## ERYTHEMA MULTIFORME

### Definition

Erythema multiforme (EM) is an acute inflammatory disorder, usually self-limiting and often recurrent. The term EM includes a wide range of clinical presentations: a form with oral involvement only (oral EM), a mucocutaneous forms of various severity, with one or more mucosal localizations (EM minor, EM major, Stevens-Johnson syndrome [SJS]), and forms affecting large areas of the body surface (toxic epidermal necrolysis [TEN]). Currently there is no agreement over the classification of the “EM spectrum” and often the different clinical forms show overlapping features.

### Epidemiology

Young adults, from 20 to 40, are most commonly affected, although children over 3 years and teenagers, represent 20% of cases. The estimated incidence ranges from 1.1 person every 1.000.000 per year in Germany, to 3.7 in the USA and up to 5-10 in Sweden.
Recurrences are seen in 37% of the cases, often characterized by a progressive worsening of the attacks. A genetic predisposition linked to HLA-DQB1*0301 allele has been reported.

### Clinical presentation

Prodromal features such as malaise, fever, cephalgia, and oro-pharyngeal burning, can precede epithelial lesions by 7-10 days. The episodes of EM are usually acute, self-limited and recurring, and often preceded by systemic symptoms such as malaise, fever, headache.The classic skin lesion of EM is the “target” or “iris” lesion, which consist of concentric erythematous rings separated by skin of near-normal appearance; the tissue in the centre of the target may be erythematous or tan. These lesions disappear in about 1-4 weeks leaving a transiently hyperchromic skin. Extremities, especially extensor surfaces as palms and soles, are typically involved, usually with a symmetric distribution, whereas face, neck and trunk are less commonly involved.
In EM major, skin lesions usually follow mucosal lesions; they may resemble classical target skin lesions, but are often characterized by bullae and erosions which can cause epidermal loss. The early skin lesions of toxic epidermal necrolysis (TEN) (macules with a central darker area) can simulate the classical ones of EM, but they show an irregular edge and lack the oedematous ring. The lesions of EM affect the face, limbs and trunk. The disease can also start with a severe diffuse erythema; quickly evolving into large flaccid blisters, resulting in a massive epidermal loss.
Early oral EM presents erythematous spots which progress to blisters that quickly break, resulting in erosion and/or ulcers. Oral involvement varies from a few aphthous-like lesions to multiple, superficial, widespread erosions. Lesions are irregular but well demarcated, sometimes

associated with pseudomembranes or crusting. The reported incidence of oral lesions in EM varies considerably, ranging from 25 to 70%, but several authors have reported exclusive intraoral lesions in EM patients. Any area of the mouth may be involved, especially the lips and the anterior part of the oral cavity (tongue and buccal mucosa); gingival involvement can also be seen. Symptoms range from mild discomfort to severe pain that can leave patients unable to open the mouth, to speak or to eat.
The mucosal involvement in EM major and TEN, is early and constant, affecting the oral cavity (95-100% of the cases), eyes (70-75%), genitalia (60-65%) and occasionally pharynx, larynx, oesophagus and respiratory tract.

**Aetiopathogenesis**

Although many factors may be involved in the EM, often the basic cause of the disease is unknown. In contrast to skin EM, which is mostly caused by systemic drugs (principally anticonvulsants, sulfonamides, non-steroidal anti-inflammatory drugs and antibiotics) and herpes simplex virus (HSV) infection, the aetiologic agents remain obscure in many oral EM cases. Many studies from dermatological clinics, based on cohorts with cutaneous involvement, found a relation between EM and HSV infection which has not always confirmed in studies of stomatological cohorts. HSV-DNA has been demonstrated in cutaneous and oral lesions, but the role of HSV in the aetiology of oral EM remains uncertain.

**Diagnosis**

Since there are no specific markers for EM, the diagnosis is based mainly on the clinical features and history.
All the patients referred to a stomatological clinic should also have a dermatological examination (including genitalia), in order to evaluate the presence of lesions involving the skin and/or other mucosal sites. The role of precipitating agents such as herpes infection and drugs should be established. Herpes involvement can be established by evaluating the following criteria: recurrent EM, history of recurrent herpes, recent clinical herpes (preceding EM by 3 weeks), and demonstration of a recent HSV infection (seroconversion). Drug involvement is possible if there is a chronological relationship between drug use and the eruption.
The differential diagnosis includes pemphigus vulgaris, mucous membrane pemphigoid and lichen planus (which have specific histopathological and immunopathological features), in addition it must always be considered oral primary HSV infection, characterized by frequent gingival involvement (rare in the EM). EM has no specific or consistent histological pattern. Pathological parameters can be useful for differential diagnosis in cases with an overlapping clinical aspect. Biopsies must be assessed by means of routine haematoxylin and eosin staining, to exclude any other pathology

with a similar clinical pattern but a specific histopathological one. In questionable cases, a standard direct immunofluorescence can also be performed.

**Treatment**

Treatment depends on the form of EM. Considering the self-limiting nature of the condition and unidentifiable aetiology in many, specific treatment is available for few patients. Systemic anti-inflammatory/immunoregulating agents seems to be the most effective treatment to control oral EM. In particular, prednisone is the most frequently used drug, sometimes associated with azathioprine. Frequently the shortness of the therapy (a full dose of prednisone for 3 days only and then taper the dose) does not require additional azathioprine. In the case of oral EM, topical corticosteroids (fluocinonide or clobetasol in adhesive base) can be useful. However, given the frequent wide extent of the oral lesions and the high prevalence of extra-oral lesions, systemic drugs are often used.

Anti-viral drugs are justified in cases of proved HSV involvement. In SJS and TEN it is mandatory to identify and withdraw the suspected drug. Systemic corticosteroids may be used for the treatment of the SJS. TEN must be treated in a hospital able to manage scalded patients. There is no agreement on the usefulness of high doses of systemic corticosteroids or the effectiveness of other treatment, such as plasmapheresis, hyperbaric oxygen therapy or other immunomodulating drugs such as azathioprine, cyclophosphamide, ciclosporin or high-dose intravenous immunoglobulins.

**Prognosis and complication**

In case of severe SJS or TEN the mortality rate ranges from 10% to 30%. In cases of oral EM, EM minor and moderate SJS, appropriate therapy generally gives a complete resolution within 10-15 days.

**Prevention**

There are no means to reliably prevent EM episodes nor recurrences. Some authors suggest the prophylactic use of an antiviral agent such as aciclovir in patients with oral recurrent EM with a putative viral cause. However there are insufficient data to support this. It is important to remember that drug use can cause a wide range of EM manifestations. For this reason, at the first episode of EM it is imperative to look for any drug that could be responsible, in order to avoid future administration - since the severity of the manifestations often increases in further episodes and in case of severe SJS or TEN this could be lethal.

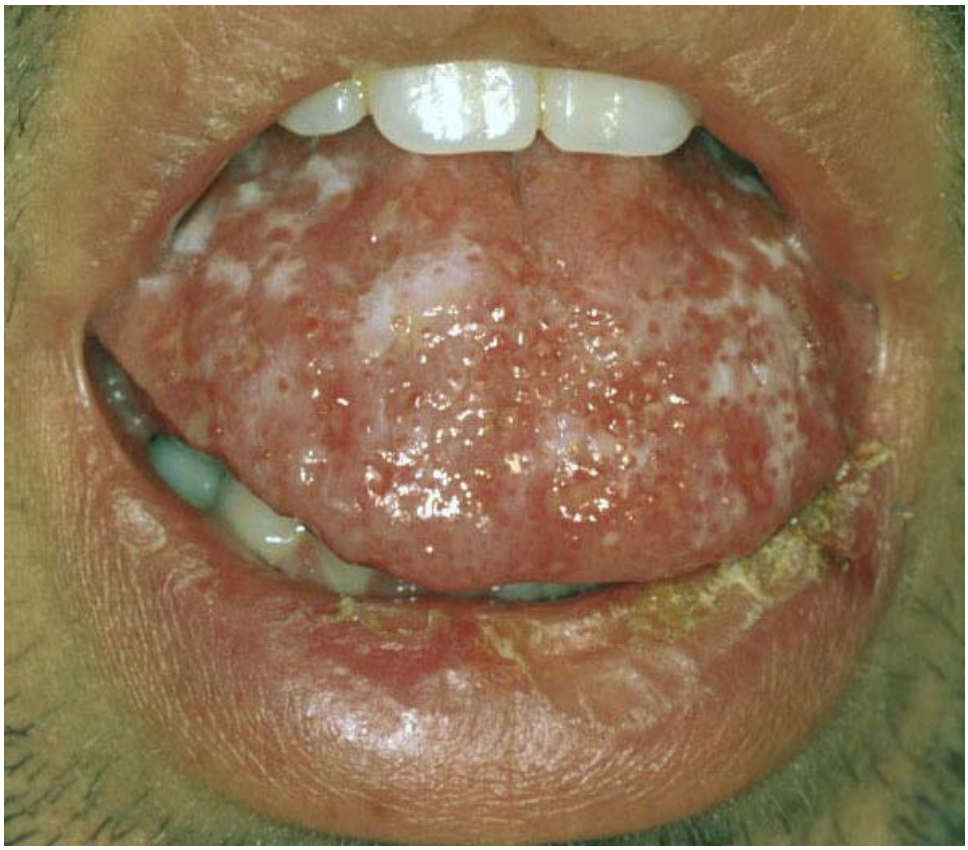

**Figure 1.** Erythema multiforme: oral and labial lesions

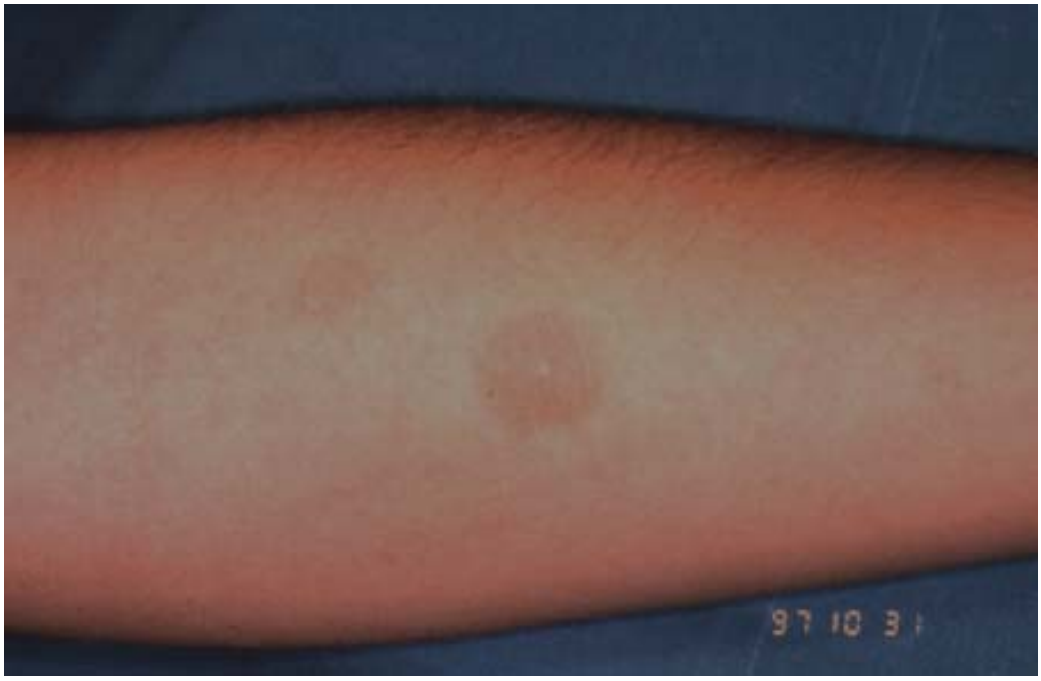


**Figure 2.** Erythema multiforme: cutaneous lesions

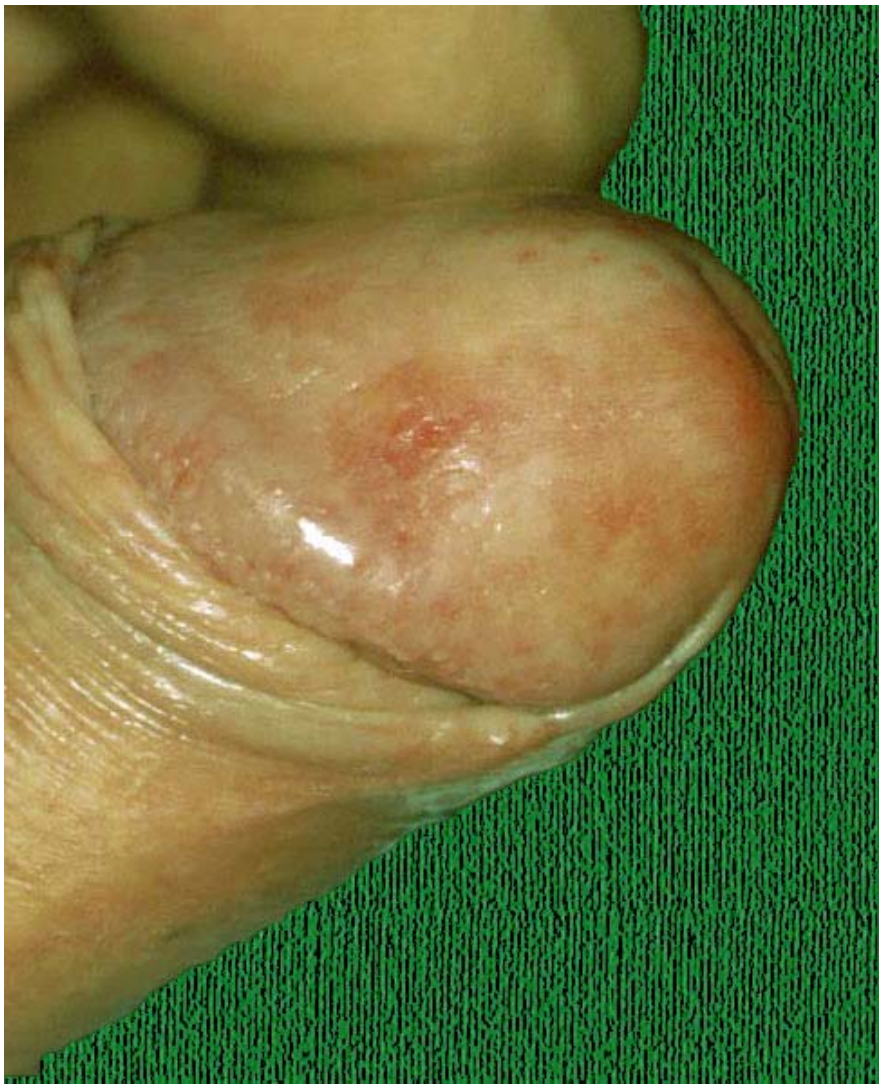

**Figure 3.** Erythema multiforme: genital lesions

**Further reading**


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4 Ayangco L, Rogers RS 3rd. Oral manifestations of erythema multiforme. Dermatol Clin. 2003 ; 21:195-205