Herpes esophagitis: a comprehensive review

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Key words: Herpes simplex virus, esophagitis, immunodepression

INTRODUCTION

Herpes esophagitis (HE) was first described by Pearce and Dagradi in 1943 [1]. For 30 years the diagnoses were made in post mortem studies of immunocompromised patients [2-4]. Then, the development of endoscopy allowed an earlier diagnosis [5,6].

HE is a well-known complication of immunodepression, and the esophagus is the viscus most often involved during the dissemination of herpes simplex virus (HSV) infection [7]. HE is observed in up to 5% of patients treated for malignant hematologic diseases [8], 1-6% of solid organ transplant recipients [9,10] and 10-15% of bone marrow-transplanted patients [11]. HE is also an AIDS-defining condition [12] and a frequent site of disseminated neonatal HSV infection [13,14]. Interestingly, HE has also been anecdotally described in immunocompetent patients, in whom it is a self-limited illness [15]. We give here an extensive review of HE, including its pathophysiology, clinical manifestations, treatment and outcome.

POPULATIONS AT RISK

Several types of immunodeficiencies have been described as risk factors for HE (Table 1), but cellular immunity is the key factor for the control of herpes simplex infection, while the role of antibodies and complement is less important [16,17]. Thus, patients with quantitative defects of T-lymphocytes are particularly prone to develop HSV infections. Indeed, we recently reported such a complication during the late stages of HIV infection [18]. Qualitative defects of T-lymphocytes also represent a risk factor; this is particularly true for liver and renal transplant patients [19]. Furthermore, cellular immunodepression favors the presence of HSV in the saliva [20], which may be a potential source of esophageal infection during swallowing [7,21].

Corticosteroids and anticancer chemotherapy are also well-known risk factors for visceral HSV infection [7]. Indeed, corticosteroids are able to inhibit the activation, proliferation, differentiation and functions of virtually all cells involved in the immune response, but particularly T-cell proliferation [22-24]. Anticancer chemotherapy and radiotherapy have immunosuppressive effects but are also associated with the loss of normal esophageal mucosal integrity, which enhances the risk of HSV reactivation [25].

Previous upper digestive tract endoscopy or insertion of gastric tube are reported in 33-71% of cases during the weeks before HE [4,7,18,26]. Nasogastric intubation may favor the development of HE by trauma and/or viral autoinoculation [7,27]. However,
Table 1 Populations at risk for HE

<table>
<thead>
<tr>
<th>Hematologic malignancies, with or without neutropenia: 6–8, 27, 62, 65, 75, 79, 82, 87, 95, 97, 102, 107, 109, 117, 118</th>
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<tr>
<td>Solid tumors: 3, 27, 27, 57, 62, 68, 68, 78, 87, 88, 97, 102, 107, 116, 119, 120</td>
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</table>
| Systemic or inflammatory diseases [24]: systemic lupus erythematosus [62, 120, 121], Wegener's granulomatosis [7, 62], polyarteritis nodosa [7], giant cell arteritis [27], rheumatoid arthritis [27, 68, 75, 102], polymyositis [102], Crohn's disease [7, 62], ulcerative colitis [57], rapidly progressive glomerulonephritis [7], tuberculosis [2], HIV infection [18, 27, 38–44, 62, 92, 102, 107, 109], Extensive burns [7], Recent trauma [7], Alcoholism [102, 120], Diabetes mellitus [27, 57, 102, 120, 122], Cystic fibrosis [120], Heart insufficiency [57], Renal insufficiency [78], Gastro-esophageal acid reflux [29, 78, 120], Mental retardation [123], Iatrogenic factors: Radiation therapy (particularly for mediastinal tumors) [6, 27, 75, 87, 102, 119], Solid organ transplantation—cyclosporin [19, 27, 62, 107, 124–127], Bone marrow transplantation [80, 95, 102, 109], Anti-CD3 monoclonal antibodies [32], Immunosuppressive agents: cyclophosphamide, azathioprine [68, 120], Systemic steroid therapy [27, 57, 68, 75, 87, 102, 120, 121], Inhaled steroids [128], Recent surgery [129]—trigeminal nerve surgery [21].

no definitive conclusion concerning its role in favoring HE can be drawn in the absence of case-control studies in immunocompromised patients. Endotracheal intubation and nasogastric tubes should be avoided in such patients in case of patent labial or buccal herpetic infection [28]. Gastroesophageal reflux has also been cited as a possible risk factor for HE [29].

Herpes esophagitis in solid organ transplant recipients [28]

HSV reactivation is mostly observed during the first month post-transplantation, and HSV infections occur within the first 2 months after transplantation [30]. In a prospective study of infectious esophagitis following liver and renal transplantation, the authors discovered HE in 3/47 liver transplants post-transplantation (6%) and in 1/21 renal transplants post-transplantation (5%). These data showed a lower prevalence of HE than that observed after marrow transplantation [11, 31]. In the latter paper [31], no association between HE and administration of prednisone or blood level of cyclosporin A was found. HE has also been reported after cardiac transplantation, but no clear data on the prevalence were reported [10]. After transplantation, the use of anti-CD3 monoclonal antibodies has also been associated with an increased frequency of HSV reactivation, including HE [32].

Herpes esophagitis during bone marrow transplantation

There is no significant difference in HE incidence between autologous and allografted bone marrow recipients [33]. Prior to the prophylactic use of acyclovir, 80% of seropositive patients excreted HSV during the first 50 days after bone marrow transplantation, with a peak excretion during the second or third week [33]. By contrast, fewer than 2% of seronegative patients excrete HSV after transplantation, suggesting that HSV infection after transplantation is mostly due to reactivation [33, 34]. During a prospective study of 44 episodes of unexplained nausea and vomiting after allogeneic bone marrow transplantation, Spencer et al [31] documented HE in five cases occurring 1–4 months after transplantation. HSV infection was less common than cytomegalovirus (CMV) infection in two series [11, 31], probably because of the frequent use of prophylactic acyclovir. Among 39 bone marrow transplant recipients, 21 had infectious esophagitis, including six isolated HE cases and four co-infections with CMV or Candida sp. HE occurred mostly in non-neutropenic patients within a mean of 72 days after transplantation and earlier than fungal esophagitis [11]. Surveillance cultures of the oropharynx obtained 1–7 days before the endoscopy were not useful in predicting the organism causing esophagitis [11]. Three of six patients with HE died without resolution of their esophagitis. The same authors reported postmortem data showing evidence of esophageal infection in 25/59 patients, including six due to HSV [11]. In the neutropenic population, herpetic ulcerations have been reported to be a portal of entry for various bacterial and fungal infections [35].

Herpes esophagitis in AIDS patients

During HIV infection, HSV seroprevalence is 80–95% for type 1 and 20–30% for type 2 [36]. HIV and HSV-1 enhance reciprocally their replication in macrophages and keratinocytes [37]. During HIV-1 infection, HE has been considered to be relatively uncommon and classically less frequent than esophagitis due to CMV [38–40], in contrast to results reported in other studies [41–43]. In HIV-1 patients, HE was the cause of 4–16% of esophageal symptoms [38, 39, 41–43] and occurred in four out of 154 patients (2.5%) followed prospectively [43]. We recently reported 34 AIDS patients with HE [18]. In that paper, the mean CD4 cell count was 15/μm³ and recent predisposing factors (nasogastric procedures, steroid therapy, anticancer therapy) were noted in 47% of patients. Only 15% of our patients relapsed, most of them having an iatrogenic pre-
disposing factor (steroids, anticancer therapy). HE has also been reported during HIV primary infection [44].

**Herpes esophagitis during disseminated neonatal HSV infection**

In neonates, the esophagus is frequently involved in the dissemination of HSV infection [14]. The exact prevalence has not been precisely described, but histologic changes consistent with HE were demonstrated in up to 75% of fatal cases [45]. In the absence of skin vesicles (20%), the clinical signs of disseminated HSV infection are often non-specific, mimicking those of neonatal bacterial sepsis [14]. HE by itself may be responsible for feeding difficulties, deglution disorders, hypersalivation, glottic edema and vomiting [46].

**Herpes esophagitis in immunocompetent patients**

HE may occur in immunocompetent patients [15,29,47–68]. In such cases, HE is similar to that occurring in immunocompromised patients, but is rarely diffuse and necrotic [55]. It spontaneously disappears within a few days or weeks, but esophageal recurrence has been described [55]. Because HE occurring in immunocompetent patients may be paucisymptomatic, it is probably underdiagnosed [55,60].

**PATHOGENIC MECHANISMS OF ESOPHAGEAL INVOLVEMENT**

The factors that determine HSV-1 virulence in humans are not known, although experimental models have helped in deciphering host genetic and immune factors, as well as viral genes conferring increased virulence. Herpes simplex viremia has not been documented in adults, and does not represent a significant route of viral replication. However, viremia occurs in neonates infected at birth with HSV-2 [69], and has been reported in HSV-1-infected children receiving immunosuppressive therapy [70]. Therefore, esophageal infection is most often secondary to a viral recurrence, most of the time by regional extension of buccal or pulmonary localization [71]. It is now well established that after infection of the oral epithelium, viral particles are taken up by the peripheral nerve endings of sensory neurons that innervate the primary site of infection, and are transported by retroaxonal axoplasminic flow to the neuronal bodies, located in the sensory ganglia. Latent virus has been detected in the nodose ganglia innervating the gastrointestinal tract [72]. Experimental murine models have clearly shown that oral HSV-1 inoculation in the esophageal lumen leads to latency in the sensory ganglion of the tenth cranial nerve [73]. Furthermore, HSV-1 was shown to spread considerably through all levels of the enteric nervous system, infecting mucosal nerve fibers directly in contact with the epithelium [74]. These findings might explain why HSV is a frequent cause of recurrent esophageal disease in humans.

The respective roles of HSV-1 and HSV-2, primary infection and recurrence, and the main mechanisms explaining the esophageal localization, are summarized in Table 2. In adults, HE is mostly caused by HSV-1 [15,55,57,75], but HSV-2 may also seldom be incriminated [76].

**CLINICAL FEATURES**

HE symptomatology is protean [62]. Major symptoms are dysphagia and esophageal pain. The main clinical

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**Table 2 Pathophysiology of herpes esophagitis**

<table>
<thead>
<tr>
<th>Population</th>
<th>Virus</th>
<th>Main pathogenic mechanism</th>
<th>Mechanisms of esophageal localization</th>
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<tbody>
<tr>
<td>Neonates [14]</td>
<td>HSV-2</td>
<td>Primary infection</td>
<td>Viremia</td>
</tr>
<tr>
<td>Immunocompetent children and adults</td>
<td>HSV-1</td>
<td>Primary infection</td>
<td>Regional extension</td>
</tr>
<tr>
<td>Immunoocompromised patients [111]</td>
<td>HSV-1a</td>
<td>Recurrence</td>
<td>Regional extension</td>
</tr>
<tr>
<td>Hematologic malignancies or solid organ transplantation</td>
<td>HSV-1a</td>
<td>Recurrence</td>
<td>Regional extension</td>
</tr>
<tr>
<td>AIDS [18]</td>
<td>HSV-1a</td>
<td>Recurrence</td>
<td>Regional extension</td>
</tr>
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</table>

*HSV-2 anecdotally

*May occasionally be a primary infection, transmitted by direct person-to-person contact or via the allograft [130].
symptoms reported during large series of HE [18, 62, 77] are mentioned in Table 3. Chest pain or upper digestive tract hemorrhage may reveal HE [78, 79], the latter being reported in 11–25% of the cases [18, 62]. Chronic hiccups is rarely described during HE [18, 80]. Postmortem and endoscopic series clearly demonstrated that HE may be asymptomatic [3, 4, 18]. Ulcerative oropharyngeal mucosal lesions are inconstantly present (12–38% of cases) [18, 77] but may contribute to the diagnosis in patients with esophageal symptoms. Therefore, the absence of mucocutaneous herpetic does not in any way rule out the diagnosis of HE. HE may be associated with other HSV visceral localizations in patients with hematologic malignancies [7], in neonates [7, 62] and in patients who have undergone solid organ transplantation [81], but, interestingly, not in AIDS [18].

RADIOLOGY

Barium esophagography should include simple and double contrasted films [65, 82, 83]. Small ulcerations which predominate in the distal part of the esophagus are the most typical radiologic features [65, 84–86]. However, radiologic aspects are often less specific [27, 55, 87]. Indeed, large ulcers indistinguishable from those observed in fungal esophagitis have also been reported [86, 88].

ENDOSCOPY

Since confirmation of diagnosis is obtained by histology or culture of esophageal specimens, endoscopic examination must be carried out [55, 87, 89]. It can be done first when a patient complains of odynophagia suggestive of ulcerated esophageal lesions, or after the failure of an empirical systemic antifungal treatment, as recently proposed for AIDS patients [90].

The classic predominance of lesions in the lower half of the esophagus in immunocompromised patients [75] was confirmed in AIDS patients [18]; indeed, the lower third was affected in 50% of the cases, the median third in 12% and the upper third in only one case. In one-third of these cases, lesions were spread throughout the entire esophagus.

The most typical macroscopic appearance is only seen during early HE, with vesicles and/or volcano ulcers whose size varies from a few millimeters up to 2 cm. Later in the evolution, they may coalesce, and the mucosa becomes friable with diffuse erosions and/or superficial potentially hemorrhagic ulcers [11, 62, 75, 77].

Diffuse superficial ulcers encountered in the majority of HE cases help to distinguish HE from CMV, which causes deeper ulcerations [87, 91]. Non-ulcerated erythematous esophagitis is nonetheless possible but rare; it was found in 9% of our AIDS patients [18]. The presence of pseudomembranes without esophageal candidiasis, and bullous esophagitis, has also been described with HSV [11, 18, 62]. Anecdotally, ulcerated exophytic stenosis [18], tracheoesophageal fistula [92], spontaneous esophageal perforation [93] and aspects mimicking a lye burn in a child [61] have been reported in isolated case reports.

Margins of esophageal ulcers and islands of squamous epithelium have to be biopsied and brushed [77, 94]. Indeed, biopsies of the ulcer's base are usually non-diagnostic [77]. Interestingly, HE may be unsuspected endoscopically in several patients [18, 77], confirming the need for biopsies and brushings in immunocompromised patients with esophageal symptoms [62]. The association of HE with herpetic gastritis

<table>
<thead>
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<th>Table 3 Clinical symptoms of herpes esophagitis</th>
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<td><strong>Underlying conditions (%)</strong></td>
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<tr>
<td>Dysphagia</td>
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<tr>
<td>Odynophagia</td>
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<tr>
<td>Chest pain</td>
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<tr>
<td>Fever</td>
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<tr>
<td>Extraesophageal herpes</td>
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<tr>
<td>Nausea/vomiting</td>
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<tr>
<td>Digestive hemorrhage</td>
</tr>
<tr>
<td>Hypersalivation</td>
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<tr>
<td>Chronic hiccups</td>
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<tr>
<td>Asymptomatic</td>
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</table>
is rare [95], as viral ulcers are most often located only in the Malpighian epithelium and thus above the esophagogastric junction.

In immunocompromised patients, HE may be associated with various opportunistic diseases such as candidiasis, CMV and Kaposi's sarcoma [18,57,62,87].

Finally, HE can disappear with fibrous scarring and subsequent esophageal stenosis that may necessitate dilation [13].

**HISTOLOGY**

Brush cytology is very useful for HE diagnosis [96–98], and may also help in the diagnosis of esophageal candidiasis [97]. Cytologic preparations have better cell preservation, and may provide a more definitive diagnosis [97]. The most typical cytologic aspects are ground-glass nuclei and multinuclear giant cells [96]. Brushing allows the sampling of larger areas than biopsies [97], and was sometimes reported to be more useful than histology [87] with a definitive diagnosis in 20–100% of cases.

Histologic studies should be performed on formaldehyde-fixed, paraffin-embedded biopsy samples stained with hematoxylin–eosin and Giemsa. Grocott's methenamine silver and periodic acid–Schiff are necessary to eliminate the diagnosis of fungal esophagitis. Typical HE pathologic changes are mostly found only at the edge of ulcers [99].

Characteristic histopathologic aspects found by light microscopy include ballooning degeneration, ground-glass nuclei with margined chromatin and eosinophilic nuclear inclusions (Cowdry type A inclusions) of squamous epithelial cells as well as multinuclear giant cells [99]. Typical Cowdry A inclusions are rarely encountered when samples are not fixed in Zenicker's acetic acid or Bouin's solution [99]. By electron microscopy, they appear to be para-crystalline viral structures [94,100,101]. Giant cells and small complexes of squamous cells are mostly seen on the epithelial border of the ulcer [99].

Intranuclear inclusions cannot differentiate between HSV and varicella-zoster infections, but in the absence of disseminated pox, these inclusions are highly suggestive of HE [97]. Ground-glass nuclei can also be observed during CMV esophagitis; however, during the latter they also involve mesenchymal and glandular epithelial cells [99]. The floor of the ulcer contains inflammatory cells, fibrin and necrotic debris [99]. When typical herpetic changes are not seen, aggregates of large mononuclear cells (mostly CD68-positive macrophages and activated T-cells) [102] with convoluted nuclei are also characteristic of HE [102].

Histology allowed a definitive diagnosis in 40–67% of the cases [11,18,94].

Immunohistochemistry [99,103], immunofluorescence [104], in situ hybridization (ISH) [103, 105], or in situ polymerase chain reaction may be warranted when the herpetic nature of ulcerated esophagitis has not been demonstrated by standard techniques [102]. ISH (using biotinylated probes) and immunohistochemistry are used to rapidly detect viral nucleic acids in formalin-fixed, paraffin-embedded tissues [103]. These two methods appear equally effective for the diagnosis of HE, and their results are better correlated with the presence of viral inclusions than with culture results [103]. ISH stains are more difficult to interpret; thus immunohistochemistry, which is also less expensive than ISH, may be preferable for routine clinical practice work [103]. Furthermore, the presence of the HSV genome within a cell without viral inclusions or immunohistochemical or histologic changes should be interpreted with caution [106]. Immunohistochemistry results may disclose granular to homogeneous reaction product within the nuclei and the cytoplasm of squamous cells infected by HSV [99]. The normal esophageal squamous epithelium at some distance from the ulcer, as well as inflammatory and mesenchymal cells, does not stain with anti-HSV [99].

In some cases, histologic and ultrastructural studies may disclose mixed viral and fungal esophageal infections [100].

**VIROLOGY**

The most sensitive and specific diagnostic method for confirming HSV infection remains isolation of the virus from tissue cultures [10,81]. Indeed, it allowed a definitive diagnosis in 70–100% of the cases [11,18,62,94]. Specimens must be transported to the laboratory in virus-stabilizing media [81] and cultured by inoculation onto human embryonic lung fibroblasts or rabbit kidney cells. Viruses are identified by typical cytopathic changes, in most samples within 48–96 h after inoculation. HSV can be identified rapidly by immunohistochemical staining of a centrifuged culture suspension after 24–36 h [77]. Virus isolation also allows subtyping, gene sequence mapping and antiviral sensitivity testing [81].

**DIAGNOSTIC STRATEGY**

The diagnostic evaluation of an immunodepressed patient with esophageal symptoms should involve both histology and viral esophageal cultures, whose combination gives the better diagnostic value. However, the exact sensitivity and specificity of all these methods are
Table 4 Major differential diagnoses of herpes esophagitis

<table>
<thead>
<tr>
<th>Differential Diagnoses</th>
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<tbody>
<tr>
<td>Esophageal infections</td>
</tr>
<tr>
<td>Common infections</td>
</tr>
<tr>
<td>Candida albicans [91,132]</td>
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<tr>
<td>Cytomegalovirus [91,132-134]</td>
</tr>
<tr>
<td>Uncommon infections</td>
</tr>
<tr>
<td>Human immunodeficiency virus [135-137]</td>
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<tr>
<td>Epstein–Barr virus [138]</td>
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<tr>
<td>Herpes zoster [139]</td>
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<tr>
<td>Papilloma virus [140]</td>
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<tr>
<td>Mycobacterium tuberculosis [141-143]</td>
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<tr>
<td>M. avium intracellulare complex [43]</td>
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<tr>
<td>Bacteria from the oral flora [144]</td>
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<tr>
<td>Nocardia asteroides [145]</td>
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<tr>
<td>Treponema pallidum (tertiary syphilis) [146]</td>
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<tr>
<td>Helicobacter pylori [147]</td>
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<tr>
<td>Aspergillus sp. [148]</td>
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<tr>
<td>Histoplasma capsulatum [149]</td>
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<tr>
<td>T. vaginalis [150]</td>
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<tr>
<td>Cryptosporidium [151]</td>
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<tr>
<td>Pneumocystis carinii [152]</td>
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<tr>
<td>Leishmania donovani [153]</td>
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<tr>
<td>AIDS-related idiopathic ulcers [154,155]</td>
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<tr>
<td>Malignancies</td>
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<tr>
<td>Kaposi’s sarcoma [91]</td>
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<tr>
<td>Malignant lymphoma [91]</td>
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<tr>
<td>Carcinoma–sarcoma</td>
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<tr>
<td>Peptic esophagitis</td>
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<tr>
<td>Medications [156]</td>
</tr>
<tr>
<td>Common: tetracyclines, potassium, quinidine, aspirin and non-steroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>Uncommon: zidovudine [157], ertapenem, clindamycin, captopril, theophyllin, ascorbic acid, alendronate [158]</td>
</tr>
</tbody>
</table>

Still questionable, as they have not been studied with adequate methodology. As all of the above described diagnostic methods may be falsely negative, suspected HE may be finally confirmed by the efficacy of the acyclovir therapeutic test [18,107].

Finally, it has to be noted that the detection of anti-HSV antibodies does not have any clinical utility for the diagnosis of HE in immunocompromised individuals [108]. Major differential diagnoses of HE are described in Table 4.

TREATMENT

Although HE may resolve spontaneously, in immunocompetent [66] but also in immunodepressed patients [18], antiviral treatment is always indicated to prevent the diffusion of the infection, and/or to limit the risk of dehydration, malnutrition and local sequelae.

Acyclovir remains the treatment of choice for HE, although very few controlled studies are available. Oral administration seems as efficient as the intravenous route, but is frequently impossible because of dysphagia, odynophagia and vomiting. Intravenous administration (15 mg/kg/day or 250 mg/m²/day) is usually rapidly effective in solid organ transplant recipients [28], AIDS patients [18] or marrow transplant recipients [33]. In immunodepressed patients, treatment failure may be explained by esophageal co-infections or other esophageal disease [18,31]. Some HE may be due to acyclovir-resistant viral strains [109,110], more frequently in patients who have been repeatedly exposed to this drug [111]. Such cases should be treated with foscarin [112], which is superior to vidarabine for acyclovir-resistant mucocutaneous herpes infections in AIDS [113].

Primary prophylactic acyclovir treatment can be considered in high-risk immunodepressed patients, but not in AIDS patients. Indeed, when given 3 days before bone marrow transplantation, it prevented HSV reactivation and reduced the incidence of HSV infections from 50–80% to less than 10% [114,115]. In AIDS, HE recurrences are uncommon [18] and suppressive therapy should not be systematically prescribed. However, in cases of frequent or severe recurrences, a preventive regimen (600–1000 mg in 3–5 divided oral doses per day) may be administered [116].

CONCLUSION

HE is common in immunocompromised patients and should be systematically suspected in cases of odynophagia, chest pain, unexplained nausea or upper digestive tract bleeding. Most of the time, HE results from HSV-1 reactivation and the regional extension of an oral or pulmonary infection. Diagnosis is suggested through endoscopy, which usually displays ulcerated esophagitis predominantly in the lower third. The combination of brush cytology, histology and viral cultures allows the best diagnostic sensitivity. Empirical acyclovir treatment also allows a presumptive diagnosis when it is rapidly effective. Finally, HE most often presents as a benign condition when it is diagnosed early and treated.

References
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