Title page

Title: Oral health status in patients with inherited epidermolysis bullosa: a comparative multicenter study

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Abstract (250 words)

Background: Epidermolysis bullosa (EB) is a rare genetic mucocutaneous disorder characterized by epithelial fragility leading to blister formation on skin and mucous membranes with even minor mechanical trauma. Most EB oral health publications give fragmented information, focusing on only one oral health aspect or one EB type. The aim of this study was to expand the knowledge of the overall oral health status of individuals with dystrophic, junctional and simplex EB.

Methods: A comparative multicenter study, including a control group, and based on questionnaires and clinical examinations, was undertaken in three EB expert centers.

Results: Most EB (90.2%) participants brushed their teeth at least once a day despite the pain. The prevalence of enamel defects and caries experience did not differ between the 42 EB participants and the 42 age-/sex-matched healthy controls. Gingival inflammation unrelated to dental plaque accumulation was found in EB participants. Blisters, erythema, erosion/ulceration mainly involved gingiva, buccal mucosa, lips and palate, with different topographical patterns according to EB type. EB patients whatever the age showed a similar lesion distribution. Simplex and Dystrophic EB patients under 12-year-old displayed higher lesion severity than junctional EB ones. Only Dystrophic type exhibited microstomia and ankyloglossia.

Conclusion: Oral health status seemed to benefit from a close collaboration between dentist and dermatologist, and from regular dental examination, starting at a young age and with a focus on prevention. The new appreciation of oral health involvement highlighted by this study is essential for EB patients care, regarding comorbidities and quality of life.

Oral health status in patients with inherited epidermolysis bullosa: a comparative multicenter study

1 | INTRODUCTION

Inherited epidermolysis bullosa (EB) is a group of rare genodermatoses characterized by mechanical fragility of skin/mucous membranes as a result of cleavage within dermal-epidermal layers leading to blistering. Bullous lesions can severely handicap individuals because of their local and systemic consequences [1] (**Figure 1[A-B]**). People with EB have general complications such as digestive, respiratory, ocular and urogenital manifestations and possible malignant degeneration. In the most severe cases, the condition is life-threatening, and life expectancy is shortened (by about 30 years) [1]. Moreover, this disease has a significant impact on quality of life [2]. Four major types of EB are described, based on the localization of the split at the epidermal ultrastructural level: simplex EB (SEB; intra-epidermal cleavage), junctional EB (JEB; dermal-epidermal split), dystrophic EB (DEB; intradermal cleavage) and Kindler's syndrome (multifocal) [3]. None of acquired form of EB were considered in this study.

The oral cavity is especially affected because of constant exposure to oral functions from an early age. Oral lesions are characterized by erythema, blistering and their aftermath (e.g., erosions, ulcerations, crusts and atrophic scarring)[4]. Number, frequency and severity of the lesions depend on the type of EB [5] (**Figures 2 [A-D]** and **3[A-B]**). Except for Wright et al. [6-9] in the 1990s (including a cohort of 292 patients) and Fortuna et al. [5] (92 patients) reports, most studies bring fragmented information focusing on only one aspect of oral health (oral soft-tissue lesions, oral hygiene, caries or enamel defects) [4,5,10-12] or only one type of EB [13-16]. Recently, our group reported that the distribution of oral mucosal lesions depends on the type of disease and that gingival inflammation might be a specific feature reflecting the intrinsic fragility of

the gingival tissues [17]. However, many questions remain on EB oral health status, such as the prevalence of functional sequelae [15] (in particular ankyloglossia and microstomia), caries experience, enamel defects, oral hygiene and dietary habits. This information is especially relevant in the pediatric population, requiring special attention.

The aim of this study was to report global oral health (prevalence and distribution of oral lesions at the level of mucosa, periodontal tissues and dental structures) and oral health-related habits (hygiene and diet) in a cohort of individuals with DEB, JEB and SEB as compared with age and sex-matched controls.

2 | MATERIALS and METHODS

2.1 | Study design

This comparative multicenter study including a control group was conducted in three EB expert centers, in Belgium (Leuven) and France (Nice, Toulouse) between September 2017 and December 2019. The protocol received institutional approval (Commission Nationale de l'Informatique et des Libertés : CNIL, identifier no. R0172003095), and the study was registered at ClinicalTrials.gov (NCT04217538).

2.2 | Participants

EB group: All EB patients, regardless of gender, age and type of inherited EB, in any of the three expert centers were invited to participate during the dental consultation, part of their regular care. To be eligible, patients and/or guardians needed to understand French (Nice and Toulouse) or Dutch (Leuven) in order to capture all information and to provide their consent. If oral clinical examination could not be performed, mostly because of a lack of cooperation, the patient was excluded.

Control group: For each individual enrolled in the EB group, we included an age- and sex-matched healthy patient consulting (for regular treatment or check-up only) in the same time frame at the Toulouse hospital dentistry department.

2.3 | Questionnaire and clinical procedures

All seven dental practitioners involved in the clinical examinations are teachers in oral pathology or pediatric dentistry, they perform their clinic in pediatric dentistry, periodontology or special care. Before the beginning of the study, all examiners met several times to discuss different representative clinical control and EB cases to calibrate theselves for the diagnosis, until reaching a full agreement. The oral clinical examination was performed following World Health Organization recommendations [18]. The reference indices chosen to describe the oral health condition of the participants were the Decayed, Missing, Filled Teeth index (DMFT) to summarize dental caries experience (cavitated lesions), the Plaque Index (PI) to describe the presence of dental plaque accumulation reflecting the level of oral hygiene and the Gingival Index (GI) to describe the extent of gingival inflammation. Presence of enamel hypoplasia was reported. The Epidermolysis Bullosa Oropharyngeal Severity (EBOS) [19] score (range 0 to 60) was used to assess the severity of oral mucosal involvement.

Examinations took place in a dental setting with use of a dental probe, mirror and light source. Data collection was completed with information obtained by asking a few questions regarding their dietary habits, oral hygiene practices and dental attendance (Table I).

All data were entered in an anonymized file that was designed by all expert dentists involved in the study. In some cases, when indicated, radiography was performed for diagnostic purposes but was not part of data collection within the frame of this study.

2.4 | Statistical analyses

Frequencies (percentages) are given for categorical variables and mean ± SD or range for continuous variables. As patients under 12 years old undergo periodontal changes with regular local inflammation caused by physiological dentition changes, that could also influence the presence of EB lesions. Thus, a subdivision of the sample at 12 years old was decided as a cutoff for comparison in each EB and control groups in order to improve the relevance of the results for oral examination, by making sure that the physiological changes were not the reason of the oral lesion, as all permanent teeth (except the wisdom teeth) are erupted.[20]

The Wilcoxon test was used for comparing groups. Stata software (STataCorp., College Station, TX) was used for analysis. If one of the groups had missing data, the associated unpaired data were excluded from analyses. $P<0.05$ was considered statistically significant.

3 | RESULTS

3.1 | Participants characteristics

Among the 42 individuals with EB included in this study, 25 (59.5%) had a diagnosis of DEB (4 dominant and 21 recessive forms), 5 (11.9%) JEB and 12 (28.6%) SEB. The mean age of the EB group was 13 ± 15.1 years (range 2 to 78), with a female:male ratio of 19:23. In the <12-year-old subgroup, the mean age was 7 ± 2.9 years (range 2 to 12), with a female:male ratio of 11:18. We included 42 age- and sex-matched controls.

3.2 | Dental attendance, hygiene and dietary habits (Table II)

Both EB participants and controls had regular follow-up and prophylaxis consultations with the dentist. Most EB (90.2%) and control (97.6%) participants brushed their teeth at least once every day. These results were similar for patients under 12 years old. Nevertheless, less than half of EB participants (43.9%) reported brushing only once a day, whereas most controls

(73.8%) brushed twice a day. More than half of EB participants (predominantly those with DEB) reported difficulties with toothbrushing. The main issues mentioned by all EB patients were “pain” and “limitation of mouth opening” (42.9% and 16.7%, respectively), more frequently in DEB than in other participants (52.0% and 20.0%). In addition, DEB and JEB participants reported difficulties with chewing and swallowing; one-third of them consumed only soft food. For patients under 12 years old, brushing was generally performed by the parents, especially for those with JEB (100.0%) or DEB (94.1%) as compared with the control group (66.6%). The frequency of “gingival bleeding when brushing” was higher for EB participants than controls (32.5% vs 17.5%), regardless of age. The frequency of sugar consumption did not differ between EB participants and controls.

3.3 | Oral mucosa examination (Table III, Figure 4[A-B])

EB participants exhibited mainly oral mucosal erythema, blisters and erosions/ulcerations. Ten (23.8%) EB participants (predominantly SEB) did not show any oral mucosal lesions on clinical examination.

The mean EBOS score was 3.3 ± 3.0. DEB participants had the highest mean score (4.4 ± 2.9) and SEB participants the lowest (1.4 ± 2.1). Microstomia and ankyloglossia were found only in DEB (40.0% and 48.0% of total DEB, respectively). Oral lesions showed a wide distribution over the mucosal surfaces, in all types of EB, with the exception of the oral cavity floor, which was never affected in SEB. Gingiva (81% of total EB), oral mucosa on the cheeks (73.8% of total EB), lips (64.3% of total EB) and palate (61.9% of total EB) were the most affected areas. Despite the overall similar oral mucosa lesion distribution within each EB group, SEB and DEB patients under 12 years old had more severe symptoms than their over 12 years old counterparts.

3.4 | Periodontal examination

GI and "gingival bleeding when brushing" scores revealed gingival inflammation level and severity. EB participants showed higher mean GI and frequency of "gingival bleeding when brushing" than controls, regardless of age [17]. The mean GI and "gingival bleeding when brushing" frequency were higher for DEB than for SEB and JEB participants (1.8 ± 0.8; 47.8% vs 1.2 ± 0.7; 8.3%, and 1.1 ± 0.6; 40.0%); mean PI did not differ among groups (DEB: 1.7 ± 0.7: SEB: 1.6 ± 1.0; JEB: 1.80 ± 0.6). Under 12-year-old participants showed similar results.

3.5 | Dental examination

Sixty percent of JEB participants showed enamel hypoplasia, which was significantly higher than what was observed in DEB (12.0%), SEB (8.3%) and control participants (11.9%) (Table II). Caries experience and enamel hypoplasia frequency did not differ significantly between EB participants and controls, regardless of age. Among all participants including controls, DEB participants had the lowest mean DMFT score (3.1 ± 5.3). EB participants' and controls' DMFT scores did not differ (3.9 ± 6.1 vs 5.03 ± 5.5; $p = 0.1$), regardless of age (3.8 ± 4.3 vs 5.1 ± 4.3, $p = 0.1$ for patients <12 years old).

4 | DISCUSSION

This work on the global oral health condition of individuals with inherited EB highlighted that distribution of the lesion on mucosa or gingiva depend on EB type while their severity depend on age. Analysis with an age cutoff allowed us to show that for DEB and SEB patients, individuals under 12 years old were the ones most severely affected.

The size of the sample in this study is quite large for a rare condition and is one of the largest published among those that investigated the three major types of EB. The number and diversity

of EB participants and the inclusion of a matched (by sex and age) control group adds value in comparison with previously published case series or cohort studies [8,19,22,23]. Furthermore, our results were sustained by the systematic examination according to validated scales for oral health - teeth, periodontium, mucosa - key components and their daily oral maintenance habits records. Due to practical team and services organization, the control group including patients for regular treatment and oral check-up was only recruited at the Toulouse hospital. Even so it could be considered as a limitation of the study, there are no recent data on oral health patients in France, so we decided to compare the EB population with the one treated as the hospital as they were also treated at the hospital. Given our respective experiences and expertise as dental hospital professionals, it was considered representative of the oral health status of the population of all our dental care centers. Furthermore, EB patients came from all over France or Belgium, it would have been impossible to find matched patients in every town.

Most of the participants exhibited oral lesions, with a mean EBOS score of 3.3 (maximum 21.0), which is lower than the mean score reported by Fortuna et al. [19] (12.9, maximum 23.8). This finding can be explained by the smaller size of our sample (42 vs 92), a lower proportion of participants with DEB (60.0% vs 75.0%) and the regular (annual or semestrial) dental follow-up of our participants. JEB and DEB individuals showed a different distribution of lesions and were the most severely affected [11,13,18,19]. Although the mucosal lesions' topographic distribution was the same regardless of age, the oral mucosal lesions' severity was higher for under 12 years-old DEB and SEB patients. Age and EB type mainly contribute to lesion severity and distribution, respectively. This heterogeneity in lesion distribution and severity highlights the critical necessity to follow and document our patients' oral health status.

Periodontal considerations have been mainly reported in people with Kindler EB subtype, displaying early and rapidly progressive periodontitis as a common feature [24]. In other EB types, plaque accumulation and gingival inflammation data were reported higher than in our study [8,9,13], which may have masked an intrinsic gingival inflammation. Indeed, we reported that DEB

participants showed substantial and constant gingival inflammation and high frequency of "gingival bleeding when brushing", which couldn't be justify with oral hygiene clinically level (i.e the quantity of dental plaque) [17]. In this situation, gingival inflammation cannot be associated with a lack of oral hygiene [26] but rather reflects a specific feature of DEB [(17,25)]. The extent, severity and progression of gingival lesions can be affected by systemic factors, such as impaired gingiva due to genetic mutation, which underlines changes in the organization of the periodontal tissues [25]. Our findings might be explained by the role of the mutated protein (collagen 7, for example, in DEB type) in oral mucosal physiology [27]. Because long-term gingival inflammation generally leads to periodontitis, management of the oral hygiene of these patients is mandatory to prevent periodontitis and tooth loss.

Enamel structural defects (i.e., hypoplasia) have been described in EB patients and are related to EB genetic mutations that also affect ameloblastic differentiation [8,21,28]. However, the work of Kirkham et al. and Wright et al. concluded that the enamel of DEB patients was normal [12] and that only JEB patients display developmentally compromised enamel with mineral defects [7] (more frequently in molars than incisors [29]), whereas SEB patients seemed less affected [7]. In the present work, we did not observe significant differences in the prevalence of enamel hypoplasia between EB participants and controls. This finding might be explained by the increase in the enamel defect prevalence in the general population, especially molar incisor hypomineralization (affecting up to 40.0% of the population) and hypomineralized second primary molars (up to 7.0%) [30] and the low proportion of JEB individuals in our sample.

Only DEB patients showed ankyloglossia and microstomia, as previously reported [8,25,26,28]. These tissue retractions reduce access to the oral cavity and also explain the altered dietary habits because of chewing and swallowing difficulties [5,12,14]. Microstomia tends to worsen without interception if developed at a young age, so it requires our attention and follow-up. Eventually, it will lead to severe difficulties in maintaining good oral hygiene and limitations in access to the posterior part of the oral cavity when dental treatment is needed. This situation

will result in ethical reflections regarding the need for and timing of posterior teeth extractions before treatments become completely impossible. Although feeding through a gastrostomy is often implemented for individuals with severe microstomia, some still consume juices or other types of sugary food. In combination with unproper oral hygiene, this consumption will increase the development of carious lesions. A protocol using exercises is currently being tested and shows encouraging results in interfering with the development and progression of microstomia.

The present study demonstrated no difference in sugar consumption frequency between EB and control groups, in accordance with Harris et al. [13] results, but not with previous reports [10]. These seemingly conflicting results might be attributed to the increased attention given to children's sugar restriction in general. In line with Wright et al. [11], the present study confirms that caries development is not a specific sign of EB but rather a consequence of impaired oral health-related habits. Our participants had better oral health, dental care and dietary habits, with better oral hygiene levels and lower caries experience, than reported in previous studies [16,31]. These results can be explained by the fact that these participants were included in a multidisciplinary program with regular follow-up by a dentist and dermatologist working collaboratively. Moreover, participants followed strict preventive recommendations [31], including daily toothbrushing using a fluoride containing toothpaste, fluoride applications every 6 months and restriction of sugar intake. Despite frequent parental support with brushing (more frequent for EB groups), oral hygiene remains a point of attention requiring continuous education and motivation of patients and parents for brushing/cleaning techniques.

Some recommendations [31, 32] are meant to help dental practitioners to care for these patients. Specific precautions are needed to be followed to treat those that suffer from the most sensitive mucosa and frequent oral lesions, such as lubricate the mouth or any dental instruments prior to treatment, and never use suction.

Investigating oral health habits of our patients raised an important element for professionals: the use of chlorhexidine mouthwash was widely advocated for gingivitis prevention in patients

with EB due to its antiseptic properties [31]. However, two recent Cochrane meta-analysis concluded that there was insufficient evidence to prove that chlorhexidine (whatever its concentration) was efficient to reduce discrete to severe gingivitis [33], and its role for caries prevention is very controversial [34]. Furthermore, side effects of long use of chlorhexidine, such as transient taste disturbance, extrinsic tooth staining, and calculus build up, are not negligible. Thus, systematic use of chlorhexidine mouthwashes is not recommended for EB or any patients. However, in case of extensive and severe mucosal lesion occurrence, chlorhexidine mouthwashes anti-inflammatory property can help in reducing pain and inflammation, thus supporting tooth brushing [32] when used for a short period of time.

5 | CONCLUSION

This large study highlights new appreciations regarding oral health involvement in people with EB, allowing improvements in patient care. Firstly, we observed an EB type-dependent topographical distribution pattern of oral mucosal lesions. Secondly, patients under 12 years old seem to exhibit more severe clinical signs than those over 12 years old, but long-term follow-up is needed to confirm this clinical trend. Thirdly, DEB participants displaying more severe lesions also showed stronger gingival reaction to dental plaque accumulation. Finally, oral health status seems to benefit from a close collaboration between the dermatologist and dentist. General dental practitioners are qualified to treat these patients in the context of regular dental care, including prevention and oral health education. They can refer to a specialist when needed for heavier treatment, or for the most severely impaired patients, in particular in DEB type condition.

References

1. Silva LCP, Cruz RA, Abou-Id LR, Brini LNB, Moreira LS. Clinical evaluation of patients with epidermolysis bullosa: Review of the literature and case reports. Spec Care Dentist. 2004;24(1):22-27.
2. Tabolli S, Sampogna F, Di Pietro C, et al. Quality of life in patients with epidermolysis bullosa. Br J Dermatol. 2009;161(4):869-877. doi:10.1111/j.1365-2133.2009.09306.x
3. Rao R, Mellerio J, Bhogal BS, Groves R. Immunofluorescence antigen mapping for hereditary epidermolysis bullosa. Indian J Dermatol Venereol Leprol. 2012;78(6):692-697.
4. Feijoo JF, Bugallo J, Limeres J, Peñarrocha D, Peñarrocha M, Diz P. Inherited epidermolysis bullosa: an update and suggested dental care considerations. J Am Dent Assoc. 2011;142(9):1017-25.
5. Fortuna G, Lozada-Nur F, Pollio A, et al. Patterns of oral mucosa lesions in patients with epidermolysis bullosa: comparison and agreement between oral medicine and dermatology. J Oral Pathol Med. 2013;42(10):733-740.
6. Wright JT, Johnson LB, Fine JD. Development defects of enamel in humans with hereditary epidermolysis bullosa. Arch Oral Biol. 1993;38(11):945-955.
7. Wright JT, Hall KI, Deaton TG, Fine J-D. Structural and Compositional Alteration of Tooth Enamel in Hereditary Epidermolysis Bullosa. Connect Tissue Res. 1996;34(4):271-279.
8. Wright JT, Fine JD, Johnson LB. Oral soft tissues in hereditary epidermolysis bullosa. Oral Surg Oral Med Oral Pathol. 1991;71(4):440-446.
9. Wright JT, Fine JD, Johnson L. Hereditary epidermolysis bullosa: oral manifestations and dental management. Pediatr Dent. 1993;15(4):242-248.

10. De Medeiros RA, Leal SC, Lia EN, et al. Higher Dental Caries Prevalence and Its Association with Dietary Habits and Physical Limitation in Epidermolysis Bullosa Patients: A Case Control Study. J Contemp Dent Pract. 2016;17(3):211-216.
11. Wright JT, Fine JD, Johnson L. Dental caries risk in hereditary epidermolysis bullosa. Pediatr Dent. 1994;16(6):427-432.
12. Kirkham J, Robinson C, Strafford SM, et al. The Chemical Composition of Tooth Enamel in Recessive Dystrophic Epidermolysis Bullosa: Significance with Respect to Dental Caries. J Dent Res. 1996;75(9):1672-1678.
13. Harris JC, Bryan RA, Lucas VS, Roberts GJ. Dental disease and caries related microflora in children with dystrophic epidermolysis bullosa. Pediatr Dent. 2001;23(5):438-443.
14. Louloudiadis AK, Louloudiadis KA. Case report: Dystrophic Epidermolysis Bullosa: dental management and oral health promotion. Eur Arch Paediatr Dent Off J Eur Acad Paediatr Dent. 2009;10(1):42-45.
15. Stellingsma C, Dijkstra PU, Dijkstra J, Duipmans JC, Jonkman MF, Dekker R. Restrictions in oral functions caused by oral manifestations of epidermolysis bullosa. Eur J Dermatol. 2011;21(3):405-409.
16. Scheidt L, Sanabe ME, Diniz MB. Oral Manifestations and Dental Management of Epidermolysis Bullosa Simplex. Int J Clin Pediatr Dent. 2015;8(3):239-241.
17. Christine Chiaverini, Mathieu Marty, Sophie-Myriam Dridi, Sophie Caroline Campana, Thibault Canceill, Isabelle Bailleul-Forestier, Veroniek Verhaeghe, Dominique Declerck, Thomas Hubiche, Philippe Kémoun, Juliette Mazereeuw-Hautier, Clara Joseph. Oral status in patients with inherited epidermolysis bullosa: A multicentric observational study. J Am Acad Dermatol. 2021 Nov 25;S0190-9622(21)02908-X. doi: 10.1016/j.jaad.2021.11.039. Online ahead of print.

18. World Health Organization, ed. Oral Health Surveys: Basic Methods. 5th edition. World Health Organization; 2013.
19. Fortuna G, Chainani-Wu N, Lozada-Nur F, et al. Epidermolysis Bullosa Oropharyngeal Severity (EBOS) score: A multicenter development and reliability assessment. J Am Acad Dermatol. 2013;68(1):83-92.
20. Nelson S.J. Wheeler's Dental Anatomy, Physiology and Occlusion. 1st SAE Elsevier Health Sciences, 2015. pp. 394.
21. Pekiner FN, Yücelten D, Ozbayrak S, Sezen EC. Oral-clinical findings and management of epidermolysis bullosa. J Clin Pediatr Dent. 2005;30(1):59-65.
22. Serrano-Martínez MC, Bagán JV, Silvestre FJ, Viguer MT. Oral lesions in recessive dystrophic epidermolysis bullosa. Oral Dis. 2003;9(5):264-268.
23. Uitto J, Has C, Vahidnezhad H, Youssefian L, Bruckner-Tuderman L. Molecular pathology of the basement membrane zone in heritable blistering diseases: Matrix Biol. 2017;57-58:76-85.
24. Wiebe CB, Petricca G, Häkkinen L, Jiang G, Wu C, Larjava HS. Kindler Syndrome and Periodontal Disease: Review of the Literature and a 12-Year Follow-Up Case. J Periodontol. 2008;79(5):961-966.
25. Chapple ILC, Mealey BL, Van Dyke TE, et al. Periodontal health and gingival diseases and conditions on an intact and a reduced periodontium: Consensus report of workgroup 1 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. J Clin Periodontol. 2018;45 Suppl 20:S68-S77.
26. Page RC, Schroeder HE. Pathogenesis of inflammatory periodontal disease. A summary of current work. Lab Investig J Tech Methods Pathol. 1976;34(3):235-249.
27. Abe M, Osawa T. The structure of the interstitial surfaces of the epithelial basement membranes of mouse oral mucosa, gingiva and tongue. Arch Oral Biol. 1999;44(7):587-94.

28. Stavropoulos F, Abramowicz S. Management of the oral surgery patient diagnosed with epidermolysis bullosa: report of 3 cases and review of the literature. J Oral Maxillofac Surg Off J Am Assoc Oral Maxillofac Surg. 2008;66(3):554-559.
29. Kirkham J, Robinson C, Strafford SM, et al. The chemical composition of tooth enamel in junctional epidermolysis bullosa. Arch Oral Biol. 2000;45(5):377-386.
30. Silva MJ, Scurrah KJ, Craig JM, Manton DJ, Kilpatrick N. Etiology of molar incisor hypomineralization - A systematic review. Community Dent Oral Epidemiol. 2016;44(4):342-353.
31. Krämer SM, Serrano MC, Zillmann G, et al. Oral Health Care for Patients with Epidermolysis Bullosa - Best Clinical Practice Guidelines: Clinical Guidelines for Oral Care in Epidermolysis Bullosa. Int J Paediatr Dent. 2012;22:1-35.
32. Haute Autorité de Santé. Protocole National de Diagnostic et de Soins (PNDS) Épidermolyses bulleuses héréditaires. Septembre 2021. https://www.has-sante.fr/jcms/c_2028188/fr/epidermolyses-bulleuses-hereditaires
33. James P, Worthington HV, Parnell C, Harding M, Lamont T, Cheung A, Whelton H, Riley P. Chlorhexidine mouthrinse as an adjunctive treatment for gingival health. Cochrane Database of Systematic Reviews 2017, Issue 3. Art. No.: CD008676.
34. Walsh T, Oliveira-Neto JM, Moore D. Chlorhexidine treatment for the prevention of dental caries in children and adolescents. Cochrane Database of Systematic Reviews 2015, Issue 4. Art. No.: CD008457.