

## Erythema Multiforme — Definition and Treatment

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**Erythema multiforme (EM) is a type of cytotoxic dermatitis, which can be triggered by many factors; mainly herpes simplex infection and drugs being the implicating factors. Although it is self-limiting, recurrences are common. In this article, definition, epidemiology, aetiology, pathology, pathophysiology, symptoms, diagnosis, differential diagnosis, therapy, prognosis and progression of EM will be discussed.**



### Definition of Erythema Multiforme

EM is a self-limiting disease and is caused due to **cell mediated hypersensitivity** (type IV hypersensitivity). This hypersensitivity is mainly due to drugs and infections. It is clinically characterized by macular, papular and urticarial lesions. **Target lesions** are characteristic of this disease.

Initially, EM was considered to be a part of a clinical spectrum varying from mild to severe cases from EM, **Stevens - Johnson syndrome (SJS)** to **toxic epidermal necrolysis (TEN)**. However, recently, **EM minor** and **EM major** are considered as separate entities

than SJS and TEN, which are considered to be mainly drug hypersensitivity reactions.

## Epidemiology of Erythema Multiforme

**Incidence:** EM incidence is not known. However, a few studies have shown the incidence globally as 1.6 – 2 million cases per million per year.

**Age:** EM occurs in age group of 3 years to 50 years. The peak incidence occurs in between 20 years and 40 years. EM occurs in children in 20% of cases. Severe and extensive type of EM occurs in children less than 5 years of age.

**Sex:** EM occurs a little more commonly among males than females. Male to female ratio of involvement of EM is 3:2.

## Etiology of Erythema Multiforme

Many factors have been implicated to trigger EM. The most common triggers are **herpes simplex** infections (genital or facial) and **mycoplasma** infections. Other factors implicated can be categorized as follows:

1. **Viral infections:** AIDS, **adenovirus**, **cytomegalovirus**, infectious mononucleosis, **hepatitis**, poliomyelitis.
2. **Bacterial infections:** Many bacterial infections have been implicated, such as **rickettsiae**.
3. **Fungal infections:** Histoplasmosis.
4. **Drugs:** Longitudinal studies of cases of EM have shown that drugs are known to trigger only 10% of EM cases. Anecdotal reports have shown many drugs to induce EM. Nonsteroidal anti-inflammatory drugs (**NSAIDs**), antibiotics (**penicillins** and **sulphonamides**) and anti-epileptics are the most commonly implicated. Reports of vaccinations triggering EM have also been reported.
5. **Miscellaneous:** Other diseases associated with EM are **lupus erythematosus**, **carcinoma**, lymphoma, leukemia, polymorphic light eruption, **polyarteritis nodosa**, **sarcoidosis**, etc.

Besides the triggering factors, immunology has been shown to have a role in the etiology of EM. Patients with recurrent EM cases have shown **HLA-B62 (B15)**, **HLA-B35** and **HLA-DR53**.

## Pathology and Pathophysiology of Erythema Multiforme

EM is caused due to a **delayed type IV hypersensitivity reaction**. The herpes virus infection causes an increase of **CD54** and major histocompatibility complex class 1 molecules. **HSV DNA** is found in EM lesions caused by the **herpes virus**. This HSV DNA is phagocytosed by peripheral blood mononuclear antigen presenting cells and taken to distant skin sites. This leads to activation of SP 1 and INF-alfa. This leads to activation of an **inflammatory cascade**.

Histopathology of EM shows a varied pattern depending on the age of the lesion. The most important change seen is **necrotic keratinocyte** in **epidermis** and upper **dermis**.

# Symptoms of Erythema Multiforme

EM has been divided into different types based on their clinical features:

1. **EM minor: papular or simplex form:** This type is the most common form comprising 80% of cases. The lesions are macular, papular, urticarial or the typical target lesions, which are a dull red in color. The lesions can be small or increase in size to 1 to 5 cm diameter with time. Lesions are mainly present over palms, feet, extensor aspects of elbows and knees. At times, trunk, oral and **genital mucosa** may be involved. Lesions appear in successive bouts for a few days and subside in 1 to 2 weeks leaving behind a discoloration.
  - **Target/iris lesions:** These lesions are characteristically seen in typical cases of EM. They are rounded lesions with a size less than 3 cm in diameter and consisting of three zones: a central zone of dusky **erythema** or purpura, a middle zone of edema which looks pale and a peripheral zone of erythema with well-defined margins. The most common site of involvement is **acral areas**.
  - **Atypical target lesions:** These are similar to the typical **target lesions**, but have only two zones.
2. **Localized vesicobullous form:** The skin lesions are mainly present as erythematous macules or plaques. These lesions often have a central bullous lesion and vesicles forming a ring at the periphery; this is known as **Herpes iris of Bateman**. Mucosal involvement is often seen.
3. **EM major:** This is a severe form with extensive involvement of skin and mucous membrane. The skin lesions are preceded by **prodromal symptoms** 1 to 13 days prior to the eruptions.
4. **Rowell syndrome:** This syndrome consists of EM like skin lesions in lupus erythematosus patients with immunological tests positive for speckled antinuclear antibodies, anti-La antibodies, anti-Ro antibodies and positive rheumatoid factor.

## Diagnosis of Erythema Multiforme

The diagnosis of EM is mainly a clinical diagnosis. The investigations are done in severe cases to aid in the management of patients.

1. **Complete blood count and differential blood counts:** This shows a moderate **leukocytosis** with atypical lymphocytes and **lymphopenia**. Neutropenia and eosinophil counts greater than  $1,000/\text{mm}^3$  may be seen.
2. **Electrolytes and kidney function tests:** These are done in severe cases to rule out and monitor the organ involvement.
3. **Skin biopsy:** A skin biopsy is required to rule out other disorders, such as **vesicobullous diseases**. Histopathology of EM typically shows a vacuolar interface dermatitis with the dermoepidermal junction (**DEJ**) showing lymphocytic infiltrate. The basal keratinocytes show **dyskeratosis** and hydropic changes. The vacuolar change is typically due to the necrotic keratinocytes due to apoptosis and is typical of EM.
4. **Polymerase chain reaction and immunofluorescence of skin:** PCR is used to detect HSV DNA in skin samples. A direct immunofluorescence study is done to rule out other blistering diseases, such as linear IgA.

## Differential Diagnoses

- Acute febrile neutrophilic dermatosis
- Acute hemorrhagic edema of infancy
- Allergic contact dermatitis
- Bullous pemphigoid
- Dermatologic aspects of Behcet's disease
- Dermatologic manifestations of staphylococcal scalded skin syndrome
- Dermatologic manifestations of Stevens-Johnson Syndrome and toxic epidermal necrolysis
- Urticarial vasculitis
- Drug eruptions
- Irritant contact dermatitis
- Paraneoplastic pemphigus

## Therapy of Erythema Multiforme

Management of EM is done as per the severity of the disease.

1. Localized EM is managed symptomatically. Ocular involvement should be referred to an ophthalmologist.
2. EM major: This requires good nursing care in dermatological high dependency units or intensive care units or burns units. Other than this, the medications which have been tried are:
  - **Systemic steroids:** The role of systemic steroids is not clear; however, systemic symptoms, such as fever, are controlled by steroid use.
  - **Antiviral therapy:** Antiviral therapy has been found to have no role in acute cases of EM triggered by Herpes simplex infections. However, in recurrent EM which may or may not be attributed to herpes simplex infections, antiviral therapy given prophylactically have shown to reduce relapses of EM.
  - Other drugs which have shown decrease relapses when given prophylactically are: thalidomide, dapsone, azathioprine, **ciclosporin** and **mycophenolate mofetil**.

## Progression and Prognosis of Erythema Multiforme

EM is a self-limiting disease. **EM minor** usually subsides by 2 to 3 weeks and lesions heal without scarring. However, recurrences are more in this type of EM. Almost 30% cases are known to have recurrences.

**EM major** has a longer course and may take 3 to 6 weeks to subside. Skin lesions heal leaving behind pigmentation. The mortality rate of 5% is seen among these patients. Some known poor prognostic factors are: visceral involvement, older age, a previous history of bone marrow transplantation and increased urea nitrogen levels.

### Important points to remember

- EM is a self-limiting disease due to a delayed type of hypersensitivity to certain factors.
- Most common triggers for EM are **herpes simplex infections** and drugs.
- The most characteristic lesion of EM is target/iris lesions mainly involving acral areas.

- Histopathology of skin lesions shows vacuolar interface dermatitis due to characteristic **necrotic keratinocytes**.

## Review Questions on Erythema Multiforme

The correct answers can be found below the references.

1. **A 24-year-old presents with three maculopapular lesions with a central purpuric area (target lesions) over the hands and palm. He had an oral herpes simplex infection seven days back. What is the possible diagnosis?**
  - A. Stevens-Johnson Syndrome
  - B. Toxic epidermal necrolysis
  - C. Erythema multiforme
  - D. Erythema nodosum
2. **A 20-year-old female had a fever for which she had taken acetaminophen seven days back. She had `target` lesions over her palms. A tentative diagnosis of erythema multiforme was made. What could be the histopathology of the target lesion?**
  - A. Vacuolar interface dermatitis with necrotic keratinocytes
  - B. Multinucleated giant cells with lymphocytic infiltrate
  - C. Epidermal bulla with acanthocytes
  - D. Miescher's radial granuloma
3. **A 30-year-old woman presented to the physician with `target` lesions on her hands. She also gave a history of photosensitivity and joint pains. Investigations revealed a positive rheumatoid factor, anti-La and anti-Ro antibodies. What is the most probable diagnosis?**
  - A. Polyarteritis nodosa
  - B. Lupus erythematosus with Rowell's syndrome
  - C. Toxic epidermal necrolysis
  - D. Systemic sclerosis

## References

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**Fitzpatrick's Dermatology in General Medicine** (2008). 7<sup>th</sup> edition. McGraw-Hill Professional. PP 343-348.

Chan M, Goldman R.D. **Erythema multiforme in children**. Canadian Family Physician. 2013, (59):635-636.

[Erythema Multiforme Differential Diagnoses](#) via medscape.com

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**Correct answers: 1C, 2A, 3B**

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