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REVIEW



Periodontal and dental health in inflammatory bowel diseases: a systematic review

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ABSTRACT

Introduction: An increased risk of dental caries and periodontal diseases has been reported for inflammatory bowel disease (IBD) patients and are challenging conditions to manage.

Areas covered: The authors searched international databases to find all studies assessing dental/periodontal outcomes in patients with IBD and other immune-mediated inflammatory disease (IMID), as well as the association between IMID medications and dental/periodontal status.

Expert opinion: IBD are associated with a higher risk of both periodontitis and caries. Some evidence from rheumatoid arthritis suggests that periodontitis may be associated with a lower response to anti-TNF. There is no reliable evidence that IBD patients may be at greater risk of complications during routine dental care. On the basis of current data, guidelines can be proposed for the dental management focusing on the detection and eradication of infectious foci prior to the implementation of immunosuppressants/biologics and modified dental treatment protocol for invasive dental procedures that includes antibiotic prophylaxis.

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Crohn's disease; ulcerative colitis; caries; periodontal diseases; dental

1. Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are chronic disabling and destructive inflammatory bowel diseases (IBDs). In addition to affecting the intestinal tract, the disease can show extra-intestinal manifestations that significantly influence the quality of life and functional state of the patient. Oral lesions are common in IBD patients and have been observed in up to 50% [1]. Although oral mucosa, lip, and tongue lesions are well described in the literature, less is known about dental and periodontal conditions of patients with IBD.

An increased risk of dental caries and periodontal diseases, the two most prevalent forms of chronic oral disease, has been reported in IBD patients over the last few decades. Dental caries are the most widespread of noncommunicable diseases and result from an elevated abundance of specific bacteria (*Lactobacilli* (LB) and *Streptococcus mutans* (SM)), decreased salivary flow, insufficient oral hygiene, and poor dietary habits, including high sugar consumption, as well as socioeconomic factors. They can lead to apical infections, i.e. infection-induced inflammatory bone lesions localized to the terminal end of the dental root, which occur as a result of complications of untreated caries (pulp necrosis) or the failure of dental root treatment (devitalization treatment). Such apical infections are considered to be foci of infection that must be treated or eliminated before starting a targeted immunotherapy treatment.

Periodontitis and IBD share common pathophysiological processes, as they both involve a complex combination of

genetic influences and environmental factors [2] in which disturbed host-microbiome interactions likely play a significant role [3]. Periodontitis is a chronic inflammatory disease triggered by oral dysbiosis with a specific role of the keystone pathogen, leading to irreversible periodontium destruction. It leads to gingival bleeding and tooth mobility and loss, and negatively affects the general health of the patient by altering critical functions, such as nutrition, swallowing, and phonation, as well as self-perception [4]. Periodontitis is associated with low-grade inflammation, chronic bacteremia, and the swallowing of bacteria, which influence numerous chronic diseases and dental or periodontal outcomes may influence IBD course. IBD medications, including steroids, immunosuppressants, and biologics, may influence the risk and course of dental or periodontal manifestations, as well as their management.

We therefore performed a systematic review to assess current knowledge on dental and periodontal diseases that occur in patients with IBD. We aimed to provide a clinically useful summary of the existing evidence to assist physicians in their therapeutic decisions and to provide an algorithm for the management of dental/periodontal care of IBD patients.

2. Methods

Our study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Article highlights

- IBD patients have an increased risk of developing periodontitis due to modifications of their oral microbiota and common inflammatory processes.
- Evidence is very limited for IBD but some evidence from rheumatoid arthritis suggests that periodontitis, especially untreated periodontitis, may be associated with a lower response to anti-TNF therapy, although the underlying mechanisms are still unknown.
- There is no reliable evidence that IBD patients may be at greater risk of complications during routine dental care than the general population but there is a general acceptance that patients on steroids and other immunosuppressive therapies have an increased risk of infections but there is no clear evidence to support an increased incidence of complications associated with dental care.
- On the basis of current scientific data, guidelines can be proposed for the dental management focusing on three issues: detection and eradication of dental infectious foci prior to the implementation of immunosuppressants/biologics and modified dental treatment protocol for invasive dental procedures that includes antibiotic prophylaxis.

(PRISMA) extension statement for the reporting of systematic reviews [5].

2.1. Data sources and search strategy

We searched Pubmed, Embase, and Scopus up to 1 May 2020 using the following terms: 'dental' or 'periodontal' or 'periodontitis' or 'caries' combined with 'Crohn's disease' or 'ulcerative colitis' or 'inflammatory bowel disease' or 'steroids' or 'azathioprine' or 'methotrexate' or 'anti-TNF' or 'infliximab' or 'adalimumab' or 'ustekinumab' or 'vedolizumab' or 'tofacitinib.' The search was restricted to human studies. No language restrictions were applied. Two authors (KA and MF) independently reviewed the titles and abstracts to identify eligible studies. The full texts of the selected articles were examined for inclusion and relevant references in their lists were hand searched to identify studies missed by the electronic search.

2.2. Selection criteria and data extraction

All studies were referral center-, hospital-, or population-based studies. The study inclusion criteria were (1) peer-reviewed interventional or observational studies, (2) English or French language, (3) including patients with Crohn's disease (CD) or ulcerative colitis (UC), and reported (4) dental or periodontal outcomes or impact of medications (steroids, immunosuppressants, or biologics) on dental or periodontal outcomes in IBD. Studies were excluded if they were review articles, did not focus on dental or periodontal outcomes in patients with IBD, did not investigate patients with IBD, or provided insufficient data for outcomes of interest. Case reports were not eligible for inclusion. Each article was carefully assessed. The following data were extracted from each selected study and recorded on a standardized form: first author, journal and year of publication, study design and duration, number of participants, patient characteristics (age, concomitant or previous treatments, disease type, disease duration, and disease activity), diagnosis, characteristics of the dental/periodontal condition as well as main outcomes of interest.

3. Results

A summary of the search and selection process is presented in Figure 1. In total, 1,996 citations were identified through the search strategy. After the removal of duplicates and careful screening of titles and abstracts, 1,633 articles were excluded. An additional 25 studies were excluded after full-text review of the manuscripts, as they did not meet the inclusion criteria: trials not reporting the outcome of interest (10), systematic reviews (1), or non-IBD population (14). Finally, 34 studies [6–39] were included in our systematic review. A summary of the main characteristics of the included studies is presented in Tables 1 and 5. The study period ranged from January 1960 to April 2019. There were 5 retrospective cohort studies, 8 cross-sectional studies, 16 case-control studies, and 2 prospective cohort studies. Most studies were monocentric ($n = 26$). In total, 184,042 patients were evaluated, including 16,541 with CD and 2,952 with UC. The mean duration of follow-up varied from 8 weeks to 13 years.

3.1. Oral hygiene and caries

Seven studies [6–12] compared the risk of caries in a total of 6,006 IBD patients and 5,796 controls (Table 1). All reported an increased risk of caries among IBD patients. Zhang et al. evaluated the risk of caries in 389 IBD patients and 265 controls and reported an increased risk of caries in IBD patients after adjustment for confounding factors, including age, sex, education level, smoking, and the daily frequency of tooth-brushing (odds ratio (OR) = 3.6, 95%CI: 2.2–5.3), with no difference between UC and CD [6]. Grossner-Schreiber et al. observed a prevalence of caries of 40% in IBD patients versus 22% in controls (Risk Ratio (RR), 2.82; $p = 0.03$). Similar results were observed for children and adolescents with IBD, who showed a significantly higher number of decayed, missing, or filled teeth than healthy controls [7]. Three studies [12–14] reported the risk of caries risk to be higher in patients with a longer course of disease. One study [10] also observed an association with a history of intestinal resection. Disease activity was not associated with an increased risk of caries, although one study reported more infectious foci on panoramic radiographs in the teeth of patients with active CD than in those with inactive disease [14,15].

Three studies suggested an increased susceptibility of IBD patients to apical infections [15–17]. One reported that the prevalence of apical infections was higher for CD patients with active disease [15].

Available data on the risk factors for caries, such as sucrose intake, tooth brushing, and frequency of visits to the dentist, were conflicting [6,8,11,13,18]. However, the Plaque Index, an oral hygiene marker (index used to assess the oral hygiene status by evaluating the amount of dental plaque on the tooth surface or the proportion of each tooth covered by it), was consistently reported to be higher for IBD patients [6,7,10], except for children [8], without a difference between UC and CD. Four studies evaluated *Streptococci Mutans* (*Sm*) and *Lactobacillus* counts in IBD patients [10,14,18,19]. Among them, four [10,14,18,19] reported a high level of *Sm* and three a high level of *Lactobacillus* [10,14,18]. Szymanska et al.

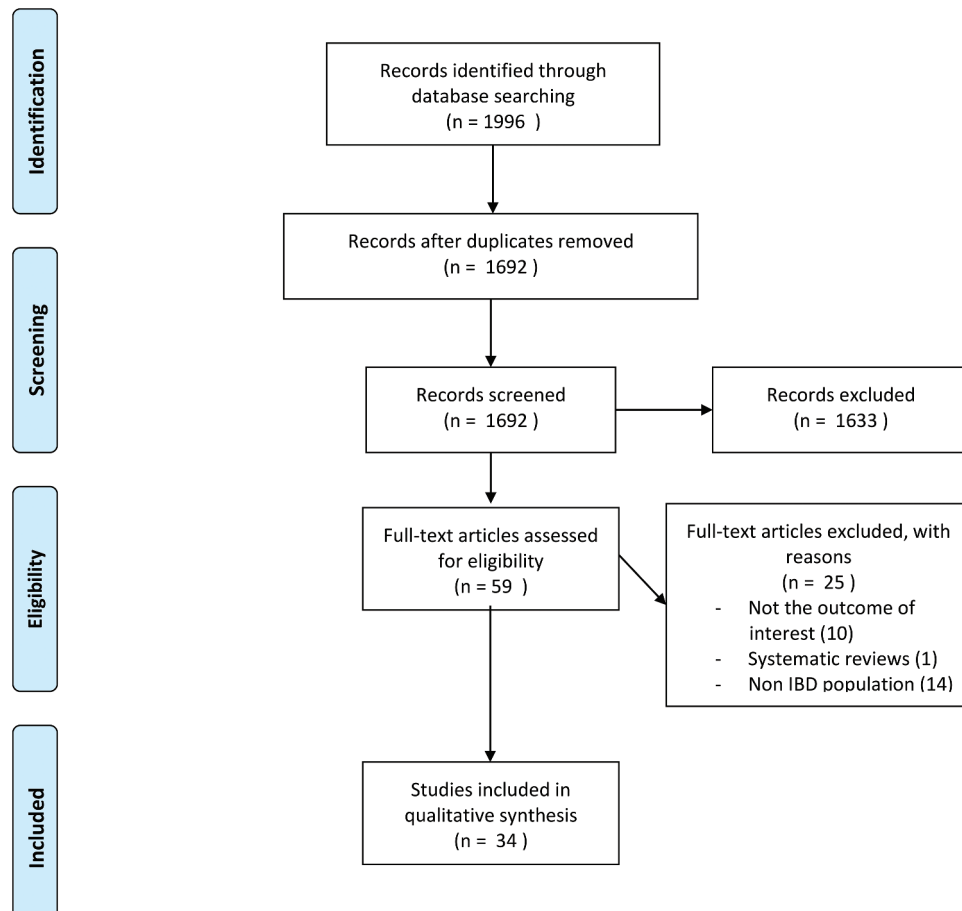


Figure 1. Study selection – Flow-Chart.

observed significantly higher counts of *Sm* and *Lactobacillus* in CD patients than controls [10]. Four studies reported a normal saliva flow rate and buffer capacity for IBD patients [10,14,15,19], whereas one, which included 15 patients, reported lower than normal values for the resting salivary flow rate, with eight of the subjects showing resting flow rates of 0.1 mL/min or less [18].

3.2. Overall risk of periodontitis in IBD patients

Ten studies [6–8,20,21,23–27] evaluated the risk of periodontitis in IBD patients, including a total of 13,141 IBD and 157,200 control patients. Seven [6–8,20,21,23,27] were case-control /cross sectional studies and three cohort /population vs referral studies [24–26].

Flemmig et al. first observed a higher prevalence of periodontitis in IBD by comparing the oral status of 107 IBD patients to a historical cohort of the US population [20]. This finding was later confirmed by several case-control studies [7,21,23–27]. Grossner-Schreiber observed a higher number of sites in IBD patients, with a clinical attachment loss (CAL, the distance from the cemento-enamel junction to the junctional epithelium as measured with a periodontal probe – estimated position of structures that support the tooth as measured with a periodontal probe; provides an estimate of a tooth's stability and of loss of bone support.) ≥ 4 mm, suggesting a history of destructive periodontal disease (Figure 2) [7]. Conversely, two

other studies [21,23] observed periodontitis of higher severity in patients with IBD, especially in UC patients. Two recent population-based cohort studies (NIHR Taiwan) confirmed a higher risk of periodontitis for IBD patients than for a non-IBD group, especially for the CD subgroup (adjusted HR: 3.95; 95% CI: 1.59–9.82 and adjusted HR: 1.36; 95% CI: 1.25–1.48, respectively) [24,25]. Another study from the same registry conducted on more than 135,000 patients followed for 13 years further reported that the risk of having UC is higher for patients with periodontitis (adjusted HR: 1.56 (1.13–2.15)) [26]. Vavricka et al. identified the presence of peri-anal disease and a Harvey-Bradshaw index > 10 as risk factors for periodontitis (OR 2.7 to 4.46) [27]. The link between IBD and periodontal disease has also been found in pediatric-onset IBD (4–18 years), in which the prevalence of gingivitis, a superficial form of periodontal disease, was twice as frequent, despite comparable oral hygiene [8]. The role of oral hygiene in explaining the higher frequency of periodontitis in IBD is debated. Only two studies have found poorer oral hygiene in IBD [6,23].

Smoking is a major risk factor for periodontitis [40] and individuals who smoke have a higher risk of CD but a lower risk of UC [41]. The data are heterogeneous concerning the potential effect of tobacco in the interaction between periodontitis and IBD. In four studies, two cross-sectional [8,20] and two cohort studies [24,25], the smoking status was not reported or smokers were excluded. In two other studies, the

Table 1. Risk of caries among patients with inflammatory bowel disease.

Author. year	Design; Setting	Patients: n, (M/F); mean age	Smoking; dietary habits	IBD (disease phenotype; duration; activity)	IBD medication (drugs; duration)	Dental (DMFT/ DMF-S; prevalence of caries)	Oral hygiene
Zhang et al. 2020	Cross-sectional; Hospital	IBD: 389 (245/144); 34y Ctl: 265(150/115); 26y	Smoking: 21% CD, 14% UC, 22% Ctl Diet: CD and UC consume fewer sugar than Ctl ($p \leq 0.001$)	CD: 265 ; <3y: 49.1% ; 3–9y: 39.6% ; >9y: 11.3%-active :36.2% UC: 124; <3y: 49.2% ; 3–9y: 38.7% ; >9y: 12.1%-active : 39.5%	No Ttt: 6.4%CD, 3.2%UC, 5ASA: 9.8% CD, 54.8% UC; CS: 3.8% CD, 14.5%UC; IMM: 40%CD, 21.8%UC; BIO: 40%CD, 5.7% UC	Caries in IBD: OR = 3.45, (95% CI: 2.25–5.31, $p < 0.001$) CD vs UC: no difference	Tooth brushing <2times/d: 21.5% Ctl, 41.9% CD, 43.5% UC; ≥2times/d: 78.5% Ctl, 58.1% CD, 56.5% UC; Plaque index CD = 0.68; UC = 0.70; Ctl = 0.28 ($p < 0.001$) CD vs UC: no difference
Grössner-Schreiber et al. 2006	Case-control; Hospital; private dental practice	IBD: 62(24/38); 38.4y Ctl: 59(24/35); 38.2y	Smoking: 40% IBD; 41% Ctl Diet: 44% IBD reported higher meal frequency but smaller amounts of food	CD: 46 UC: 16 35% IBD were active	CS: 20; IMM: 24; 5ASA: 39; BIO: 13, ATB: 12	Caries in IBD: OR = 2.37 (95% CI: 1.0–5.8, $p = 0.033$)	Plaque index IBD: 42.3%, Ctl: 29.9% (RR 1.027)
Koutsochristou et al. 2015	Case-control; Hospital; private dental practice	IBD: 55(25/30); 12.32y Ctl: 55(25/30); 12.21y	Smoking : excluded Diet : NR	CD: 36; 3.5y UC: 19; 4.4y	CS + 5ASA: 20; CS + IMM: 3; 5ASA + IMM 16; 5ASA + BIO: 5; IMM + BIO: 2.	DMF-T IBD = 5.81 (± 2.05), Ctl. = 2.04 (± 0.85) ($p < 0.001$)	IBD vs Ctl: no difference
Rooney TP. 1984	Case-control; Hospital	IBD: 21; 26.5y Ctl: 42; 26.5y	NR	CD: 21	NR	DMF-T CD = 16.10 (± 6.36), Ctl1 = 11.52 (± 6.15), Ctl2 = 10.81 (± 5.43), ($p < 0.025$);	NR
Szymanska. et al. 2014	Case-control; Hospital;	IBD: 150(77/73); 47.5y Ctl: 75(30/45); 48.6y	Smoking: 44% IBD; 6% Ctl Diet: higher sugar drinks consumption in CD	CD: 150 with RS: 71; 22y NRS: 79; 8y	NA/NR	DMF-S CD RS = 50.7; Ctl = 36.5 ($p = 0.01$); DMF-S correlates to IBD duration ($r = 0.374$, $p = 0.01$)	Visible Plaque Index CD RS = 53.7; Ctl = 22.6 ($p = 0.001$); NRS = 45.3; Ctl = 22.6 ($p = 0.001$)
Singhal et al. 2011	Case-control; Hospital	IBD: 83(1:2.5 ratio); 45.31y Ctl: 54(1:0.8 ratio); 55.28y	NR	CD: 57 UC: 26 6.27 \pm 0.55 y	NA/NR	Frequency of caries CD: 54.5%; UC: 76.9%; Ctl: 83.3% ($p = 0.007$)	Higher frequency of dental/ interdental brushing ($p = 0.005$) and breath freshener use ($p < 0.001$) in IBD

(Continued)

Table 1. (Continued).

Piras et al. 2017	Retrospective cohort; Hospital; private dental practice	IBD: 110(49/61), 46y Ctl: 110(53/57), 41y	NR	IBD duration : 12 ± 7.5 y	Prevalence of AI: 65% Biologic Medication; 69% higher risk for BM women (OR 1.69, 95% CI:0.68–3.9, p > 0.05); BMs = 74, CS = 36	DMF-T higher in women with IBD (p < 0.05) Nb teeth with apical infection: IBD = 3.9; Ctl = 2.8, p < 0.05	NR
Poyato-Borrego et al. 2019	Case-control; Hospital; private dental practice	IBD: 54(31/23), 43.1y Ctl: 54(31/23), 43.1y	Smoking: 13% IBD; 20% Ctl Diet : NR	CD: 28, UC: 26	CS: 3 UC, 6 CD; SASA: 26 UC, 18 CD; IMM: 8 UC, 16 CD; BIO: 3 UC, 2 CD	Risk of apical infection: OR 5.7, (95% CI:1.7–19.1, p = 0.0048)	NR

SASA: 5-aminosalicylate; AI: Apical infection; ATB: antibiotics; BIO/BM: biological medication; CD: Crohn's Disease; CS: corticosteroids; Ctl: Control; DMF-S: decayed missing filled surfaces; DMF-T: decayed missing filled teeth; IBD : Inflammatory Bowel Disease; IMM: immunosuppressant; NoTtt : no treatment; NR: Not reported; NRS : non-resective Surgery ; OR: Odds Ratio; RS : Resective Surgery ; UC : Ulcerative colitis patients ; y: years

Table 2. Studies reporting the biological rationale for the relationship between inflammatory bowel disease and caries.

Study	Design; Setting	Patients: N (M/F), mean age	smoking; dietary habits	IBD (disease phenotype; duration; activity)	IBD medication (drugs; duration)	Dental (microbial count; saliva)
Szymanska et al., 2014, Sweden	Case-control; Hospital; National Statistic Organisation	IBD: 150 (77/73), 47.5y Ctl: 75 (30/45), 48.6y	Smoking: 6% Ctl; 44% CD Diet: more sugar drinks in CD (p = 0.001)	CD : 150, 8–22y; (71RS et 79 NRS)	NR	<i>S mutans</i> : CD RS = 1.5 vs Ctl = 0.9 (p = 0.01); <i>Lactobacilli</i> : CD RS = 10,000 bact/mL vs Ctl = 1000 bact/mL (p = 0.011)
Rodrigues et al., 2019, Portugal	Cross-sectional; Hospital	IBD: 30(13/17), 55.1y	Smoking: 23.3% IBD; Diet: IBD eat more fresh fruit (70%), (p = 0.03)	UC: 30, 14.97y; 7(23.3%) active 23(76.7%) in remission	SASA : 13, CS: 2, IMM: 4, BIO:7, no Ttt: 4	↑ <i>S mutans</i> (73.3%), ↑ <i>Lactobacillus</i> sp (60%); ↑ <i>Sm</i> (88.9%) when longer disease duration (p = 0.58); Normal salivary flow
Halme et al., 1993, Finland	Descriptive study; Hospital	IBD: 53(29/24), 41.4y	Smoking: 37.73% CD	CD: 53, 8.8 y; (42 RS, 11 no RS) 37 active, 16 inactive	NR	Saliva flow and qualitative characteristics: n.s between active and inactive CD
Bevenius, 1988, Sweden	Pilot study; Association of Patients with GI Disease or referred by dental practitioners	IBD:15(2/13), 38y	no well-balanced diets; ↓ protein, fruit & vegetables; ↑ incidence of carbohydrates	12 y (1–28y); 11 pts ≥5y;	NR	↑ <i>Lactobacillus</i> and <i>S mutans</i> ; ↓ Resting saliva: 0.13 mL/min (normal 0.25–0.35); buffer capacity: 3.16 (4.25–4.75);
Sundh et al., 1989, Sweden	Case-control; Hospital	IBD:21(10/11), 44.5y	NR	NR	11 Codeine phosphate	n.s <i>cariogenic bacteria</i> normal saliva flow rate and buffer capacity

SASA: 5-aminosalicylate therapy; BIO: biological therapy; CD: Crohn's Disease; CS: corticosteroids; Ctl: Control; IBD : Inflammatory Bowel Disease; IMM: immunosuppressants; No Ttt : no treatment; NR: Not reported; NRS : non Resective Surgery; OR: Odds Ratio; RS : Resective Surgery ; UC : Ulcerative colitis patients.

control group and patients with IBD were matched for their smoking status [7] or this factor was controlled for in the multivariate analysis [6]. Among the remaining studies, Brito et al. observed that smoking was an effect modifier. There was no difference in the prevalence of periodontitis among non-smoking controls and nonsmoking patients with IBD, but the prevalence of periodontitis was greater among smokers with UC than those without [21]. In the study of Habashneh et al., patients with UC were more likely to be ex-smokers [23]. In the study of Vavricka et al., patients with CD who had smoked and those with clinical activity were at a higher risk for

periodontitis [27]. No study reported an increased risk of periodontitis for patients exposed to steroids.

3.3. Biological rationale for the relationship between IBD and periodontitis

There are currently two hypotheses to explain the association between IBD and periodontitis: (i) the infectious hypothesis, and (ii) the inflammatory hypothesis.

The role of the oral microbiota is the most studied pathway thus far. Several studies have highlighted significant

Table 3. Risk of periodontitis in patients with inflammatory bowel disease.

Study	Design; Setting	Patients (n; M/F; mean age)	Extras (smoking; dietary habits)	IBD (disease phenotype; duration; activity)	IBD medication (drugs; duration)	Perio (CAL, PPD, REC, BOP, OR et RR)	Oral hygiene
Zhang et al., 2020, China	Cross-		sectional; Hospital	IBD: 389(245/144), 34y; Ctl: 265(150/115), 26y	Smoking: 21% CD, 14% UC, 22% Ctl Diet: IBD consume less sugar than Ctl ($p \leq 0.001$)	CD: 265 ; <3y: 49.1% ; 3–9y: 39.6% ; >9y: 11.3% active :36.2% UC: 124; <3y: 49.2% ; 3–9y: 38.7% ; >9y: 12.1% active : 39.5%	No TTT: 6.4%CD, 3.2%UC, AMS: 9.8% CD, 54.8% UC; CS: 3.8%CD, 14.5%UC; IMM: 40%CD, 21.8%UC; BIO: 40%CD, 5.7% UC
IBD: ↑ risk of PD; OR = 4.54; no difference UC vs CD	Tooth		brushing <2times/d: 21.5% Ctl, 41.9% CD, 43.5% UC; ≥2times/d: 78.5% Ctl, 58.1% CD, 56.5% UC; Plaque index CD = 0.68; UC = 0.70; Ctl = 0.28 ($p < 0.001$) CD vs UC: no difference				
Grössner-Schreiber et al., 2006, Germany	Case-control;	Hospital; private dental practice	IBD: 62(24/38), 38.4y Ctl: 59(24/35), 38.2y	Smoking: 40% IBD; 41% Ctl Diet: 44% IBD eat smaller amount but more frequently	CD: 46 UC: 16 35% IBD were active	CS: 20; IMM:24; AMS: 39; BIO: 13, ATB: 12	Mean PPD: IBD = 2.08 mm vs Ctl = 2.23 mm, ($p = 0.014$), RR = 0.245; CAL ≥4 mm: 81% IBD vs 64% Ctl, ($p = 0.07$); CAL ≥5 mm: 63% IBD vs 46% Ctl, ($p = 0.07$), RR = 2.47
Dental plaque score IBD: 42.3%, Ctl: 29.9% (RR 1.027)							
Koutsochristou et al., 2015, Greece	Case-control;	Hospital; private dental practice	IBD: 55(25/30), 12.32y Ctl: 55(25/30), 12.21y	Smoking : excluded Diet : NR	CD: 36; 3.5y UC: 19; 4.4y	CS + AMS: 20; CS + IMM: 3; AMS + IMM 16; AMS + BIO: 5; IMM + BIO: 2.	Gingival bleeding: 36% IBD, 45% Ctl Healthy periodontium: 40% Ctl and no IBD
IBD vs Ctl: no difference Flemmig TF. Et al., 1991, USA CAL: 93.5% CD (1.4 mm), 95.1% UC (1.5 mm); PPD: 28.3% CD (2.4 mm), 29.5% UC(2.3 mm); ↑ PD Prevalence : 11.9% higher in IBD; ($p \leq 0.01$)	Cross-		sectional; Hospital	IBD:107(58/49), 40.5y	NR	CD: 46 UC: 61	NR
	Dental plaque score						
CD (0.5), 59% UC (0.4);							
Brito F. et al., 2008, Brazil	Case-control; Hospital	IBD: 179 (64/	115),41.15y Ctl: 74(24/50), 40.3y	Smoking: 12.1% CD, 8.7% UC, 12.2% Ctl Diet: NR	CD: 99; 72 months, 22 (22.2%) active; UC: 80; 72 months; 19 (23.7%) active	CD: 26, 21 IMM, 17 AMS +IMM; 8 AMS+CS, 9 IMM+CS, 9 AMS +IMM+CS, 7 anti-TNFα, 8 ATB, 4 no TTT; UC: 52 AMS, 4 IMM, 9 AMS+IMM, 9 AMS+CS, 2 IMM+CS, 4 AMS + IMM +CS, 3 anti-TNFα, 1 ATB	Higher prevalence of periodontitis in UC (90%, $p < 0.001$) and CD (81.8%, $p = 0.03$) vs Ctl (67.6%);

(Continued)

Table 3. (Continued).

NR							
Habashneh RA, 2012, Jordan	Case-control; Hospital	IBD: 160 (94/66), 39.4y; Ctl: 100 (62/38), 39.4y	Smoking: 52.5% CD, 16.8% UC, 49% Ctl; No sugar: 96.2% CD, 93.1% UC; IBD eat smaller amount (93.8% CD, 76.8% UC) but more frequently (91.7% CD, 76.5% UC)	CD: 59, UC: 101	NR	Risk of periodontitis: CD (OR = 4.9, 95% CI = 1.8–13.2), UC (OR = 795%, 95% CI = 2.8–17.5);	↓ Site with plaque: CD = 38.2% (less), p = 0.017
Yu et al., 2018, Taiwan	Retro-spective cohort; Registry	IBD: 27(17/10), 38y; Ctl: 108 (54/54), 36.3y	NR	CD: 7 UC: 20	NR	Risk of periodontitis: IBD (adj.HR:1.82), CD (adj.HR:3.95)	No brushing: 18.1% IBD, 24% Ctl;
Chi et al., 2018, Taiwan	Retro-spective cohort;		Database	IBD:6657 (3082/3575); Ctl: 26,628 (12,328/14,300)	NR	NR	5ASA, AZA, IMM, CS
Risk of periodontitis: CD (adj. HR:1.36)	NR						
Lin et al., 2018, Taiwan	Retro-spective cohort;		Database	PD: 27,041 (13,973/13,068); no PD: 108,149 (55,882/52,267)	With periodontitis: 16.2% without periodontitis: 11.1% Diet: NR	CD: 5220, UC: 192	NR
Risk of UC in presence of periodontitis: adj HR 1.56, p < 0.05	NR						
Vavricka et al., 2013, Switzerland	Case-control; Hospital	IBD: 113 (65/48), 40.6y Ctl: 113 (58/55), 39.4y	Smoking: 30.43% CD, 4.54% UC, 18.58% Ctl Diet: NR	CD : 69, 12.4 y UC : 44, 8.5 y	CD: 12 CS, 8 5ASA, 17 IMM, 36 BIO UC : 12 CS, 29 5ASA, 17 IMM, 9 BIO	Risk of periodontitis in IBD: (OR = 3.92);	Brushing/day: CD = 2.1, UC = 2.2, Ctl = 2.1; Flossing/w: CD = 1.5, UC = 2, Ctl = 2.8

5ASA: 5-Aminosalicylate Therapy; ATB: Antibiotics; BIO: Biological Treatment; BOP: Bleeding On Probing; CAL: Clinical Attachment Loss; CD: Crohn's Disease; CS: Corticosteroids Therapy; Ctl: Control; IBD : Inflammatory Bowel Disease; IMM: Immunosuppressant therapy; No Ttt : no Treatment; NR: Not Reported; OR: Odds Ratio; PD: Periodontal Disease; PPD: Periodontal Probing Depth; TNFα : Tumor Necrosis Factor alpha; UC : Ulcerative Colitis patients ;

differences between the composition of the oral microbiota of IBD patients and that of healthy controls but the cause and consequences of such differences in the oral ecosystem remain unclear. Van Dyke et al. were the first to report a high prevalence of “unusual bacteria,” representing more than 90% of the total flora and described as small motile rods, of the *Wollinella* genus, in the periodontal pockets of IBD patients relative to those of non-IBD patients. They also observed an impaired response of polymorphonucleocytes (PMNs) against these bacteria species [28]. Two other studies, one in adults and one in pediatric (2–21 years) patients, confirmed the differences in the composition of the sub-gingival flora between IBD and non-IBD patients. The bacterial species found were, however, highly variable, depending on the study [22,29]. Similar results were found in saliva and lingual biofilm samples [30,31]. Strauss et al. investigated the potential role of oral bacteria on the intestinal status. They observed an elevated prevalence of *Fusobacterium nucleatum* (Fn), a periodontal pathogen, in colon biopsies of IBD patients. The Fn

strains identified in biopsy of inflamed tissue were more invasive than those isolated from healthy tissue from either IBD or control patients [32].

On the other hand, few studies have studied cytokines in the serum, gums, or intestinal tissue of IBD patients and control subjects. The cytokine profile in crevicular fluid of IBD patients and healthy controls with similar periodontal clinical parameters were shown to be broadly similar, except for IL-4 levels, which were higher in the healthy subjects [33]. The same authors observed significant differences in cytokine clustering patterns in the gums and intestinal biopsies of IBD patients [34]. They showed a correlation between inflammation scores in the gut and those in gingival tissue, calculated from the mean levels of pro-inflammatory cytokines in the respective tissues, and suggested that IBD activity influences cytokine expression in gingival tissue. Another study observed that the severity of periodontitis was associated with MMP8 levels in CD patients, whereas it was not in UC or healthy patients [35].

Table 4. Studies reporting the biological rationale for the relationship between inflammatory bowel disease and periodontitis.

Study	Design; Setting	Patients: n, (M/F); mean age	Smoking; dietary habits	IBD (disease phenotype; duration; activity)	IBD medication (drugs; duration)	Perio (microbial count, inflammation biomarkers)
Brito et al. 2013, Brazil	Cross-sectional; Hospital	IBD: 30(15/15), 42.25y Ctl: 15(7/8), 42.1y	Smoking: 21.4% CD; 6.7% UC 6.7% Ctl	CD: 15; 98.5 m UC: 15; 94.4 m active UC: 3	NR	↑ bacterial count in IBD vs Ctl ↑ bacterial count in CD vs UC
Van Dyke et al. 1986, USA	Case-control; Hospital	IBD: 20 ; Ctl: 8	NR	NA/NR	CS: 50%	↑ <i>Wolinella</i> strains in IBD ↓ neutrophil chemotaxis
Kelsen et al. 2015, USA	Prospective cohort; Hospital	Discovery cohort : 35 CD, 46 Ctl; 13 yrs; Validation cohort : 44 CD, 31 Ctl, 13 yrs	NR	Discovery cohort 79 CD; 1 m – 6 y Validation cohort 1 week –6 months;	5ASA, IMM, CS, BIO, ATB	Oral bacteria count: ↑ <i>Capnocytophaga</i> (p = 0.001), <i>Rothia</i> (p = 0.001), <i>Saccharibacteria</i> (p = 0.004) in CD without ATB
Said et al. 2014, Japan	Case-control; Hospital	IBD:35 ; Ctl: 24	NR	21 CD, 14 UC	NR	Oral bacteria count: IBD : ↑Bacteroidetes, ↓ Proteobacteria Biomarkers of inflammation in saliva: ↑ LL37, IL-1b, IgA, ↓ lysozyme in IBD vs Ctl (p < 0.01)
Docktor et al. 2012, USA	Case-control; Hospital	IBD: 71(43/28), 14y Ctl: 43(19/24), 14y	NR	CD: 40 (23% active) UC: 31 (45% active)	IMM: 75%CD, 39%UC	CD: ↓ microbial diversity in CD (p = 0.015), ↓ <i>Fusobacteria</i> (p < 0.0002), <i>Firmicutes</i> (p = 0.022), ↑ <i>Spirochetes</i> (p = 0.006), <i>Synergist</i> . (p = 0.009), <i>Bacteroidetes</i> (p = 0.03); UC: ns
Strauss et al. 2011, Canada	Case-control; Hospital	IBD: 22(6/16), 41.5y Ctl: 34(17/17), 55y <i>Fusobacterium spp</i> : 63% IBD, 26.5% Ctl (p = 0.01)	NR	17 CD, 4 UC, 1	indeterminate colitis	NR
Figueredo et al., 2011, Brazil	Case-control; Hospital	IBD:30(15/15), 41.6y Ctl: 15(7/8), 42.1y	Smoking: 20% CD, 6.66% UC, 13.33% Ctl	CD: 15 (5 active), 7.7y UC : 15 (3active), 7.8y	No Ttt: 2 CD IMM: 7 CD, 1UC; 5ASA: 4 CD, 9UC; IMM+5ASA: 2 CD, 5UC	GCF of IBD vs Ctl: ↓ IL-4 (p = 0.046) Serum of IBD vs Ctl: ↑ IL-18 (p = 0.018); IBD: correlation between IL-6 in GCF and IFN γ in serum (r = 0.948, p < 0.001); UC: correlation between IL-1b in GCF and IL-18 in serum (r = 0.636, p = 0.01)
Figueredo et al., 2017, Brazil	Cross-sectional; Hospital	IBD: 21 (4/17), 40.52y	NR	10 CD, 11 UC 8 active IBD	5ASA: 7, 5ASA+IMM: 8 5ASA+IMM+BIO: 4 5ASA +CS: 2	Intestinal biopsy: ↓ IL-31, TNF α ; gingival biopsy: ↑ IL-23, IFN γ , IL-4, IL-10, IL-21, correlation between gingival/intestinal inflamm. score (r = 0.548; p = 0.01); Smoking: 46.66% CD, 33.89%
Schmidt et al., 2018, Germany	CD: 30 (15 active), 13 ± 10y UC: 29 (3 active), 5.08 ± 2.53 y 5ASA + IMM: 14%; 5ASA +BIO: 5%; IMM +BIO: 3%; CS +BIO: 5%; CS +5ASA: 2%; CS +IMM: 2%; IMM: 25%	IBD vs Ctl: ↓ <i>E nodatum</i> (6%), <i>E corrodens</i> (19%) (p = 0.01); ↑ MMP-8: 28.2 ±18.2 ng/mL (p < 0.01) CD vs UC: ↑ <i>E corrodens</i> (33%) (p = 0.04);	Cross-sectional; Hospital	IBD: 59(25/34), 49.8y Ctl: 59(25/34), 51.3y		

5ASA: aminosalicilate ; ATB: antibiotics; BIO: biologics; CD: Crohn's Disease; CS: corticosteroids; Ctl: Control; GCF: Gingival crevicular fluid; IBD : Inflammatory Bowel Disease; IFN γ : Interferon gamma ; IgA : Immunoglobulin A ; IL- : Interleukin ; IMM: immunosuppressants ; LL37: cathelicidin; MMP-8 : matrix metalloproteinase 8; no Ttt : no treatment; NR: Not reported; OR: Odds Ratio; TNF α : Tumor necrosis factor alpha; UC : Ulcerative colitis

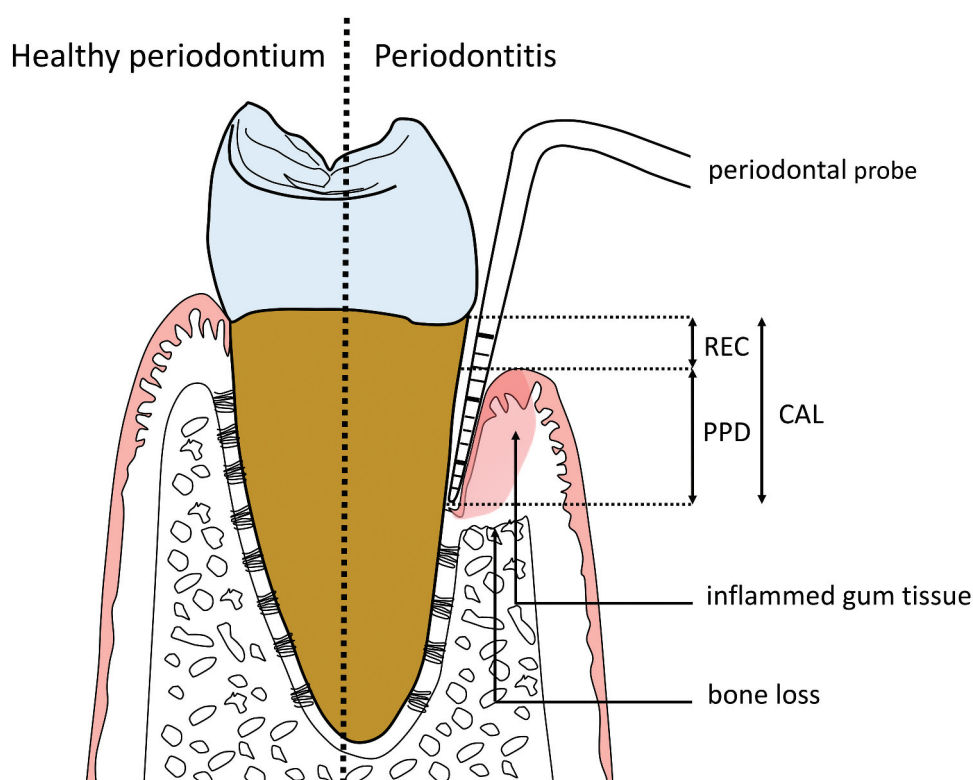


Figure 2. Periodontitis.

In addition, a possible role of shared genetic variants in the link between IBD and periodontitis has been investigated in a handful of studies [36–38]. The results were, however, inconclusive, probably due to the multifactorial origin of these pathologies and the large number of genes potentially involved. Only one study suggested that the TNF- α A allele of rs361525 may be a risk factor for oral lesions in CD patients and associated with more severe periodontitis [38].

3.4. Association between IBD medications and periodontal status

There is little reliable data available concerning the link between IBD medications and periodontal conditions. However, certain conclusions can be extrapolated from studies conducted on other autoimmune diseases, in particular chronic inflammatory rheumatic diseases, in which similar medications are used.

3.4.1 Impact of medication on dental and periodontal outcomes in patients receiving immunosuppressants or biologics

3.4.0.1. Periodontal outcomes. Overall, studies in patients with rheumatoid arthritis (RA) have consistently reported a protective effect of anti TNF- α on periodontal disease. In a cross-sectional study, Mayer et al. compared the periodontal status of 20 RA patients (10 infliximab-treated, 10 biologic-free) to 10 healthy controls. Although oral hygiene and smoking status were comparable among the three groups, RA patients treated with anti-TNF- α had less severe periodontal disease and lower levels of TNF- α in their gingival crevicular

fluid, suggesting that TNF- α blockers may prevent the periodontal destruction process [42]. Other studies have reported similar benefits of anti-TNFs on periodontal clinical indices, alveolar bone resorption, and the level of inflammatory biomarkers in patients with RA and ankylosing spondylitis [42–46]. In one study, however, infliximab appeared to aggravate gingival inflammation, whereas a protective effect on periodontal tissue breakdown was maintained, as indicated by lower loss of attachment after infliximab treatment [43]. Kobayashi et al. compared serum protein profiles before and after treatment with adalimumab [44] in 20 patients with RA. Among a total of 495 proteins, nine were significantly lower in abundance at three months, although dental plaque levels were comparable, corresponding to five proteins: complement factor H, phospholipase D, serum amyloid A, complement component 4, and alpha-1-acid glycoprotein. The authors concluded that the improvement in periodontal conditions may be related to differences in serum protein profiles before and after anti-TNF treatment. It has also been suggested that conventional synthetic DMARDs (csDMARDs), including methotrexate and sulfasalazine, may influence the response to periodontal therapy in RA patients. Four weeks after non-surgical treatment of periodontitis, a greater improvement in periodontal clinical parameters (reduction in probing depth and gain in clinical attachment) was observed for patients receiving csDMARDs [47]. The effect of immune-mediated inflammatory disease (IMIDs) on the composition of the oral microbiota was studied in patients with ankylosing spondylitis. Higher numbers of staphylococci were found in ankylosing spondylitis patients, regardless of age, sex, or oral condition,

than in healthy controls, independently of their treatment [48]. On the other hand, no studies have evaluated the risk of periodontal care complications in IBD patients treated with immunosuppressants or biologics.

3.4.0.2. Dental outcomes and peri-apical lesions. We found no evidence of an effect of immunosuppressants or biologics treatment on the risk of carious diseases. However, a prospective 24-month follow-up study of 33 patients with IBD, including 19 on anti-TNF, with 44 teeth affected by apical lesions suggested that treatment of apical dental lesions with conventional root canal therapy is possible for patients with IBD without any complications. Furthermore, anti-TNF- α was associated with faster radiological healing of apical lesions than in controls [39]. On the other hand, no studies have evaluated the risk of dental care complications in IBD patients treated with immunosuppressants or biologics.

3.4.1. Can dental or periodontal outcomes influence IBD course?

The belief that infectious oral diseases may in turn influence systemic diseases is not new. The best arguments in support of this theory come from pivotal clinical studies that showed the positive effect of periodontal treatment on glycemic control in patients with diabetes [49], endothelial function [50], or RA activity [51]. Similarly, it has been speculated that untreated periodontitis may contribute to an altered response to IMIDs therapy. Groselj et al. attempted to predict the clinical response of 14 active CD patients to infliximab based on dental, periodontal, and oral mucosa parameters. The authors fit a multivariate model based on eight selected oral parameters. The resulting model was acceptable for predicting the response to anti-TNF treatment at eight weeks but not at three months [52]. Savioli et al. prospectively evaluated the effect and evolution of the periodontal status of 18 patients with RA who received first-line anti-TNF therapy. At six months, the RA outcomes improved only for patients without periodontitis at baseline and those with untreated periodontitis showed no response to the anti-TNFs, as indicated by no significant changes in disease-activity parameters (DAS28, ESR, and CRP) [53]. In a retrospective nationwide population-based RA cohort, patients with a diagnosis of periodontitis within five years had a significantly increased risk of etanercept failure [54].

3.5. Summary of evidence

IBD patients have an increased risk of developing periodontitis due to modifications of their oral microbiota and common inflammatory processes. Differences in the risk among patients with CD or UC are yet to be clarified. The results are similar for the risk of caries and apical infections, which generally concern complications of deep caries, but the level of evidence is lower. The underlying mechanisms are unclear but may be related to common risk factors and pathophysiological mechanisms, as well as to the level of oral hygiene and dietary habits, for which current data are conflicting.

Few studies have evaluated the effect of the oral condition and treatment on IBD. Evidence is very limited for IBD but

some evidence from other IMIDs, particularly RA, suggests that periodontitis, especially untreated periodontitis, may be associated with a lower response to anti-TNF therapy, although the underlying mechanisms are still unknown.

Finally, one important question for clinical practice remains: is dental and periodontal treatment associated with an increased risk of complications for IBD patients? According to the American Academy of Oral Medicine (AAOM), the risks associated with dental care involve: (i) patient-based considerations (potential for bleeding, infections, poor wound healing, airway obstruction, medical-emergencies, and behavioral, cognitive, or emotional issues) and (ii) treatment-based considerations (use of drugs and drug-interactions or adverse effects and invasiveness and duration of dental procedures) [55]. There is no reliable evidence that IBD patients may be at greater risk of complications during routine dental care than the general population. NSAIDs frequently prescribed by dentists as analgesics should be avoided by IBD patients, especially those on methotrexate [56,57]. There is also a general acceptance that patients on steroids and other immunosuppressive therapies have an increased risk of infections [58–64] but there is no clear evidence to support an increased incidence of complications associated with dental care.

This review provides some important key points for oral care in IBD patients. As periodontitis and dental caries and subsequent infections lead to low-grade inflammation and bacterial challenge, patients should be treated whenever they require care. It is accepted that oral infections and/or treatments induce transient bacteremia that may increase the risk of adverse systemic complications, especially for patients with immune deficiencies. The incidence of transient bacteremia can vary from 10 to 100%, depending on the patient and the procedure [65]. It can also occur apart from dental care during routine activities (tooth brushing, chewing, or flossing), especially for patients with poor oral health [66–68], which emphasizes the importance of preventive measures (good oral hygiene and regular dental follow-up). Two types of oral care are commonly distinguished according to the associated risk of bacteremia. Dental treatments that involve injury to the mucosal tissues or periapical region that cause significant bleeding present a high risk of bacteremia and are called “invasive dental procedures”, such as (i) tooth extractions, (ii) periodontal procedures, including surgery, scaling, root planing, and probing, (iii) endodontic instrumentation or surgery beyond the tooth apex, (iv) dental implant surgical procedures, and (v) tooth reimplantation [69,70]. Other types of treatment are considered to be “non-invasive dental procedures.” It is commonly accepted that antibiotic prophylaxis may be considered for “invasive dental procedures” for immunocompromised patients because of their illness or treatment [70]. The recommended protocols vary widely and there is little scientific evidence to support any of them. Indeed, the results of studies reporting the potential benefit of antibiotic prophylaxis to control or prevent bacteremia after dental procedures are conflicting [71,72]. Overall, the benefit of antibiotic prophylaxis to prevent adverse systemic or local post-operative complications after dental treatments for immune-compromised patients remains uncertain.

3.6. Summary of current guidelines for dental management of IBD patients

There is no consensus and there are no guidelines on the dental management of IBD patients. There are, instead, fragmentary recommendations from national scientific societies [73–80], largely based on expert opinion, on what to do for dental care when using various biotherapies. They focus on three issues: (i) preventive measures, (ii) prophylactic antibiotic therapy, and (iii) interruption of drug therapy for the purpose of invasive dental procedures.

- (i) Preventive measures: Preventive strategies, including oral hygiene (toothbrushing 2 to 3 times per day and interdental cleaning once a day), a non-cariogenic diet, the use of fluoridated topicals, and regular oral follow-up, with regular scaling (2/year) are still the best way to reduce the risk of oral infections, both for immunocompetent and immunodeficient patients.
- (ii) Antibiotic prophylaxis: Overall, the recommended measures are based on the usual guidelines for antibiotic prophylaxis in dentistry. Thus, antibiotic prophylaxis may be considered prior to invasive

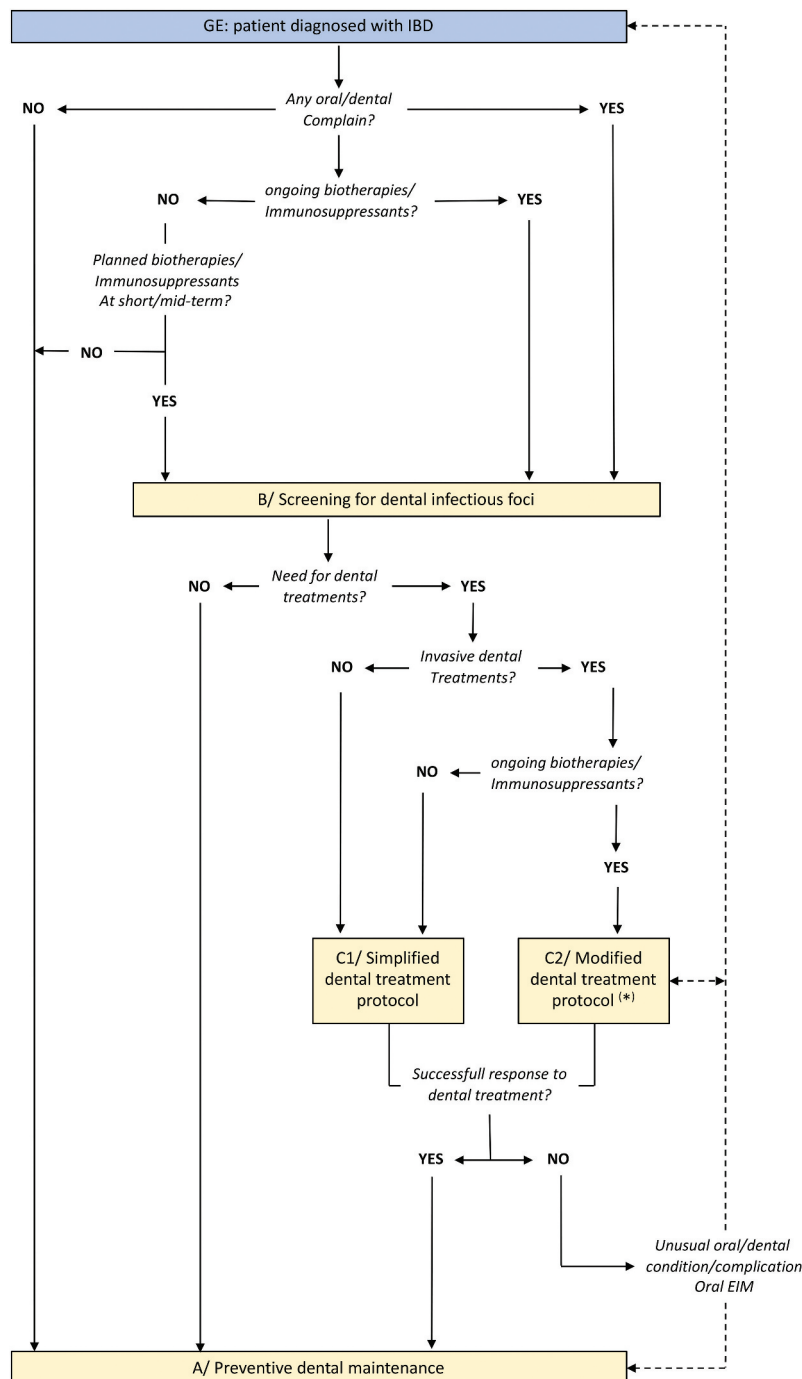


Figure 3. Algorithm for dental care for patients with inflammatory bowel disease.

dental treatment for a patient with immune deficiencies related to his/her condition or treatment. The decision should be made in collaboration between the dentist/periodontist and the prescribing physician.

- (iii) Interruption of treatment: There are varying conflicting recommendations concerning the relevance of a therapeutic window for immunosuppressants and biologics to limit the risk of post-surgical infection. Some recommendations advocate a two to four-week interruption that can be extended according to the infectious risk level of the surgery [80]. Others recommend stopping for a period equal to three to five half-lives of the molecule [79]. In 2004, the British Society of Rheumatology proposed to discontinue anti-TNF α , without a distinction between products, two to four weeks before any “major” surgery and to resume treatment after healing, in the absence of signs of infection [74]. In a more recent update, it was proposed to modulate the need for discontinuation and its duration according to the type of surgery and the risk of disease rebound, but to discontinue anti-TNF α within three to five times the half-life of the molecule for surgeries with a significant risk of infection [78]. No specific recommendations are currently available worldwide for IBD. The recent ECCO guidelines state that current evidence suggests that preoperative treatment with anti-TNF therapy, vedolizumab, or ustekinumab does not increase the risk of post-operative complications in patients with CD who undergo abdominal surgery. Cessation of these medications prior to surgery is not mandatory [81]. It is not known how these recommendations would apply to dental care. A certain degree of coordination between the prescribing physician of the biologic and the treating dentist is essential to define the most appropriate action.

4. Expert Opinion: proposal for a practical guide for dental management of IBD patients

On the basis of scientific data and current recommendations the following practical guidelines can be proposed for the dental management of IBD patients (Figure 3):

- Patients diagnosed with IBD should be referred to a dentist for the detection of potential dental infectious foci (screening for dental infectious foci), periodontal assessment, and regular follow-up (preventive dental maintenance).
- Eradication of infectious foci and periodontal treatment must be carried out prior to the implementation of immunosuppressants and biologics to prevent a potential over-risk of infection. In addition, there is low-level evidence to suggest that untreated oral infections may alter the response to immunosuppressants and biologics [53,54].
- A modified dental treatment protocol may be considered for invasive dental procedures for patients on immunosuppressants and biologics that includes antibiotic prophylaxis (Table 5), along with a discussion with the GE on the appropriateness of a therapeutic window for the biological medication. It could also be adjusted depending on the nature of the procedure (ex: root planing versus an isolated extraction versus a multiple extraction), the existence/severity of gingival inflammation, and the existence/severity of an associated infection (e.g. abscesses, etc.) and prevented by oral rinsing with a recommended antiseptic (e.g. chlorhexidine) before each invasive procedure. Noninvasive dental treatments do not require a modified dental treatment protocol (simplified dental treatment protocol). Urgent dental care should not be postponed because of immunosuppressive or biological therapy.
- In cases of an unusual dental condition, complication, or dental treatment outcome, the potential diagnosis of

Table 5. Dental procedures considered for antibiotic prophylaxis (adapted from dajani et al [69]. and Tong&Rothwell[7])

DENTAL PROCEDURES CONSIDERED FOR ANTIBIOTIC PROPHYLAXIS IN SUSCEPTIBLE PATIENTS

“Invasive” dental treatments

Antibiotic prophylaxis could be considered

- Dental extractions
- Periodontal procedures including surgery scaling, root planing and probing
- Peri implantitis treatment + bone regeneration (before implant surgery or during peri implantitis treatment)
 - Dental implant placement, reimplantation of teeth
 - Root canal therapy or surgery beyond the tooth apex
 - Intraligamentary local anesthetic injection
 - Prophylactic cleaning of teeth or implants with anticipated bleeding

“Non-Invasive” dental treatments

Antibiotic prophylaxis is not required

- Restorative dental procedures with or without retraction cord
- Local anesthetic injection (except for intra-ligamentary)
- Intracanal endodontic procedures, post-placement and build up
- Placement of rubber dam
- Post operative suture removal
- Placement of removable orthodontic or prosthodontic appliances
- Taking oral impressions
- Fluoride treatments
- Taking oral radiographs
- Orthodontic appliance adjustment
- Shedding of primary teeth

extra-intestinal manifestations should be sought in coordination with the referring GE.

Declaration of interest

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