Triggers, clinical manifestations, and management of pediatric erythema multiforme: A systematic review

Samer Zoghaib, MD, Elio Kechichian, MD, Karim Souaid, MD, Boutros Soutou, MD, Josiane Helou, MD, and Roland Tomb, MD, PhD
Beirut, Lebanon

Background: Erythema multiforme (EM) is an acute inflammatory mucocutaneous condition. EM is rarely described in children and infants.

Objective: To investigate the triggers, clinical manifestations, and treatment of pediatric EM.

Methods: Systematic literature review of pediatric EM.

Results: After full-text article review, we included 113 articles, representing 580 patients. The mean age was 5.6 years, ranging 0.1-17 years. Infectious agents were the main triggers: herpes simplex virus (HSV) in 104 patients (17.9%) and *Mycoplasma pneumoniae* in 91 patients (15.7%). In total, 140 cases (24.1%) were drug-related and 89 cases (15.3%) had other triggers, such as vaccines (19 patients, 3.2%). In total, 229 patients had EM major (39.5%). Treatment was supportive care only (180 patients, 31.1%), systemic corticosteroids (115 patients, 19.8%), antivirals (85 patients, 14.6%), and antibiotics (66 patients, 11.3%), mostly macrolides (45 patients, 7.7%). Long-term sequelae were rare (1.3%). Pediatric EM was reported in 19 infants (3.2%). The main trigger was vaccination (9 patients). Infantile EM was EM major in 2 cases and EM minor in 17. Infants were less prone to develop EM major than older children ($P < .01$). Pediatric EM was recurrent in 83 cases (14.3%), which was triggered by HSV in 36 patients (61%). Recurrence affected older children.

Limitations: Potential confusion between Steven Johnson syndrome and EM major in addition to publication bias.

Conclusion: Pediatric EM is a rare disease, mainly triggered by infections. This condition can affect all mucosal surfaces, most commonly the oral mucosae. The diagnosis is clinical, and management relies on supportive care. Vaccines are a particular trigger in infants. Recurrent cases are most commonly linked to HSV. Dermatologists and pediatricians should be aware of this potentially recurrent and severe condition. (J Am Acad Dermatol 2019;81:813-22.)

Key words: diagnosis; erythema multiforme; etiology; pediatric; treatment.

Erythema multiforme (EM) is an acute inflammatory mucocutaneous condition that is most often triggered by infectious agents, such as herpes simplex virus (HSV) or *Mycoplasma pneumoniae*.[1] EM is clinically characterized by target lesions and classified as EM minor if no more than 1 mucous membrane is involved or EM major if ≥2 mucous membranes are involved.[2] Severe mucous membrane involvement can result in significant morbidity, pain, impaired food intake, hospitalization, and long-term sequelae.[3] In adults, recurrences occur in 40% of cases, severely affect quality of life,

From the Department of Dermatology, Faculty of Medicine, Saint-Joseph University, Beirut.
Dr Zoghaib and Dr Kechichian contributed equally to this work and are both considered first coauthors.
Funding sources: None.
Conflicts of interest: None disclosed.
Accepted for publication February 24, 2019.
Reprints not available from the authors.

Correspondence to: Elio Kechichian, MD, Department of Dermatology, Faculty of Medicine, Saint Joseph University, Beirut, Lebanon. E-mail: elio.kechichian@net.usj.edu.lb.
Published online July 19, 2019.
0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2019.02.057

and might require multiple hospitalizations.[4] Pathophysiology involves B-cell and T-cell response pathways[5] and desmoplakin-specific antibodies in some cases.[4]

EM can occur in patients of all ages. However, EM is rarely described in children and infants. The triggers as well as the signs, symptoms, treatment, prognosis, and recurrence of pediatric EM can be different from that of adults.[6]

To date, little is known about the characteristics of pediatric EM. Furthermore, infantile and recurrent pediatric EM is scarce. The objective of this systematic review was to investigate the etiology, clinical presentation, and treatment of pediatric EM with a special focus on infantile and recurrent pediatric EM.

CAPSULE SUMMARY

- Erythema multiforme is most often triggered by herpes simplex virus or *Mycoplasma pneumonia* in children, whereas vaccination is the main trigger in infants.
- Diagnosis of pediatric erythema multiforme is usually clinical, with biopsy most frequently required in infants. Management includes supportive care and, if severe or recurrent, corticosteroids or antimicrobial drugs.

METHODS

On September 1, 2018, we conducted a systematic search of the English and French literature using the Medline, Embase, and Cochrane collaboration databases in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[7] The search was done using the following combination of key words: "erythema multiforme" AND "child" OR "children" OR "childhood" OR "pediatric" OR "paediatric" OR "adolescent" OR "adolescence" OR "toddler" OR "infant" OR "infancy." Candidate studies, including brief reports and case reports, were selected by 2 independent authors (Dr Kechichian and Dr Zoghaib) on the basis of their titles and abstracts. These candidate studies were obtained and read in full. Corresponding authors of unavailable articles were contacted by email. The bibliography of the retrieved articles was manually screened for additional potential studies. To be included in this review, confirmed cases of pediatric EM were required to fulfill the diagnostic criteria previously proposed in the literature, including key clinical and pathologic features and the exclusion of other diagnoses.[8] Because of the confusion between EM major and Steven Johnson syndrome, articles that reported cases of Steven Johnson syndrome misdiagnosed as EM were excluded after the mutual agreement of the 2 primary authors (Dr Kechichian and Dr Zoghaib). Studies were also excluded if they did not provide any clinical patient data, reported patients >18 years of age, or reported adult and pediatric cases without the individual pediatric EM data. Using the inclusion and exclusion criteria, the 2 first authors (Dr Kechichian and Dr Zoghaib) agreed on the final selection of studies, and any discrepancy was solved by discussion.[9] Data on the following were obtained for analysis: age, sex, comorbidities, triggers, type of pediatric EM (minor or major), type of mucosal involvement, histologic findings, treatment used, sequelae, and EM recurrence. Cases were further stratified into infants and older children and recurrent and nonrecurrent pediatric EM. Continuous and categorical variables were compared between groups by Mann-Whitney U test and the Fisher's exact test and χ^2 test, respectively. All tests were 2-sided, and P values $<.05$ were considered statistically significant. SPSS version 24 was used for statistical analysis.

RESULTS

The initial search of databases yielded 982 articles, of which 76 were duplicates; 202 were selected as candidate studies. On the basis of the inclusion and exclusion criteria, 113 were included in the systematic review. They are compiled according to the number of patients in Table I.[10-121] The stepwise approach for study selection is summarized in Fig 1.

All the included articles were case reports and case series. A total of 580 patients were included for analysis (Table I). The mean age of patients was 5.6 years, ranging from the neonatal period to 17 years (Table II). Infections were the main trigger, most often HSV (104 patients; 17.9%) or *M. pneumoniae* (91 patients; 15.7%). Other infectious triggers included Epstein-Barr virus (12 patients), varicella (7 patients), group A *Streptococcus* (6 patients), adenovirus (6 patients), cytomegalovirus (5 patients), *Chlamydia pneumoniae* (5 patients), and orf virus (3 patients). In total, 140 cases (24.1%) were drug-related; these cases were due to antibiotics in 75% (penicillin in 39%, cephalosporin in 18%, sulfonamide in 9%, erythromycin in 5%, tetracycline in 2%, other macrolides in 2%), anticonvulsants in 18%, nonsteroidal anti-inflammatory drugs in 2%, and other drugs in 5%. A total of 89 patients (15.3%) had other triggers such as vaccines (19 patients, 3.9%), including the diphtheria-tetanus-pertussis vaccine (7 patients); recombinant hepatitis B vaccine (6 patients); and the human papillomavirus, pneumococcal, measles-mumps-rubella, smallpox, polio, and rabies vaccines (1 patient each). A total of 229

Abbreviations used:

EM: erythema multiforme
HSV: herpes simplex virus

patients had EM major (39.5%). On average, 1 mucosa was affected per patient, most commonly the oral mucosa (166 patients, 40.1%). The diagnosis was mainly clinical; skin biopsy was done in only 58 patients (10%). In total, 68% of patients had a medical intervention, which was most often systemic corticosteroids (115 patients; 19.8% overall, most of them [100 patients] with EM major), followed by antivirals (85 patients, 14.6%) and antibiotics (66 patients, 11.3%), mostly macrolides (45 patients, 7.7%); whereas 31.1% (n = 130) of patients received only supportive care. Only 8 patients had long-term sequelae (1.3%).

Infantile erythema multiforme

Pediatric EM was reported in 19 infants (3.2%). The mean age was 4.4 months. The main trigger was vaccination (9 patients). When compared with older children, infants were less prone to develop EM

Table I. The included studies compiled according to the number of patients per study

Study (year)	Patients, n
Keller et al (2015)[10]	97
Stewart et al (1994)[11]	79
Langley et al (2016)[12]	65
Villiger et al (1998)[13]	42
Yang et al (1999)[14]	30
Leaute (2000)[16]	22
Mateos et al (1998),[17] Heinze et al (2017),[6] Weston and Weston (1992)[18]	20
Shklar and McCarthy (1966)[19]	16
Sinclair et al (1972)[20]	15
Weston and Morelli (1997)[21]	12
Read and Keijzers (2017)[22]	9
Prindaville et al (2014)[23]	6
Imashuku and Kudo (2013)[24]	5
Ruhrmann and Holthusen (1977),[25] Weston et al (1997),[26] Ackerman et al (1971),[27] Bean and Quezada (1983),[28] Dikland et al (1986)[29]	3
Leung (1984),[30] Frederiksen et al (2004),[31] Hosoya et al (1981),[32] Prais et al (2001),[33] Wolf et al (1994),[34] Major et al (1978),[35] Huff et al (1980),[36] Neale (1948),[37] Martinez and Atherton (2000),[38] Schalock et al (2006)[15]	2
McMurray and Garber (2015),[49] Khan and Fitzgerald (2012),[50] Mamishi et al (2009),[51] Nayak and Chan (1981),[52] Cai et al (2012),[53] Cieza et al (2013),[54] Ang-Tiu and Nicolas (2013),[55] Kaur and Handa (2008),[56] Joon Cho et al (2011),[57] Ashkenazi et al (1992),[58] Torrelo et al (2003),[59] Karincaoglu et al (2007),[60] Ocariz et al (1998),[61] Griffith and Miller (1988),[62] Hosaka et al (2010),[63] Nakai et al (2011),[64] Schmidt (2003),[65] Bernardini et al (2006),[66] Eun et al (2010),[67] Monastirli et al (2017),[68] Meyer (1970),[69] Andersen et al (1981),[70] Leung (1985),[71] Ecran and Ozmen (2016),[72] Ferrando et al (1997),[73] Uemura et al (1994),[74] Chan et al (2000),[75] Martire et al (2005),[76] Lopez et al (2018),[77] BaniHani et al (2015),[78] Shimizu et al (2012),[79] Fustes-Morales et al (2001),[80] Maman and Medhioulo (2017),[81] Salim and Young (2002),[82] Arditi et al (1988),[83] Kaur et al (2001),[84] Wang et al (1997),[85] AlFar et al (2015),[86] Verma (2013),[87] Di Lernia et al (1994),[88] Loche et al (2000),[89] Coates et al (2018),[90] Cañueto et al (2009),[91] Neri et al (2009),[92] Özdemir et al (2011),[93] Weston and Brice (1998),[94] Mourtada et al (2000),[95] Werchninak and Schwarzenberger (2004),[96] Messina et al (2011),[97] Wiedemeyer et al (2007),[98] Kishore et al (2014),[99] Pérez-Carmona et al (2010),[100] Williamson (1973),[101] Pérez-Carmona et al (2010),[102] Chen et al (2008),[103] Dentan et al (2013),[104] Jain et al (2010),[105] Johnston et al (2002),[106] Rosa and Ong (2012),[107] Elfatoiki and Chiheb (2015),[108] Maquet et al (2008),[109] Ashton et al (2018),[110] Chen et al (2017),[111] Petrosino et al (2016),[112] Athreya and Coriell (1964),[113] Webster and Simon (1971),[114] Marinho et al (1999),[115] Kalick et al i (2016),[116] Darmstadt and Cohen (1994),[117] Pope and Krafchik (2005),[118] Sebastian et al (2009),[119] Grosber et al (2007),[120] Osterne et al (2009),[121] Brajon et al (2013),[39] Mangal et al (2015),[40] Rock et al (2014),[41] Wells et al (2000),[42] Karincaoglu et al (2005),[43] Welch et al (1987),[44] Martinez-Perez et al (2016),[45] Britz and Sibulin (1975),[46] Waters and Chen (2018),[47] Wine et al (2006)[48]	1

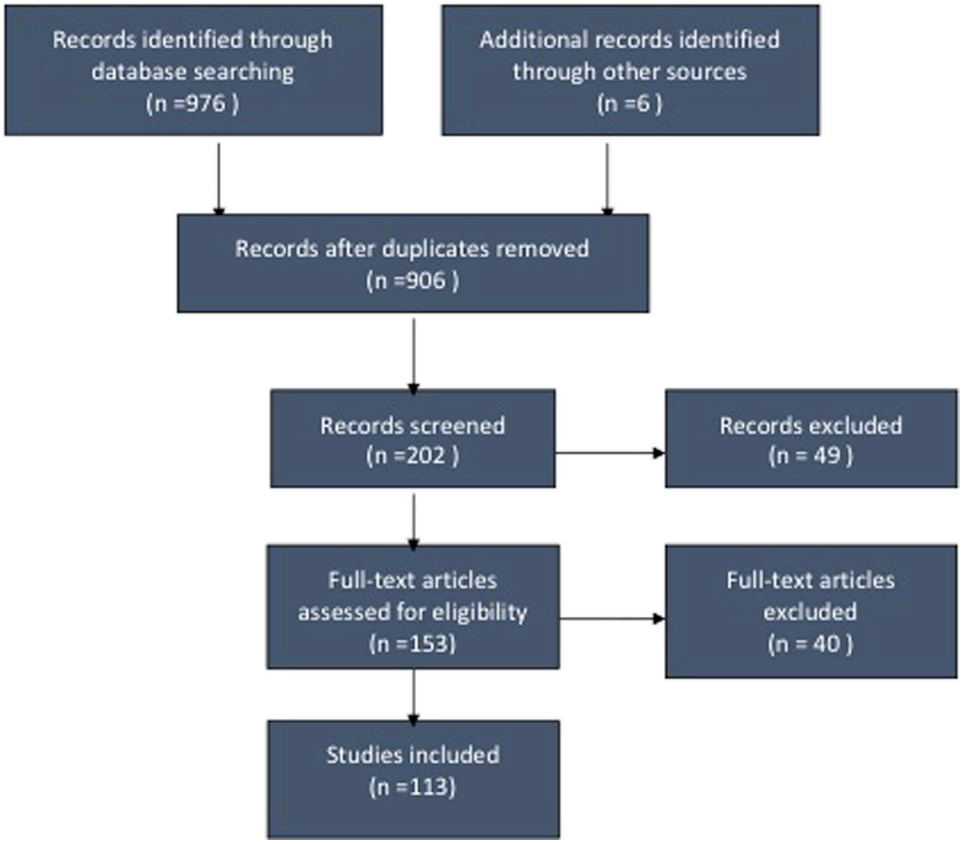

Fig 1. Flow chart of included studies.

major (10.5% vs 52.2%, $P < .01$). The mucosae were affected in 10% of patients compared with 50% in older children ($P < .01$). The oral mucosa was the only affected mucosa (2 patients, 10.5%). The diagnosis was done by biopsy in 62.3% of infants. The median duration of the disease was 14 days, with no statically significant difference when compared with older children ($P = .4$).

Recurrent pediatric EM

Pediatric EM was recurrent in 83 cases (14.3%). Cases of recurrent pediatric EM occurred in older children than those of nonrecurrent pediatric EM (9.1 vs 5.9 years, respectively, $P < .01$). Male patients were more commonly affected by recurrent (76.3%) than nonrecurrent (54.7%; $P < .01$) pediatric EM. The most common trigger was HSV (36 patients, 61%). EM was predominantly EM major in recurrent cases (33 patients, 55.9 %). Although not frequently performed, the recurrent cases (22%) seemed to have more biopsies than nonrecurrent ones (11.3%, $P = .012$). Antivirals (86.4% vs 4.8%, $P < .01$) and systemic corticosteroids (49.2% vs 12.8%, $P < .01$) were more frequently used in recurrent than nonrecurrent pediatric EM cases. Systemic corticosteroids were given intermittently, whereas oral antivirals were given intermittently in 45% of cases and continuously in 55% of cases. Other systemic treatments, such as thalidomide and intravenous immunoglobulin, and (less frequently) dapsone, methotrexate, mycophenolate mofetil, cyclosporine, colchicine, and azathioprine were used in 18.6% of recurrent pediatric EM patients with variable and inconsistent results. Table III summarizes the characteristics of recurrent pediatric EM.

DISCUSSION

Pediatric EM presents with typical target lesions and affects mostly the oral mucosae. The exact incidence of EM is unknown, ranging 0.01%-1%.[122,123] EM often occurs in 20—40-year-old adults,[124] with a slight female preponderance; in contrast, pediatric EM more commonly affects male patients (57%).[122]

Infections were the main trigger of pediatric EM (48.1%). HSV represents the most common precipitating factor for both pediatric EM (17.9%) and EM in adults (41.9%).[125,126] The lower proportion of pediatric EM cases triggered by HSV might be explained by the higher incidence of other viral infections and

Table II. Characteristics of the pediatric erythema multiforme patients

Variable	Overall	Infants*	Children*	*P* value
Patients, n	580	19	270	
Age, y, mean ± standard deviation (range)	6.1 ± 5.6 (0.1-17)	0.37 ± 0.3 (0.06-0.99)	7.5 ± 5 (1-17)	
Male sex (%)	335 (57.8)	10 (52.6)	164 (60.7)	.4
Comorbidities† (%)	41 (7)			
Recurrent erythema multiforme, n (%)	83 (14.3)	1 (5.3)	41 (15.2)	.3
Trigger, n (%)				
Herpes simplex virus	104 (17.9)	1 (5.3)	49 (18.1)	.2
Mycoplasma pneumoniae	91 (15.7)	0	53 (19.6)	.02
Other infection	84 (14.5)	6 (31.5)	69 (25.6)	.5
Drug	140 (24.1)	0	38 (14.1)	.14
Vaccine	19 (3.2)	9 (47.3)	10 (3.7)	<.01
Other cause	70 (12)			
Idiopathic	80 (13.8)	3 (15.8)	48 (17.8)	1
Erythema multiforme major, n (%)	229 (39.5)	2 (10.5)	141 (52.2)	<.01
Mucosa, n (%)				
Average affected per patient	1	0.15	0.99	.009
Oral		2 (10.5)	127 (47)	<.01
Ocular		0	78 (28.9)	<.01
Ears, nose, and throat		0	9 (3.3)	<.01
Nose		0	4	
Pharynx		0	4	
Ear		0	1	
Genital		0	60 (22.2)	<.01
Skin biopsy done, n (%)	58 (10)	12 (62.3)	46 (17.0)	<.01
Abnormal blood test, n (%)	136 (23.4)	9 (47.4)	75 (27.8)	.11
Treatment used, n (%)				
Only supportive care	180 (31.0)			
Systemic corticosteroids	115 (19.8)	2 (10.5)	80 (29.6)	.11
Antiviral	85 (14.6)	1 (5.3)	39 (14.4)	.48
Macrolide	45 (7.7)	0	41 (15.2)	.08
Other antibiotic	21 (3.6)	2 (10.5)	19 (7)	.63
Topical corticosteroids	12 (2)			
Sequelae, n (%)	8 (1.3)	0	8 (3.0)	1
Duration, d, median (range)	12.4 (5-14)	14 (7-14)	12.4 (7-14)	.4

*The studies that included both infants and older children altogether without specifying the disease characteristics in each age category were excluded from this table to make the comparison possible between the 2 age groups.
†The comorbidities were convulsive disorders, psychiatric disorders such as generalized anxiety disorder, cryoglobulinemia (in a minority of cases), and atopic dermatitis.

frequent vaccinations in children. *M. pneumoniae* has a well-documented, strong association with pediatric EM (15.7%), as well as EM in adults (20.9%).[15,126] *Mycoplasma*-induced rash and mucositis, a related condition characterized by significant mucositis (oral, ocular, and anogenital) but sparse-to-absent cutaneous involvement, favors boys in the second decade of life.

Apart from viral infections, drugs are the second most frequent cause of pediatric EM.[8] The culprit medications were mostly, antibiotics which is in concurrence with the literature.[122]

Postvaccination EM is a rare condition but has been reported with most vaccines used in pediatric practice.[127] Our study showed that only 3.9% of all pediatric EM cases were triggered by vaccines, diphtheria-tetanus-pertussis vaccine being the most frequent cause, followed by the recombinant hepatitis B vaccine. However, vaccines were the trigger of 47.3% of EM cases in infants. A causal link is hard to establish due to the rarity of the disease, but similar to infections, the immune activation induced by vaccination could be the culprit.

A diagnosis of EM can usually be made in children on the basis of history and clinical findings.[127] Indeed, a skin biopsy was performed in only 10% of reported pediatric EM cases. However, in some instances, a skin biopsy is necessary to distinguish pediatric EM from other conditions, such as urticaria multiforme and autoimmune blistering diseases.

Table III. Characteristics of recurrent and nonrecurrent pediatric EM cases

Characteristic	Recurrent EM	Nonrecurrent EM	*P* value
Patients, n	59	398	
Age, y, mean ± SD (range)	9.1 ± 3.5 (0.1-14)	5.9 ± 4.8	.01
Male sex, n (%)	45 (76.3)	217 (54.7)	.001
Trigger, n (%)			
Herpes simplex virus	36 (61)	50 (12.6)	<.001
Mycoplasma pneumoniae	7 (11.9)	62 (15.6)	.5
Other infection	0	58 (14.6)	<.001
Drug	0	113 (28.4)	<.001
Other cause	0	1 (0.3)	<.001
Idiopathic	15 (25.4)	34 (8.5)	<.001
EM major, n (%)	33 (55.9)	111 (27.9)	<.001
Mucosa, n (%)			
Average affected per patient	0.89	0.55	.02
Oral	36 (61)	54 (13.6)	<.001
Ocular	10 (16.9)	29 (7.3)	.02
Ears, nose, and throat	2 (3.4)	9 (2.3)	.6
Genital	15 (25.4)	21 (5.3)	<.001
Skin biopsy done, n (%)	13 (22)	45 (11.3)	.012
Abnormal blood test, n (%)	12 (20.3)	108 (21.7)	<.001
Treatment used, n (%)			
Antiviral	51 (86.4)	19 (4.8)	<.001
Macrolide	7 (11.9)	38 (9.5)	.6
Other antibiotic	5 (8.5)	16 (4)	.12
Systemic corticosteroids	29 (49.2)	51 (12.8)	<.001
Sequelae, n (%)	2 (3.4)	6 (1.5)	.3

The studies that included both recurrent and nonrecurrent cases altogether without specifying the disease characteristics in each patient category according to the recurrence status were excluded from this table to make the comparison possible between the 2 groups.
EM, Erythema multiforme; *SD*, standard deviation.

Clinically, EM patterns can be classified into EM with and without mucosal involvement.[8] Mucosal involvement varies in location and severity. Previous observations showed that the most common mucosa involved in EM is the oral mucosa,[122] and in our review, the oral mucosa was also mainly affected (40.1%).

EM major implies severe mucous membrane involvement (≥2 mucous membranes).[2] More than 1 in 3 of our population (39.5%) had EM major, which was most probably due to publication bias because severe cases are more likely to be reported.

Although most patients experience only 1 outbreak in a lifetime, a subset of patients had repeated episodes of EM known as recurrent EM.[6] In accordance with the results of a prior study,[128] pediatric EM recurred in 14.3% of the cases included in this review. An inciting factor was identified in 74.6% of cases. Recurrence was mostly seen in HSV-associated EM (61%), which is consistent with the data in the literature estimating that 61%-100% of recurrent EM is caused by HSV.[4]

Supportive care is the cornerstone of management of pediatric EM. Systemic corticosteroids were used in 19.8% of reported pediatric EM cases, especially for EM major. The use of systemic corticosteroids in the treatment of EM has been debated in the medical literature for many decades and remains controversial. A retrospective review of 32 pediatric patients with EM major or Steven Johnson syndrome, who were treated with either large doses of systemic corticosteroids or supportive care only, showed that patients treated with corticosteroids did not recover sooner than those treated in other fashions, and the corticosteroid-treated group had a significantly increased incidence of adverse events.[129] However, many other studies support the use of corticosteroids, suggesting that the drug decreases the duration and severity of symptoms, especially in the setting of EM major. In a prospective study including 16 children with EM, Kakourou et al compared the efficacy of corticosteroids to supportive treatment only and reported that an early and short course of corticosteroids favorably influences the course of EM major in children.[130] In EM minor, symptomatic treatment usually suffices.[131]

Infantile EM is a rare condition, with only 19 previously reported cases, with a mean age of

4.4 months. Vaccines were the main triggers (47.3%). *M. pneumoniae* was not reported in any case of infantile EM. In infants, the mucosal surfaces were relatively rarely affected, therefore, EM minor was more common than EM major. Biopsies were more common in infants than older children because EM is uncommon in this subset of patients and thus more challenging to diagnose. The management and median duration of EM in infants were similar to the management and duration in older children, and no sequelae were reported.

There are several limitations to this systematic review. Due to the rarity of pediatric EM, all the included studies were case reports and case series. In addition, the lack of trials limited our review to a pooled analysis. Many cases might have been misclassified; this is why articles that described Steven Johnson syndrome or urticaria multiforme misdiagnosed as EM were excluded after the mutual agreement of the 2 primary authors (Dr Kechichian and Dr Zoghaib). Finally, publication bias is another limitation, as only published articles were evaluated.

CONCLUSION

Pediatric EM rarely affects children. It is mainly triggered by infections, mostly HSV followed by *M. pneumoniae*. In infants, vaccines were the main trigger. Diagnosis is clinical, and biopsies were rarely done except for infants. Supportive care was the mainstay of treatment, and corticosteroids were mostly used in severe cases. Dermatologists and pediatricians should be aware of this potentially recurrent and severe condition.

REFERENCES

1. Auquier-Dunant A, Mockenhaupt M, Naldi L, et al. Correlations between clinical patterns and causes of erythema multiforme majus, Stevens-Johnson syndrome, and toxic epidermal necrolysis: results of an international prospective study. *Arch Dermatol*. 2002;138(8):1019-1024.
2. Ingen-Housz-Oro S, Ortonne N, Chosidow O. The diagnosis is in the rings. *BMJ*. 2017;359:j3817.
3. Viarnaud A, Ingen-Housz-Oro S, Marque M, et al. Severe sequelae of erythema multiforme: three cases. *J Eur Acad Dermatol Venereol*. 2018;32(1):e34-e36.
4. Wetter DA, Davis MDP. Recurrent erythema multiforme: clinical characteristics, etiologic associations, and treatment in a series of 48 patients at Mayo Clinic, 2000 to 2007. *J Am Acad Dermatol*. 2010;62(1):45-53.
5. Kokuba H, Imafuku S, Huang S, Aurelian L, Burnett JW. Erythema multiforme lesions are associated with expression of a herpes simplex virus (HSV) gene and qualitative alterations in the HSV-specific T-cell response. *Br J Dermatol*. 1998;138(6):952-964.
6. Heinze A, Tollefson M, Holland KE, Chiu YE. Characteristics of pediatric recurrent erythema multiforme. *Pediatr Dermatol*. 2018;35(1):97-103.
7. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ*. 2015;350:g7647.
8. Lerch M, Mainetti C, Terziroli Beretta-Piccoli B, Harr T. Current perspectives on erythema multiforme. *Clin Rev Allergy Immunol*. 2018;54(1):177-184.
9. Oxford Centre for Evidence-Based Medicine - Levels of evidence (March 2009). Available at: https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/. Accessed July 11, 2018.
10. Keller N, Gilad O, Marom D, Marcus N, Garty BZ. Nonbullous erythema multiforme in hospitalized children: a 10-year survey. *Pediatr Dermatol*. 2015;32(5):701-703.
11. Stewart MG, Duncan NO, Franklin DJ, Friedman EM, Sulek M. Head and neck manifestations of erythema multiforme in children. *Otolaryngol Head Neck Surg*. 1994;111(3 Pt 1):236-242.
12. Langley A, Anooshiravani N, Kwan S, Zeller J, Pope E. Erythema multiforme in children and *Mycoplasma pneumoniae* aetiology. *J Cutan Med Surg*. 2016;20(5):453-457.
13. Villiger RM, von Vigier RO, Ramelli GP, Hassink RI, Bianchetti MG. Precipitants in 42 cases of erythema multiforme. *Eur J Pediatr*. 1999;158(11):929-932.
14. Yang YH, Tsai MJ, Tsau YK, et al. Clinical observations of erythema multiforme in children. *Acta Paediatr Taiwan*. 1999;40(2):107-111.
15. Schalock PC, Dinulos JGH, Pace N, Schwarzenberger K, Wenger JK. Erythema multiforme due to *Mycoplasma pneumoniae* infection in two children. *Pediatr Dermatol*. 2006;23(6):546-555.
16. Léauté-Labrèze C, Lamireau T, Chawki D, Maleville J, Taïeb A. Diagnosis, classification, and management of erythema multiforme and Stevens-Johnson syndrome. *Arch Dis Child*. 2000;83(4):347-352.
17. Martín Mateos MA, Roldán Ros A, Muñoz-López F. Erythema multiforme: a review of twenty cases. *Allergol Immunopathol (Madr)*. 1998;26(6):283-287.
18. Weston JA, Weston WL. The overdiagnosis of erythema multiforme. *Pediatrics*. 1992;89(4 Pt 2):802.
19. Shklar G, McCarthy PL. Oral manifestations of erythema multiforme in children. *Oral Surg Oral Med Oral Pathol*. 1966;21(6):713-723.
20. Sinclair MC, Lane JM, Donald WJ, Esco LC. Complications of smallpox vaccination in Alabama, 1968. *South Med J*. 1972;65(1):41-44.
21. Weston WL, Morelli JG. Herpes simplex virus-associated erythema multiforme in prepubertal children. *Arch Pediatr Adolesc Med*. 1997;151(10):1014-1016.
22. Read J, Keijzers GB. Pediatric erythema multiforme in the emergency department: more than "just a rash". *Pediatr Emerg Care*. 2017;33(5):320-324.
23. Prindaville B, Newell BD, Nopper AJ, Horii KA. *Mycoplasma pneumonia*—associated mucocutaneous disease in children: dilemmas in classification. *Pediatr Dermatol*. 2014;31(6):670-675.
24. Imashuku S, Kudo N. *Chlamydia pneumoniae* infection-associated erythema multiforme. *Pediatr Rep*. 2013;5(2):35-37.
25. Ruhrmann G, Holthusen W. *Mycoplasma* infection and erythromycin therapy in childhood. *Scott Med J*. 1977;22(5):401-403.
26. Weston WL, Morelli JG, Rogers M. Target lesions on the lips: childhood herpes simplex associated with erythema multiforme mimics Stevens-Johnson syndrome. *J Am Acad Dermatol*. 1997;37(5 Pt 2):848-850.

27. Ackerman AB, Penneys NS, Clark WH. Erythema multiforme exudativum: distinctive pathological process. *Br J Dermatol*. 1971;84(6):554-566.
28. Bean SF, Quezada RK. Recurrent oral erythema multiforme. Clinical experience with 11 patients. *JAMA*. 1983;249(20):2810-2812.
29. Dikland WJ, Oranje AP, Stolz E, van Joost T. Erythema multiforme in childhood and early infancy. *Pediatr Dermatol*. 1986;3(2):135-139.
30. Leung AK. Erythema multiforme following DPT vaccination. *J R Soc Med*. 1984;77(12):1066-1067.
31. Frederiksen MS, Brenøe E, Trier J. Erythema multiforme minor following vaccination with paediatric vaccines. *Scand J Infect Dis*. 2004;36(2):154-155.
32. Hosoya R, Miwa M, Nishimura K, Yamamoto T. Erythema multiforme syndrome associated with varicella. *N Engl J Med*. 1981;305(10):582.
33. Prais D, Grisuru-Soen G, Barzilai A, Amir J. Varicella zoster virus infection associated with erythema multiforme in children. *Infection*. 2001;29(1):37-39.
34. Wolf P, Soyer HP, Fink-Puches R, Huff JC, Kerl H. Recurrent post-herpetic erythema multiforme mimicking polymorphic light and juvenile spring eruption: report of two cases in young boys. *Br J Dermatol*. 1994;131(3):364-367.
35. Major PP, Morisset R, Kurstak C, Kurstak E. Isolation of herpes simplex virus type 1 from lesions of erythema multiforme. *Can Med Assoc J*. 1978;118(7):821-822.
36. Huff JC, Weston WL, Carr RI. Mixed cryoglobulinemia, 125I C1q binding and skin immunofluorescence in erythema multiforme. *J Invest Dermatol*. 1980;74(5):375-378.
37. Neale AV. Erythema exudativum multiforme in childhood. *Arch Dis Child*. 1948;23(115):183-189.
38. Martinez AE, Atherton DJ. High-dose systemic corticosteroids can arrest recurrences of severe mucocutaneous erythema multiforme. *Pediatr Dermatol*. 2000;17(2):87-90.
39. Brajon D, Bursztejn A-C, Goffinet L, Schmutz J-L, Barbaud A. Lip synechiae after erythema multiforme [French]. *Ann Dermatol Venereol*. 2013;140(4):291-295.
40. Mangal S, Narang T, Saikia UN, Kumaran MS. Fuchs syndrome or erythema multiforme major, uncommon or underdiagnosed? *Indian J Dermatol Venereol Leprol*. 2015;81(4):403-405.
41. Rock N, Belli D, Bajwa N. Erythema bullous multiforme: a complication of *Mycoplasma pneumoniae* infection. *J Pediatr*. 2014;164(2):421.
42. Wells JM, Weedon D, Muir JB. Erythema multiforme: a case with unusual histopathological features. *Australas J Dermatol*. 2000;41(4):257-259.
43. Karincaoglu Y, Coskun BK, Seyhan M. An unusual complication of erythema multiforme and its treatment. *Skinmed*. 2005;4(1):53-55.
44. Welch KJ, Burke WA, Irons TG. Recurrent erythema multiforme due to *Mycoplasma pneumoniae*. *J Am Acad Dermatol*. 1987;17(5 Pt 1):839-840.
45. Martínez-Pérez M, Imbernón-Moya A, Lobato-Berezo A, Churruca-Grijelmo M. *Mycoplasma pneumoniae*-induced mucocutaneous rash: a new syndrome distinct from erythema multiforme? Report of a new case and review of the literature. *Actas Dermosifiliogr*. 2016;107(7):e47-e51.
46. Britz M, Sibulkin D. Recurrent erythema multiforme and herpes genitalis (type 2). *JAMA*. 1975;233(7):812-813.
47. Waters T, Chen S. 169 Erythema multiforme major with esophageal involvement. *J Investig Med*. 2018;66(1):A137.
48. Wine E, Ballin A, Dalal I. Infantile erythema multiforme following hepatitis B vaccine. *Acta Paediatr*. 2006;95(7):890-891.
49. McMurray K, Garber M. Taking chances with strep throat. *Hosp Pediatr*. 2015;5(10):552-554.
50. Khan MAU, Fitzgerald K. Low-dose sertraline-induced erythema multiforme in a child. *J Child Adolesc Psychopharmacol*. 2012;22(2):179-180.
51. Mamishi S, Fattahi F, Pourpak Z, et al. Severe cutaneous reactions caused by barbiturates in seven Iranian children. *Int J Dermatol*. 2009;48(11):1254-1261.
52. Nayak AJ, Rao PN. Erythema multiforme secondary to acetazolamide (Diamox) (a case report). *Indian J Ophthalmol*. 1981;29(2):105-106.
53. Cai Y, Gu L, Qin Y, Wu D. A case report of acute lymphoblastic leukemia with delayed-type hypersensitivity. *J Pediatr Hematol Oncol*. 2012;34(3):e129-e130.
54. Cieza-Díaz DE, Campos-Domínguez M, Santos-Sebastián Mdel M, et al. Erythema multiforme in a newborn associated with acute acquired cytomegalovirus infection. *Pediatr Dermatol*. 2013;30(6):e161-e163.
55. Ang-Tiu CU, Nicolas MEO. Erythema multiforme in a 25-day old neonate. *Pediatr Dermatol*. 2013;30(6):e118-e120.
56. Kaur S, Handa S. Erythema multiforme following vaccination in an infant. *Indian J Dermatol Venereol Leprol*. 2008;74(3):251-253.
57. Cho YJ, Huh SY, Hong JS, Jung JY, Suh DH. Neonatal erythema multiforme: a case report. *Ann Dermatol*. 2011;23(3):382-385.
58. Ashkenazi S, Metzker A, Rachmel A, Nitzan M. Erythema multiforme as a single manifestation of cow's milk intolerance. *Acta Paediatr*. 1992;81(9):729-730.
59. Torrelo A, Moreno M, de Prada I, Celma ML, Zambrano A. Erythema multiforme in a neonate. *J Am Acad Dermatol*. 2003;48(5 Suppl):S78-S79.
60. Karincaoğlu Y, Aki T, Erguvan-Onal R, Seyhan M. Erythema multiforme due to diphtheria-pertussis-tetanus vaccine. *Pediatr Dermatol*. 2007;24(3):334-335.
61. de Ocariz MM, Vega-Memije ME, Muñoz-Hink H. A case of herpetic whitlow associated with erythema multiforme. *Pediatr Dermatol*. 1998;15(5):384-385.
62. Griffith RD, Miller OF. Erythema multiforme following diphtheria and tetanus toxoid vaccination. *J Am Acad Dermatol*. 1988;19(4):758-759.
63. Hosaka H, Ohtoshi S, Nakada T, Iijima M. Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis: frozen-section diagnosis. *J Dermatol*. 2010;37(5):407-412.
64. Nakai H, Sugata K, Usui C, et al. A case of erythema multiforme associated with primary Epstein-Barr virus infection. *Pediatr Dermatol*. 2011;28(1):23-25.
65. Schmidt CE. A 12-month-old girl with maculopapular lesions and lower extremity edema. *J Emerg Nurs*. 2003;29(3):204-207.
66. Bernardini ML, D'Angelo G, Oggiano N, et al. Erythema multiforme following live attenuated trivalent measles-mumps-rubella vaccine. *Acta Derm Venereol*. 2006;86(4):359-360.
67. Eun LY, Go JW, Kang WH, Kim SH, Cho HK. Erythema multiforme associated with Kawasaki disease in a Korean child. *Eur J Dermatol*. 2010;20(4):524-525.
68. Monastirli A, Pasmatzi E, Badavanis G, Tsambaos D. Erythema multiforme following pneumococcal vaccination. *Acta Dermatovenerol Alp Pannonica Adriat*. 2017;26(1):25-26.
69. Meyers W. Erythema multiforme. *Arch Dermatol*. 1970;101(6):707-708.
70. Andersen R, Bergan T, Halvorsen K, Kallings I, Orstavik I. Legionnaires' disease combined with erythema multiforme in a 3-year-old boy. *Acta Paediatr Scand*. 1981;70(3):427-430.
71. Leung A. Erythema multiforme following swimming in a chlorinated pool. *J Natl Med Assoc*. 1985;77(1):13.

72. Ecran N, Ozmen S. Corticosteroid use in the management of a pediatric erythema multiforme minor case related to *Mycoplasma pneumonia*. *Eur J Allergy Clin Immunol*. 2016;71.
73. Ferrando MF, Léauté-Labrèze C, Fleury H, Taïeb A. Orf and erythema multiforme in a child. *Pediatr Dermatol*. 1997;14(2):154-155.
74. Uemura T, Nagayama M, Kawashima M. A case of herpes-associated erythema multiforme in a Japanese child. *J Dermatol*. 1993;20(8):478-482.
75. Chan LY, Tang WY, Leung CY, Lo KK. Recurrent erythema multiforme in a child. *Hong Kong Med J*. 2000;6(3):331.
76. Martire B, Foti C, Cassano N, Buquicchio R, Del Vecchio GC, De Mattia D. Persistent B-cell lymphopenia, multiorgan disease, and erythema multiforme caused by *Mycoplasma pneumoniae* infection. *Pediatr Dermatol*. 2005;22(6):558-560.
77. López-Cedeño A, Cañedo G, Knöpfel N, Colmenero I, Pérez-Pastrana E, Torrelo A. Erythema multiforme after orf virus infection. *Pediatr Dermatol*. 2018;35(4):e237-e238.
78. BaniHani A, Nazzal H, Webb L, Toumba KJ, Fabbroni G. An unusual presentation of erythema multiforme in a paediatric patient. *Eur Arch Paediatr Dent*. 2015;16(3):297-302.
79. Shimizu M, Hamaguchi Y, Matsushita T, Sakakibara Y, Yachie A. Sequentially appearing erythema nodosum, erythema multiforme and Henoch-Schönlein purpura in a patient with *Mycoplasma pneumoniae* infection: a case report. *J Med Case Rep*. 2012;6:398.
80. Fustes-Morales AJ, Soto-Romero I, Estrada Z, et al. Unusual leukoderma after erythema multiforme: a case report. *Pediatr Dermatol*. 2001;18(2):120-122.
81. Maman M, Medhioub Y. A case of Orf disease complicated by erythema multiforme [French]. *Arch Pediatr*. 2017;24(12):1241-1243.
82. Salim A, Young E. Erythema multiforme associated with *Trichophyton mentagrophytes* infection. *J Eur Acad Dermatol Venereol*. 2002;16(6):645-646.
83. Arditi M, Shulman ST, Langman CB, Christensen M, Unti S. Probable herpes simplex virus type 1-related acute parotitis, nephritis and erythema multiforme. *Pediatr Infect Dis J*. 1988;7(6):427-429.
84. Kaur S, Thami GP, Mohan H, Kanwar AJ. Kikuchi disease with facial rash and erythema multiforme. *Pediatr Dermatol*. 2001;18(5):403-405.
85. Wang JN, Wu JM, Lin CS, Liu CC, Yang YJ. Myocarditis with complete atrioventricular block associated with herpes simplex virus infection: report of one case. *Zhonghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi*. 1997;38(5):381-384.
86. AlFar MY, AlRousan M, Almajali Z, Batarseh E, Alsaddi R. The use of corticosteroids in management of herpes associated erythema multiforme. *J Pak Med Assoc*. 2015;65(12):1351-1353.
87. Verma P. Erythema multiforme possibly triggered by rabies vaccine in a 10-year-old boy. *Pediatr Dermatol*. 2013;30(6):e297-e298.
88. Di Lernia V, Lo Scocco G, Bisighini G. Erythema multiforme following hepatitis B vaccine. *Pediatr Dermatol*. 1994;11(4):363-364.
89. Loche F, Schwarze HP, Thedenat B, Carriere M, Bazex J. Erythema multiforme associated with hepatitis B immunization. *Clin Exp Dermatol*. 2000;25(2):167-168.
90. Coates SJ, Briggs B, Cordoro KM. Tularemia-induced erythema multiforme minor in an 11-year-old girl. *Pediatr Dermatol*. 2018;35(4):478-481.
91. Cañueto J, Roncero M, Unamuno P. Erythema multiforme triggered by *Tricophytum mentagrophytes*? *J Eur Acad Dermatol Venereol*. 2009;23(5):586-587.
92. Neri I, Giacomini F, Raone B, Patrizi A. Generalized erythema multiforme after localized allergic dermatitis from dark henna tattoo. *Pediatr Dermatol*. 2009;26(4):496.
93. Özdemir PG, Yazicioğlu M, Aylanç H, Ozkayin N. EBV-induced erythema multiforme: a case report. *Allergol Immunopathol (Madr)*. 2011;39(2):116-118.
94. Weston WL, Brice SL. Atypical forms of herpes simplex-associated erythema multiforme. *J Am Acad Dermatol*. 1998;39(1):124-126.
95. Mourtada I, Le Tourneur M, Chevrant-Breton J, Le Gall F. Human orf and erythema multiforme [French]. *Ann Dermatol Venereol*. 2000;127(4):397-399.
96. Werchniak AE, Schwarzenberger K. Poison ivy: an under-reported cause of erythema multiforme. *J Am Acad Dermatol*. 2004;51(5 Suppl):S159-S160.
97. Messina MF, Cannavò SP, Aversa S, De Luca F. Transient natural killer deficiency in a boy with herpes simplex virus-associated recurrent erythema multiforme. *Scand J Infect Dis*. 2011;43(6-7):550-552.
98. Wiedemeyer K, Enk A, Jappe U. Erythema multiforme following allergic contact dermatitis: case report and literature review. *Acta Derm Venereol*. 2007;87(6):559-561.
99. Kishore BN, Ankadavar NS, Kamath GH, Martis J. Varicella zoster with erythema multiforme in a young girl: a rare association. *Indian J Dermatol*. 2014;59(3):299-301.
100. Pérez-Carmona L, Aguayo-Leiva I, González-García C, Jaén-Olasolo P. The quadrivalent human papillomavirus vaccine: erythema multiforme and cutaneous side effects after administration. *Dermatology*. 2010;221(3):197-200.
101. Williamson DM. Erythema multiforme in infectious mononucleosis. *Br J Dermatol*. 1974;91(3):345-346.
102. Pérez-Carmona L, Vaño-Galvan S, Carrillo-Gijón R, Jaén-Olasolo P. Photosensitive erythema multiforme presenting as juvenile spring eruption. *Photodermatol Photoimmunol Photomed*. 2010;26(1):53-54.
103. Chen C-W, Tsai T-F, Chen Y-F, Hung C-M. Persistent erythema multiforme treated with thalidomide. *Am J Clin Dermatol*. 2008;9(2):123-127.
104. Dentan C, Pavese P, Morand P, Mosnier E, Brion J-P, Stahl J-P. Erythema multiforme: what is your diagnosis? Measles. [French] *Med Mal Infect*. 2013;43(7), 271; 302-303.
105. Jain S, Rathore MK, Dwivedi PC, Tirkey E. Corneal lesions in erythema multiforme minor--are systemic steroids indicated? *Indian J Ophthalmol*. 2010;58(6):559-560.
106. Johnston GA, Ghura HS, Carter E, Graham-Brown RA. Neonatal erythema multiforme major. *Clin Exp Dermatol*. 2002;27(8):661-664.
107. Rosa JS, Ong PY. A case of atopic dermatitis and erythema multiforme. *Eur Ann Allergy Clin Immunol*. 2012;44(1):30-31.
108. Elfatoiki FZ, Chiheb S. Atypical erythema multiforme. *Pan Afr Med J*. 2015;20:436.
109. Maquet J, Strull N, Quatresooz P, Bricteux G. Erythema multiforme caused by a Mycoplasma infection: a case report. [French] *Rev Med Liege*. 2008;63(1):6-10.
110. Ashton R, Wong KW, Weinstein M. Pediatric lip adhesion following bullous erythema multiforme and review of similar oral complications. *J Cutan Med Surg*. 2018;22(4):427-430.
111. Chen T, Levitt J, Geller L. Apremilast for treatment of recurrent erythema multiforme. *Dermatol Online J*. 2017;23(1).
112. Petrosino MI, Attanasi M, Marcovecchio ML, et al. Erythema multiforme syndrome associated with acute acquired cytomegalovirus infection. *Arch Med Sci*. 2016;12(3):684-686.

113. Athreya BH, Coriell LL. Erythema multiforme exudativum major: a review and report of four cases. *Clin Pediatr (Phila)*. 1964;3:68-74.
114. Webster GM, Simon JF. Erythema multiforme limited to the oral cavity: report of case. *J Am Dent Assoc*. 1971;83(5):1106-1108.
115. Marinho LH, Haj M, Pereira LF. Lip adhesion: an unusual complication of erythema multiforme. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1999;88(2):167-169.
116. Kalicki B, Grad A, Dadas-Stasiak E, Skwarzec J. Sepsis complicated with erythema multiforme at 9-year-old boy. *Pediatr Med Rodzinna*. 2006;2:218-222.
117. Darmstadt GL, Cohen B. Pathological cases of the month. Erythema multiforme (EM). *Arch Pediatr Adolesc Med*. 1994;148(4):429-430.
118. Pope E, Krafchik BR. Involvement of three mucous membranes in herpes-induced recurrent erythema multiforme. *J Am Acad Dermatol*. 2005;52(1):171-172.
119. Sebastian A, Patterson C, Zaenglein AL, Ioffreda MD, Helm KF. Histiocytic erythema multiforme. *J Cutan Pathol*. 2009;36(12):1323-1325.
120. Grosber M, Alexandre M, Poszepczynska-Guigné E, Revuz J, Roujeau J-C. Recurrent erythema multiforme in association with recurrent *Mycoplasma pneumoniae* infections. *J Am Acad Dermatol*. 2007;56(5 Suppl):S118-S119.
121. Osterne RLV, Matos Brito RG de, Pacheco IA, Alves APNN, Sousa FB. Management of erythema multiforme associated with recurrent herpes infection: a case report. *J Can Dent Assoc*. 2009;75(8):597-601.
122. Sokumbi O, Wetter DA. Clinical features, diagnosis, and treatment of erythema multiforme: a review for the practicing dermatologist. *Int J Dermatol*. 2012;51(8):889-902.
123. Huff JC, Weston WL, Tonnesen MG. Erythema multiforme: a critical review of characteristics, diagnostic criteria, and causes. *J Am Acad Dermatol*. 1983;8(6):763-775.
124. Samim F, Auluck A, Zed C, Williams PM. Erythema multiforme: a review of epidemiology, pathogenesis, clinical features, and treatment. *Dent Clin North Am*. 2013;57(4):583-596.
125. Aurelian L, Ono F, Burnett J. Herpes simplex virus (HSV)-associated erythema multiforme (HAEM): a viral disease with an autoimmune component. *Dermatol Online J*. 2003;9(1):1.
126. Kechichian E, Ingen-Housz-Oro S, Sbidian E, et al. A large epidemiological study of erythema multiforme in France, with emphasis on treatment choices. *Br J Dermatol*. 2018;179(4):1009-1011.
127. Larquey M, Mahé E. Childhood postinfectious erythema multiforme. [French] *Arch Pediatr*. 2016;23(11):1184-1190.
128. Atkinson TP, Waites KB. *Mycoplasma pneumoniae* infections in childhood. *Pediatr Infect Dis J*. 2014;33(1):92-94.
129. Rasmussen JE. Erythema multiforme in children. Response to treatment with systemic corticosteroids. *Br J Dermatol*. 1976;95(2):181-186.
130. Kakourou T, Klontza D, Soteropoulou F, Kattamis C. Corticosteroid treatment of erythema multiforme major (Stevens-Johnson syndrome) in children. *Eur J Pediatr*. 1997;156(2):90-93.
131. Scully C, Bagan J. Oral mucosal diseases: erythema multiforme. *Br J Oral Maxillofac Surg*. 2008;46(2):90-95.