliferation or inflammatory infiltrate were seen in skin biopsy, and named *Eruptive pseudoangiomatosis* [21]. This skin lesions may be associated by viral agents, usually developed in children and adulthood and self limited.

**Scarlet fever:** Scarlet fever is a typical maculopapular exanthematous rash due to a bacterial infection. It is the characteristic rash caused by the erythrogenic toxin of streptococcus at the onset of disease [22]. Specifically, after prodromal symptoms of pharyngitis for 2-3 days, a minute papular rash starts in the axillary region and inguinal area, and proceeds around the neck and the back, ultimately spreading to the entire body. It is particularly distinct in skin folds, resembles sunburn, and feels warm and dry. Since measles and rubella sometimes show similar rashes, they need to be differentiated from scarlet fever. The primary characteristic differentiating scarlet fever from measles and rubella is that there are no rashes or clear findings of upper respiratory inflammation, except that the area around the mouth becomes pale and both cheeks are red. Another difference in scarlet fever is the appearance of

Pastia lines, with linear petechial hemorrhages in which erythema does not disappear when the axillary region, inguinal area, and antecubital fossa are compressed. However, scarlet fever, like measles and rubella, also shows desquamation, which appears one week after the onset of disease and persists for several weeks.

**Leptospiral infection:** Although leptospiral infections are uncommon in infants, they tend to show a pattern similar to Kawasaki disease, with petechial, purpuric hemorrhages, and continual desquamation.

**Disseminated gonococcal infection;** When gonococcal infection is hematogenously disseminated, resulting in rapid progression, papular rashes, petechiae, and hemorrhagic folliculosis appear mostly on the torso, but also systemically. *Neisseria gonorrhoeae* can be detected in these skin lesions [4].

**Mycoplasma infection;** Mycoplasma infection shows epidemiological characteristics that suddenly appear in multiple locations every 3-4 years, with maculopapular, urticaria-like, and papular rashes in the entire body in about 30-50% of cases, along with symptoms of upper and lower respiratory tract infection, and central nervous system symptoms. However, since these rashes are nonspecific, they do not lead to a diagnosis. Nevertheless, when mycoplasma infection is prevalent and there are clinical manifestations suspicious for this infection, a rash could be helpful diagnostic information.

Representative diseases with noninfectious systemic maculopapular rashes include exanthematous and collagen-vascular diseases due to hypersensitivity reactions. Exanthematous diseases caused by a hypersensitivity reaction that are commonly seen clinically include erythema toxicum of the newborn, urticaria, erythema multiforme, drug eruptions, and pityriasis rosea [23]. On the other hand, since all collagen-vascular diseases such as rheumatic fever, rheumatoid arthritis, and lupus erythematosus show highly characteristic clinical symptoms, occurrence of rashes can provide further evidence for the diagnosis, even though the rash itself is nonspecific.

**Drug eruption:** In general, drug eruptions manifest as various sudden-onset rashes, and are accompanied by systemic symptoms, including fever, arthralgias, lymphadenopathy, and liver enlargement, and can even be caused by drugs used for treatment of infectious diseases. Hence, it is not easy to distinguish a drug eruption from rashes caused by an infection, particularly those caused by a viral infection. It is therefore difficult to diagnose a drug eruption based on the pattern of the rash alone, meaning that the history is most important for diagnosis. In particular, it is necessary to check the medi-

ation history (including external preparations) from at least one week before onset of the rash, which also must be differentiated from infectious diseases [23, 24].

**Toxic erythema neonatorum:** This must be differentiated from rashes due to infectious diseases seen in newborns, such as listeria, toxoplasma, and cytomegaloviral infections, due to various patterns such as maculopapular, urticaria-like, and vesicular rashes. However, since toxic erythema rashes fade within 4-6 weeks after birth, and there is no finding related to an infection on testing and clinical examination, differential diagnosis is not difficult.

**Erythema multiforme:** This disease is caused by a hypersensitivity reaction due to sensitization by a drug (mostly sulfa drugs) and a source of infection (streptococcus, staphylococcus, mycoplasma, herpes simplex, and herpes zoster), and is accompanied by systemic symptoms, rashes with various patterns (including vesicular rashes), and fever. Mild forms of this disease result in rashes localized to the arms, hands, and feet, whereas severe forms (Stevens-Johnson syndrome) spread to the mouth, genitalia, and the mucocutaneous junction of the anus [4].

## Diffuse erythema with desquamation

Representative diseases that show a course of systemic erythema, accompanied by dermal caseation during the recovery stage, include scarlet fever, toxic shock syndrome, staphylococcal scalded skin syndrome, and Kawasaki disease. In contrast, other diseases showing systemic erythema without dermal caseation include bacteremia due to *Streptococcus viridans*, enteroviral bacteremia, graft vs. host reactions, and generalized pustular psoriasis [2].

**Staphylococcal scalded skin syndrome (SSSS):** This usually occurs in infants and toddlers and is caused by coagulase-positive staphylococci. The characteristic skin lesions of this disease have sudden-onset, and are generalized, diffusely erythematous rashes accompanied by edema around the eyes, with associated pain, and with gradual progression to a vesicular rash. Thereafter, skin lesions show Nikolsky's sign, in which the uppermost layer of skin is removed by even mild pressure or injury; tissue fluid leaks from the exposed skin, causing severe dehydration and electrolyte imbalance, and even aggravates nutritional deficiencies. In addition, the skin around the eyes and mouth is severely distorted. These skin lesions start to improve and recover after 1 week, when the systemic erythema disappears. Drug-induced toxic epithelial



dermal necrolysis also shows similar findings, including systemic erythema and desquamation. However, while SSSS shows desquamation of only the superficial, epithelial granular layer, all the epithelial layers peel off in drug-induced toxic epithelial dermal necrolysis, which allows for differentiation.

**Toxic shock syndrome:** The symptoms of this syndrome include fever, hypotension, muscular pain, and syncope; it is caused by *Staphylococcus aureus* (phage group I), with inflammatory findings in the mucosa, edematous erythema in the hands and feet, and scarlet fever-like rashes over the curved areas of the extremities. The most notable characteristic skin lesion in this syndrome is nonpitting systemic edema. Thick skin desquamation appears on the hands and feet at around 7-14 days of disease progression, and might be followed by hair desquamation or shedding of fingernails and toenails after 2-3 months.

## Vesicular rashes

A representative disease with a systemic vesicular rash is chickenpox, whereas local vesicular rashes are seen in diseases including herpes simplex and herpes zoster. Moreover, vesicular rashes can occur in children with impetigo caused by staphylococcal skin infection in the summer, and in *V. vulnificus* bacteremia that can occur in patients with gonococcal bacteremia, liver diseases, renal failure, and diabetes [25]. And infectious complications with erythematous vesicular rash in patients with hematologic malignancies are common. In particular, in such cases, disseminated viral infections can be considered most commonly, with herpes viral infection considered first; additional screening needs to be performed for enteroviral infection. In addition to infectious diseases, it is also necessary to differentiate causes including exanthema, drug eruptions, early Stevens-Johnson syndrome, contact dermatitis, and autoimmune blistering diseases including Sweet's syndrome [26]. Classification of the causes of vesicular rashes

is presented in Table 2.

**Chickenpox:** Chickenpox presents with systemic symptoms, including fever, asthenia, and a lack of appetite at the onset of the disease; rashes spread from the chest to the periphery, and then to the entire body over the course of about 3 days. Rash patterns involve the initial appearance of vesicles in a teardrop shape, followed by simultaneous occurrence of papular and macular rashes with crusting. These vesicular rashes mostly appear concentrated on the torso, the extremities, and the head, including the scalp, and can occur on the oral mucosa. In addition, rashes in chickenpox are accompanied by severe pruritus, and last for 5-6 days; during this time, the disease remains contagious until crusting is complete, and it is necessary to isolate patients [27].

**Hand-foot-mouth disease:** Papular follicles 2-10 mm in size are accompanied by pain and fever, gastrointestinal symptoms, and local lymph node enlargement. The lesions mostly occur on the oral mucosa, the hands, the feet, and buttocks. In rare cases, they might appear in the nostrils, genitalia, and conjunctiva. This disease can be spread through direct contact, and generally shows favorable progress. However, if hand-foot-mouth disease due to enterovirus type 71 spreads rapidly, paralytic neurological complications due to encephalitis and spondylitis can appear around the time that the rash subsides [28].

**Vesicular impetigo:** A systemic vesicular rash occurs in this disease, and purulent changes appear sequentially. These rashes have a characteristic distribution, mostly appearing in the inguinal area and the abdominal region, and are absent from the palms and soles. Staphylococcus is detected in these skin lesions [10].

**Herpes zoster:** Herpes zoster is a clinical skin disease caused by secondary infection by the varicella zoster virus, and does not commonly occur in children. Invasion of this virus into the peripheral nerves causes vesicular rashes in that region of skin. However, children, unlike adults, rarely have severe pain; invasion into the facial nerve can be accompanied by paraly-

**Table 2.** Causes of vesicular rash

Bacterial diseases	Non-bacterial diseases	Non-infectious diseases
Staphylococemia	Enteroviral diseases	Allergy
Gonococemia	Varicella	Plant dermatitis
Impetigo	Herpezoster	Eczema vaccinatum
<i>Vibrio vulnificus</i>	Herpes simplex	Erythema multiforme
<i>Pseudomonas folliculitis</i>	HIV	
	Parvovirus B 19	
	Tsutsugamushi disease	

sis, and invasion into the trigeminal or auditory nerve can also be accompanied by dizziness or hearing loss. These skin lesions persist for 5 days or longer [4].

**Herpes simplex viral focal infection:** Herpes simplex virus mostly presents with focal skin lesions on the skin around the lips. A macular rash suddenly evolves into a papular rash at first, and painful vesicles occur almost simultaneously. As these vesicles burst, findings of secondary infection and eschars occur, followed by natural healing. Herpes simplex viral focal infection can occur on any part of the skin.

**Fungal dermatologic infection:** This skin disease is mostly caused by *Candida albicans*, and is one of the most common infectious local skin lesions in infants. Initial rashes are maculopapular. Since it mostly occurs in the inguinal area and the neck, which are moist and creased, it is hard to differentiate from diaper rash and infantile eczema. However, since the center of the skin lesion is paler than normal skin, and the outer parts are clearly raised, and as regions of occurrence gradually spread, it becomes easier to differentiate from other diseases.

## Erythematous rashes

Some patients with acute disease show systemic erythema, but this is generally accompanied by injuries of various organs, and can include severe diseases with a poor prognosis. For example, patients with toxic shock syndrome (TSS) due to group A streptococcus infection have systemic erythema, in addition to fever, hypotension, and severe pain in muscles and bones. In addition, various toxins from *Staphylococcus aureus* cause diseases like staphylococcal toxic shock syndrome (toxic shock syndrome toxin-1, enterotoxin B or C) and staphylococcal scalded skin syndrome (epidermolysin A or B) after onset of infection, and systemic erythema accompanies the progression of these diseases. Systemic erythema can appear in cancer patients due to bacterial infection caused by *S. viridians* and *C. haemolyticum* [25]. Scarlet fever is most common in bacterial infections with mild progression, with findings of

systemic minor erythematous rashes and fever, pruritus, pigmentation, and dermal caseation. Among nonbacterial infectious diseases, ehrlichiosis due to rickettsial infection can show clinical patterns similar to TSS; erythematous rashes are rarely seen in patients with enteroviral infection. On the other hand, systemic erythema can occur in noninfectious diseases like allergy, eczema, psoriasis, lymphoma, and pityriasis rubra (Table 3). The other representative erythematous rash is erythema nodosum, which is caused by infectious diseases, including streptococcus, *Y. enterocolitica* infection, tuberculosis, fungal (coccidioidomycosis, histoplasmosis, blastomycosis) infections, and an acute inflammatory immune response in the panniculus adiposus in collagen-vascular diseases like systemic lupus erythematosus and rheumatic fever. It is common in females, and is accompanied by fever, malaise, and arthralgias, mainly appears in the lower extremities, knee joints, and wrists, and naturally disappears after about 6 weeks, although this depends on the cause [3].

### 1. Urticarial rashes

When patients with fever present with an urticarial rash, it is necessary to consider exposure to antibiotics for differentiation between infectious and noninfectious causes. In other words, the conditions that primarily need to be differentiated in febrile patients are an allergic response following administration of antibiotics, or an interaction with sources of infection (rashes that appear when penicillin derivative antibiotics are administered to patients with infectious mononucleosis due to EB virus). A representative bacterial disease with urticarial rashes is mycoplasma infection. If these rashes appear during treatment of patients with a febrile respiratory infection while this disease is prevalent, mycoplasma infection needs to be considered [1, 2]. Nonbacterial infectious diseases include Lyme disease, enteroviral infection, adenoviral infection, EB viral infection, and hepatitis viral infection, whereas noninfectious diseases include allergy, vasculitis, and cancer (Table 4).

**Table 3.** Causes of erythematous rash

Bacterial diseases	Non-bacterial diseases	Non-infectious diseases
Staphylococcal infection	Enteroviral diseases	Allergy
Streptococcal infection		Eczema
Streptococcus viridans		Psoriasis
<i>Clostridium haemolyticum</i>		Lymphoma
		Pityriasis rubra

**Table 4.** Causes of urticarial rashes

Bacterial diseases	Non-bacterial diseases	Non-infectious diseases
Mycoplasma infection	Enteroviral infection	Allergy
	Adenoidviral infection	Vasculitis
	EBV	Malignancy
	Hepatitis	Idiopathic
	HIV	
	Lyme diseases	

EBV, Epstein Barr virus; HIV, human immunodeficiency virus.

## 2. Nodular eruptions

A representative disease is nodular erythema, which is caused by an acute inflammatory immune response in the panniculus adiposus due to various causes. It is common in females, accompanied by fever, malaise, and arthralgia, mainly appears in the lower extremities, knee joints, and wrists, and naturally disappears about after 6 weeks although this depends on the cause. In addition, immunodeficient patients often show erythema nodosum caused by severe fungal infection [2].

**Erythema nodosum:** Erythema nodosum is a skin finding occurring in infectious diseases like streptococcus, *Y. enterocolitica* infection, tuberculosis, fungal (coccidioidomycosis, histoplasmosis, and blastomycosis) infection, and collagen-vascular diseases like systemic lupus erythematosus and rheumatic fever. It presents with circular or oval nodules 2-4 cm in size, with painful indurations on the anterior lower extremities appearing in a cluster. However, nodules can also occur on the upper arm. These nodules initially display a scarlet color, gradually changing to green or violet, and then to red-brown.

**Erysipelas:** This is an infection of the skin caused by streptococcus, in which scarlet erythema appears on the face, genitalia, umbilicus, hands, or feet. There may be some sensation of fever, and there is a characteristic elevation of the rash. In addition, in all ages except in infants, the erythema is sharply demarcated from normal skin.

**Eschar:** The constellation of fever, rash and eschar should alert a clinician to the possibility of a rickettsial disease. Rickettsial diseases account for approximately 1.5-3.5% of febrile travelers. In several series of travel-related rickettsioses, the most common travel-related rickettsial disease is *Rickettsia africae*. Other rickettsioses including Q fever, scrub typhus and murine typhus are considered rare among travelers [29].

## 3. Hemorrhagic rash (Petechiae and purpura)

Systemic symptoms were significantly associated with petechiae or purpura both cutaneous and mucosal. This probably

depended on the infectious etiology of the hemorrhagic pattern. In fact, since petechial and purpuric rashes appear as terminal symptoms in diseases such as meningococemia, encephal meningitis, or sepsis caused by pathogens such as bacteria, viruses, and fungi, patients with these rashes who also show acute and severe clinical symptoms must undergo proactive diagnosis in the early stages, followed by appropriate treatments. Although meningococcus infection is most common among bacterial diseases with these rashes, they can also be caused by pneumococcus, staphylococcus, and gonorrhoea bacteremia. In particular, the characteristics and progress of the rash are highly important for early diagnosis of meningococcus infection. A haemorrhagic rash, with spots that vary in size from petechiae to ecchymoses, is an important diagnostic feature of meningococcaemia [30, 31]. It is more frequent and specific than earlier symptoms (cold hands and feet, abnormal skin colour or leg pain). Viral infections that cause hemorrhagic rash include coxsackievirus A9, echovirus 9, EBV, cytomegalovirus (CMV), measles virus, arboviruses, and arenaviruses, most of which are accompanied by fever. Especially, coxsackievirus and echovirus infections in children can produce severe illness and, at times, are difficult to distinguish from meningococemia. In recent time, several investigators report that Influenza A infection can also cause a petechial exanthem. These reports highlight a viral cause during “flu season” when a febrile child with petechiae will be assumed to have bacterial meningitis. When this has been appropriately ruled out, practitioners should consider influenza [32-34].

Cytomegalovirus (HHV-5) infections are among the most common congenital infections. Typically, there is a petechial or purpuriform exanthem (blueberry muffin spots) on the skin. Among extracutaneous symptoms are hepatosplenomegaly, intrauterine growth disorders, thrombocytopenia, deafness, chorioretinitis, and severe central nervous system (CNS) damage with microcephalus and intracerebral calcifications. The diagnosis of congenital CMV in a newborn is confirmed by detection of the virus through the short-term viral culture or PCR in urine and/or a pharyngeal swab. In symptomatic congenital



**Table 5.** Causes of hemorrhagic rash

Bacterial diseases	Non-bacterial diseases	Non-infectious diseases
Meningococemia	Enteroviral diseases	Acute allergic eruption
Endocarditis	EBV	Allergic purpura
Other bacterial bacteremia or septicemia (Streptococcus, Staphylococcus, Pneumococcus etc.)	Hepatitis B	Acute thrombocytopenia
	Rubella	Hematologic malignancy
	Cytomegalovirus	Hypersensitive vasculitis
	Influenzae A	Acute rheumatic fever
		SLE
		Hyperglobulinemia
		Amyloidosis

EBV, epstein barr virus; SLE, systemic lupus erythema.

cytomegaly, quantitative CMV genome identification using PCR obtained from blood, cerebrospinal fluid (CSF), or urine should be performed. Serologic evaluation for anti-CMV IgM is less reliable and may be negative in symptomatic newborns and premature infants [35]. Classification of hemorrhagic rash by cause is presented in Table 5.

#### 4. Acute severe febrile illness with skin rash

In general, among patients who are admitted to the intensive care unit, those with fever and rashes are classified by the presence or absence of rashes and the severity at the time of hospitalization. The most common etiologies in these patients are meningococemia or meningoenephalitis, while other causes include TSS, SLE, bacterial sepsis (pneumococcal, staphylococcal, vibrio, etc.), and severe viral diseases (hemorrhagic fever, measles, dengue fever, etc.). In particular, when patients show fever and rash postoperatively, TSS, surgical scarlet fever, and cholesterol emboli syndrome should be considered, and if patients have a central venous catheter or pacemaker, fever and rash due to bacteremia must be considered. However, the most common cause of fever and rash in patients admitted to the intensive care unit is adverse reactions to drugs [36].

Although the most common cause of a rash in adult patients with bacterial meningoenephalitis and petechial or purpuric hemorrhages is meningococcal infection, early diagnosis would be very difficult when the only initial symptom of bacteremia within 24 h of onset is a rash, without other meningoenephalitis symptoms. In this case, upper airway symptoms accompanied by severe headache and muscular pain have been recently considered. On the other hand, petechiae in patients with meningococcal bacteremia and meningoenephalitis present with irregular shapes without findings in the palms or soles at onset. At this time, gram-negative diplococci and multinucleated neutral lymphocytes should be identified

by Gram staining of tissue fluid from petechial rashes for the fastest diagnosis. In addition, when patients with meningococcal bacteremia or cerebromeningitis present clinically with Waterhouse-Friderichen syndrome following invasion of the adrenal cortex, hypotension and shock occur [36]. If patients are admitted to intensive care for fever and rashes due to severe bacterial infection other than meningococcus, fulminant bacteremia caused by pneumococcus or staphylococcus must be considered. Staphylococcal bacteremia can show petechial rashes or skin necrosis on the nose, ears, and extremities, and is caused by endocarditis due to staphylococcal infection, or severe blood infection [37, 38]. On the other hand, bacteremia or sepsis caused by pneumococcus mostly presents as pneumonia and hypotension together with hemorrhagic rashes similar to meningococcal infection. Meanwhile, most patients with pneumococcal bacteremia have functional or anatomical asplenia; leukopenia and thrombocytopenia are clearly diagnosed with a blood test, making it is easy to differentiate this from other severe bacterial infections [39]. On the other hand, patients with fever and rash resulting from TSS due to toxin-secreting staphylococci could be admitted to the intensive care unit, although this is unusual. These TSS patients exhibit maculopapular, systemic scarlet fever-like rashes, including on the palms and soles, and may also present with edema around the eyes and extremities, conjunctival hyperemia, and hypotension. In addition, renal and liver function disorders are found on testing. Use of tampons in females, intraventricular hemorrhage, and surgical history need to be considered in these patients; they also need to be evaluated for nausea, diarrhea, headache, and muscular pain [40, 41]. Fever and rashes resulting from hypersensitivity reactions to drugs are the most common reasons for patients to be in the intensive care unit, with findings ranging from systemic erythema accompanied by skin edema (including vesicular rashes) and involvement of the entire skin target sign, to hypersensitive re-

**Table 6.** Differential diagnostic manifestations in acute patients with febrile illness and rash

Rashes and concomitant clinical features	Suspected diseases
Rash and shock	TSS, MC, pneumococcal sepsis, <i>Staphylococcus aureus</i> sepsis, hemorrhagic fever
Rash and conjunctivitis	Kawasaki diseases, measles, TSS, PLEVA
Rash and abdominal pain	Typhoid fever, scarlet fever, cholesterol emboli syndrome, <i>Vibrio vulnificus</i> , SLE
Rash and diarrhea	<i>Vibrio vulnificus</i> , gas gangrene, TSS, PLEVA
Rash and mental changes	SLE, MC, typhoid fever, <i>Staphylococcus aureus</i> , ABE
Rash and pulmonary infiltrates	SLE, atypical measles
Rash and relative bradycardia	Typhus, typhoid fever, drug fever
Rash and bullae lesions	<i>Vibrio vulnificus</i> , gas gangrene
Rash and purpura	MC, cholesterol emboli syndrome, hypersensitivity vasculitis
Rash and adenopathy	SLE, Rubella, scarlet fever, Kawasaki diseases
Rash and splenomegaly	Typhoid fever, rubella, SLE

TSS, toxic shock syndrome; MC, meningococemia; PLEVA, pityriasis lichenoides et varioliformis acuta; SLE, systemic lupus erythemata; ABE, acute bacterial endocarditis.

actions to drugs with petechiae and systemic maculopapular rashes, which makes early diagnosis difficult. These can show eosinophilia, thrombocytopenia, and elevation of blood sedimentation rate, and a rise in serum transaminase values in liver function tests. In addition, it is most important to consider the clinical presentation accompanying administration of drugs [41]. Clinical symptoms of severe acute diseases presenting with fever and rashes, and differences in their symptoms can be summarized as in Table 6. In addition, febrile ulceronecrotic PLEVA, which is a complication type of pityriasis lichenoides et varioliformis acuta (PLEVA or Mucha-Habermann disease), an acute clinical type of pityriasis lichenoides, is thought to be caused by primary immune complex vasculitis. This disease is accompanied by pronounced cutaneous necrosis and ulceration as well as secondary infection of the skin lesions and fever, and shows extracutaneous symptoms including sore throat, abdominal pain, diarrhea, central nervous system disorders, splenomegaly, arthritis, sepsis, interstitial pneumonitis, and conjunctival ulcers. Since its mortality rate is as high as 25%, it is a disease that is suspected to be correlated with infections requiring ICU treatment [42]. Skin biopsy must be performed for diagnosis.

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