Gastrointestinal diseases and their oro-dental manifestations: Part 2: Ulcerative colitis

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In brief

- A limited number of studies reported widely varying prevalence rates of oral signs and symptoms in patients with ulcerative colitis.
- The most pathognomonic oral sign is pyostomatitis vegetans, but also other abnormalities as oral ulcerations, caries and periodontitis are more frequently observed in patients with ulcerative colitis.
- Patients with ulcerative colitis need special attention from dental clinicians.

Ulcerative colitis is a rather common inflammatory bowel disease, especially in the industrialised world. A limited number of studies have reported the prevalence of oral signs and symptoms in these patients, and widely varying prevalence rates have been reported ranging from 2 to 34%. Pyostomatitis vegetans is the most pathognomonic oral sign but also other abnormalities as oral ulcerations, caries and periodontitis are more often seen in patients with ulcerative colitis. In this review we describe the oral manifestations of ulcerative colitis and their potential dental implications.

Introduction

Ulcerative colitis (UC) was first described by Sir Samuel Wilks in 1859[1] and is characterised by diffuse mucosal inflammation of the colon.[2] The rectum is always involved but the colitis may extend proximally in a contiguous pattern up to the entire colon (pancolitis).[2–5] Histological findings include inflammation limited to the mucosal layers with varying degrees of infiltration by plasma cells, lymphocytes and granulocytes.[4] Active disease is characterised by ulcerations, loss of goblet cells and crypt abscesses[6] (Fig. 1). Distortion of the crypt architecture with shortening and disarray of the crypts, crypt branching, atrophy and Paneth cell metaplasia is indicative of a chronic inflammatory process.[7,8]

The clinical presentation varies in severity but typically includes abdominal pain, intermittent bloody diarrhoea and painful defecation. The symptoms are also dependent on the localisation and extension of disease. Children with UC may have a reduced linear growth and a delayed pubertal development. Therefore, full assessment of children presenting with potential UC is essential for early identification of the disease, to optimise short and long term outcomes.[4] Patients with UC have an increased risk to develop colorectal cancer. The extent and duration of UC, presence of concomitant primary sclerosing cholangitis and family members with colorectal cancer are the important risk factors for the development of colonic dysplasia and subsequent cancer.[6,9]

Although UC primarily involves the bowel, it may be associated with extra intestinal manifestations (EIM). The most common EIMs involve the skin, eyes, joint and liver[5] and tend to follow the clinical course of the colitis. Less than 10% of the patients have EIMs at the initial presentation

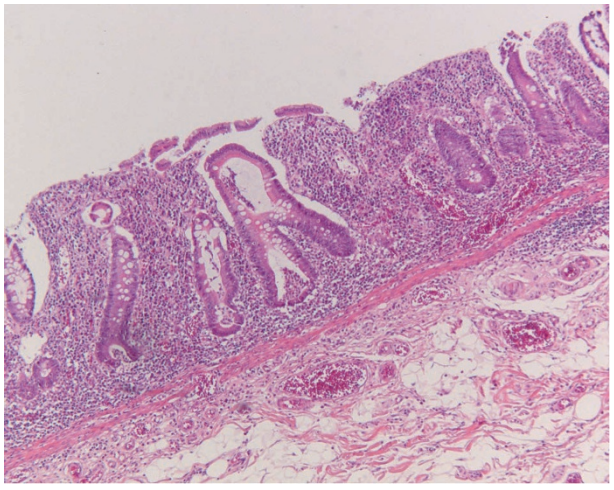

Fig. 1 Histologic slide of the colon mucosa during active disease shows typical crypt abscesses and crypt irregularities. The inflammation is limited to the mucosa, the submucosa is not involved. H&E staining (original magnification 100×) courtesy of A. Neefjes-Borst, department of Pathology, VU Medical Centre, Amsterdam, The Netherlands

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of UC, but approximately 25% of the patients will develop an EIM in their lifetime.[10]

The diagnosis of UC is made on the typical clinical symptoms combined with endoscopic and histologic evidence.[5] Colonoscopy with biopsies is currently the diagnostic gold standard. Characteristic observations during endoscopy are exudates, ulcerations, loss of the typical vascular pattern, friability, and granularity in a continuous, circumferential pattern[2,11] (Figs 2–4). Superficial inflammation associated with loss of haustration suggests UC, whereas non-continuous patches of inflammation would support Crohn's disease.[12] Particularly in the early stage of the disease, differentiating UC from CD can be challenging, but it is important as appropriate treatments and potential complications vary for these two diseases[2] (for a review of Crohn's disease and its oro-dental manifestations, see Tan *et al.*, *Br Dent J* 2016; **221** [12] – part 1 in this series).

Epidemiology

Ulcerative colitis is rather common in the developed countries of the world, particularly in North America and Western Europe, with an overall incidence of 10.4 per 100,000 persons in Europe.[13] Several studies have shown that the incidence is decreasing from North to South and that the incidence values in high incidence areas are increasing.[14]

Aetiology

The pathogenesis of UC is still not completely resolved. The most accepted hypothesis is that a dysregulated interaction between the mucosal immunology in the intestinal microflora leads to inflammation in a genetically predisposed host. Many studies have focused on the intestinal flora, without clear evidence for a specific pathogen. A considerable number of genes have been associated with UC. Most of these genes control the epithelial barrier function or the (innate) host defence.[4,15]

A positive family history is the largest independent risk factor for UC. People with UC with a first-degree relative have a 10-15-fold risk of developing the disease.[16] UC is more common in patients of Jewish origin and less frequently observed in Afro-Americans or Hispanics.[5,17,18] The strongest evidence of genetic factors contributing to susceptibility to UC comes from concordance studies in twins. The concordance for UC was 10% for monozygotic twins compared to 3% for dizygotic twins.[19,20]

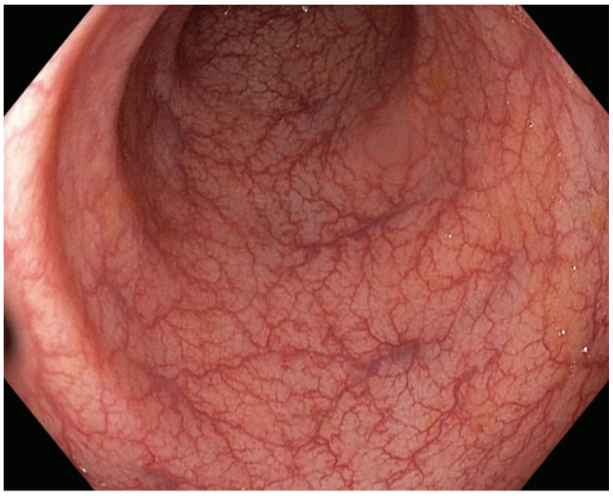

Fig. 2 Endoscopy of normal colon mucosa

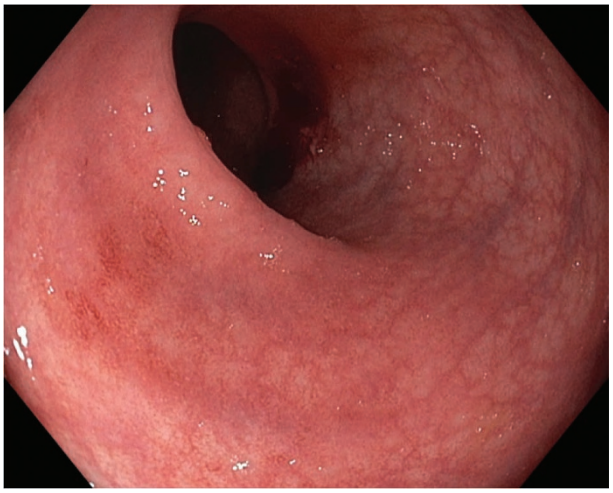

Fig. 3 Endoscopy shows loss of normal vascular pattern and erythematous colon mucosa in a mild case of UC

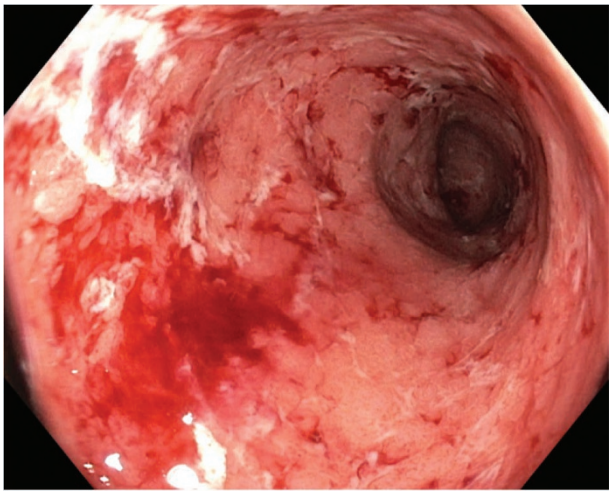

Fig. 4 Endoscopy of colon mucosa with ulceration and spontaneous bleeding in a severe case of UC

The higher incidence and prevalence rates of UC in the industrialised world suggest that environmental factors could also play a role in the aetiology.[21] This suggestion is supported by the observation that incidence rates increase when people migrate from low incidence regions to more developed countries, and the correlation of the incidence rates with the level of industrialisation in Hong Kong and mainland of China.[22] It is also supported by a study in Europe that shows a west-east gradient of UC.[23]

Smoking cigarettes is a protective factor against developing UC, as smokers have approximately 40% lower risk of UC than non-smokers.[24–26] However, compared with those who never smoked, former smokers are approximately 70% times more likely to develop the disease, which is often more extensive and refractory than those who have never smoked.[27,28] The beneficial effects of nicotine in UC are due to increased mucus production, decreased production of pro-inflammatory cytokines and nitric oxide and improvement of intestinal barrier function.[29] A study among 205 patients showed a protective effect in patients smoking fewer than ten cigarettes/day and the effect disappeared in patients smoking more than 20 cigarettes/day.[24] Appendectomy performed for appendicitis at an early age might also be protective against UC.[30–32]

Treatment

Ulcerative colitis is currently not curable. Therefore, the primary aims of therapy are to induce and maintain clinical remission, decrease the risk of complications and improve quality of life.[5,33] Important additional aims in children with UC include optimisation of nutrition and growth. Ensuring that the child is able to resume normal psychological development is important.[4]

The initial treatment of UC is based upon the severity and extent of the disease. The first line therapy in mild to moderate disease activity is administration of 5-aminosalicylic acid (5-ASA), which can be given orally or locally by suppository or enema.[34] For patients who do not respond or cannot tolerate 5-ASA, oral steroid therapy should be considered.[35] Patients with severe disease activity should be treated directly with oral steroids in combination with a high oral dose of 5-ASA. Antibiotics are recommended in patients with signs of systemic toxicity, such as high grade fever, inflammation of the peritoneum and megacolon.[36] Patients who fail to improve with this intensive treatment should be treated with induction therapy with anti-TNF or cyclosporine.[37,38] The treatment options for maintenance of remission in UC include 5-ASA derivatives, thiopurine compounds (azathioprine or mercaptopurine) or biologicals (including infliximab, adalimumab, golimumab and vedolizumab).[39–43]

Approximately 9% of the UC patients will eventually require surgical treatment.[44] Surgical treatment is indicated in UC patients who fail medical therapy or who develop acute severe colitis or cancer.[45] As previously described, longstanding UC is associated with an increased risk of developing colorectal cancer. Therefore, in UC patients screening (chromo) colonoscopies should be initiated several years after the onset of the disease.

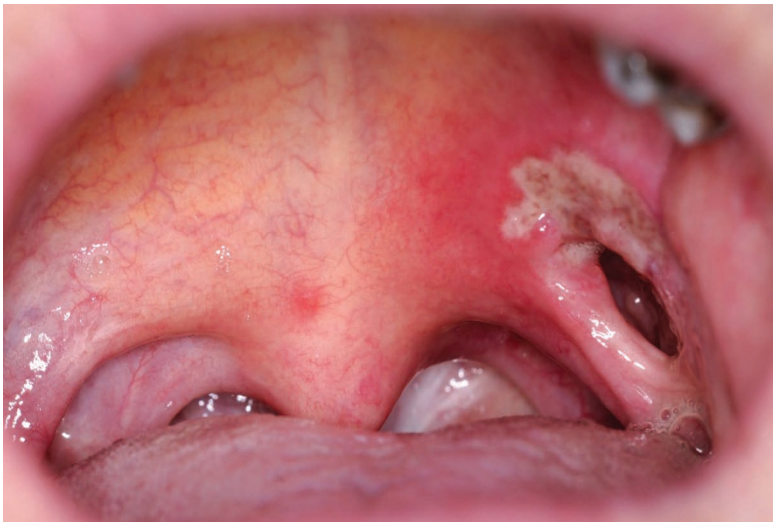

Fig. 5 Pyostomatitis vegetans (courtesy of Dr J. R. Mekkes, department of dermatology, Academic Medical Centre, Amsterdam, the Netherlands)

Oral signs and symptoms

Epidemiology

A limited number of studies have reported the prevalence of oral signs and symptoms in adult patients with UC. In a group of 50 patients who had an oral examination and completed an oral health questionnaire, 2 to 34% of the patients had oral signs and symptoms compared to 2 to 10% in a control group.[46] Another study found oral lesions in 32% of 121 patients with UC compared to 24% in the control group.[47]

Ulcerative colitis is associated with a variety of oral signs and symptoms. Oral signs include pyostomatitis vegetans, aphthous ulcerations, tongue coating, gingivitis and periodontitis while symptoms include halitosis, acidic taste and taste change, which also may be related to use of medication. The oral manifestations seem related to the severity of UC. Severe UC is associated with a higher prevalence of oral ulceration, tongue coating and halitosis.[46] In patients with active UC, a prevalence up to 50% was found for halitosis.[48]

Pyostomatitis vegetans

Pyostomatitis vegetans (PV) was first described in 1949.[49] The lesions are relatively rare but they are consistently associated with inflammatory bowel disease (IBD) and more frequently associated with UC than with Crohn's disease.[50,51] The oral lesions are benign and consist of multiple small white and yellow pustules on an erythematous and oedematous mucosal background. The pustules can rupture and fusion of the ruptured pustules can lead to a scattered, clumped or typical 'snail-track' appearance (Fig. 5).[52–60] Histological features are intraepithelial and subepithelial microabscesses with large numbers of eosinophils and neutrophils. Hyperkeratosis and acanthosis can also be present.[50,53,59,61]

Patients may experience severe oral discomfort, which is not related to clinical activity of UC, but PV lesions may also be painless.[52,61] There is a predilection for males with a male:female ratio of nearly 3:1. The lesions can occur at any age but are more prevalent between 20 and 59 years old with an average age of 34 years.[53,60,62]

Pyostomatitis vegetans can involve almost any part of the oral cavity but are most frequently observed on the labial attached gingiva, soft and hard palate, buccal mucosa and vestibular gingivae. The least affected locations are the floor of the mouth and the tongue.[52,53,58,61,62]

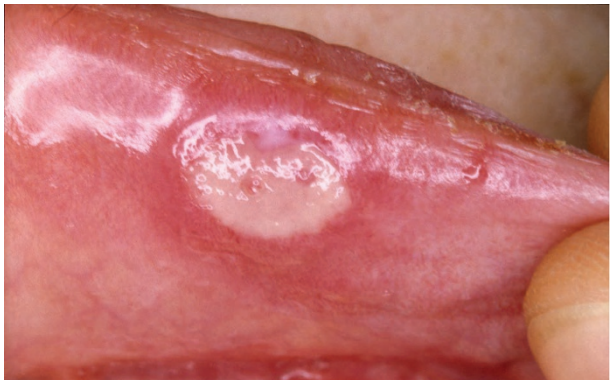

Fig. 6 Ulcer located at the lower lip

The intestinal symptoms usually precede oral PV by several months or years.[50,63]

Oral ulceration

Oral ulceration is the most common oral sign of UC.[46,64,65] These ulcers can present simultaneously with flare-ups of intestinal disease but can also present without intestinal disease activity.[66] The ulcers can be painful and cause discomfort. They usually heal within a couple of weeks, but new ulcers may develop resulting in a prolonged period of ulceration (Fig. 6).[52]

Caries

To our knowledge, only one study investigated the correlation of caries and UC specifically. UC patients had a significantly higher mean Decayed-Missing-Filled-Teeth (DMFT) index compared to controls (15.3 *versus* 12.1).[67] Other investigators have studied the correlation of caries and IBD and found that patients with IBD have a significantly higher prevalence of dentine caries compared to controls with an odds ratio of 2.37. They also found that the plaque scores in the IBD group were significantly higher due to altered dietary habits and assume this to be the reason for the higher prevalence of dentine caries.[68]

Periodontitis

A study of 80 UC patients observed significantly more frequently periodontitis, deeper pocket depths and fewer teeth in patients with UC compared to controls. Periodontitis was also more common among smoking UC patients compared to smoking controls. Furthermore, UC patients had more clinical attachment loss ≥3 mm compared to CD patients, although there was no statistical difference in dental plaque scores. This finding may indicate that the response to dental plaque may differ between the two subtypes of IBD.[67,69] Another case control study with 101 UC patients also showed a much higher prevalence of periodontitis among UC patients compared to controls for the age group <45 years with an odds ratio of 7.00. The severity of the periodontitis, measured by average pocket depth and average clinical attachment loss, was also significantly greater among UC patients compared to CD patients and controls.[69] This is in contrast with the study of Grössner-Schreiber who found that IBD subjects had more generalised but less severe periodontal disease than the general population.[68]

Other oral observations

Several studies show that halitosis is more frequent in UC patients compared to controls.[46,48] Regurgitation is also significantly more prevalent in UC patients compared to controls.[48] In a study of 50 UC patients, 20% reported a change in taste. Acidic taste and taste change were more commonly reported by patients suffering from pancolitis[46].

Dental management

Patients with UC have an increased risk of several oral problems. The causes are multifactorial, with the patient's altered immune status and medication as important factors. Preventive dental care of these patients with frequent dental check-ups, strict oral hygiene and the use of fluoride treatment seems recommended.[46,68]

The most important step in the treatment of the oral signs and symptoms is intestinal disease control.[64,66] Specific treatment of the oral signs and symptoms is usually not necessary, but can be indicated when the patient suffers from severe oral discomfort. Pyostomatitis vegetans can be treated with topical corticosteroids but this treatment is not always successful and usually systemic treatment is required. Successful use of azathioprine, dapsone, cyclosporine and adalimumab have been described in case reports.[50,53,60,63] The pain from aphthous ulcerations can be relieved with 2% viscous lidocaine. Use of a corticosteroid gel or mouthwash one to three times per day may stimulate healing of the ulcerations.[63]

The use of immunosuppressants for the treatment of UC is associated with a reduced number of white blood cells in approximately 5% of the patients, which subsequently may increase the risk of oral infections, like candida overgrowth. Prescribing non-steroidal anti-inflammatory drugs (NSAID) should be avoided, when possible, in patients with UC as they may trigger a flare-up of the gastrointestinal symptoms. Paracetamol can be used as an alternative for pain control.[70]

Conclusion

Patients with ulcerative colitis may develop oral health problems. Dental clinicians need to be aware of these problems to provide personalised dental care with special attention for prevention. In complex cases, special teams consisting of dedicated dental clinicians and gastroenterologist are to be consulted.

1. Wilks S. Morbid appearances in the intestine of Miss Bankes. *Med Times Gazette* 1859; **2:** 264–265.
2. Langan R C, Gotsch P B, Krafczyk M A, Skillinge D D. Ulcerative colitis: diagnosis and treatment. *Am Fam Physician* 2007; **76:** 1323–1330.
3. Lukas M, Bortlik M, Maratka Z. What is the origin of ulcerative colitis? Still more questions than answers. *Postgrad Med J* 2006; **82:** 620–625.
4. Lemberg D A, Day A S. Crohn disease and ulcerative colitis in children: an update for 2014. *J Paediatr Child Health* 2014; **51:** 266–270.
5. Feuerstein J D, Cheifetz A S. Ulcerative colitis: epidemiology, diagnosis, and management. *Mayo Clin Proc* 2014; **89:** 1553–1563.
6. Boirivant M, Cossu A. Inflammatory bowel disease. *Oral Dis* 2012; **18:** 1–15.
7. Danese S, Fiorino G, Peyrin-Biroulet L *et al*. Biological agents for moderately to severely active ulcerative colitis. *Ann Intern Med* 2014; **160:** 704–711.
8. Appleman H D. What are the critical histologic features in the diagnosis of ulcerative colitis? *Inflamm Bowel Dis* 2008; **14 Suppl 2:** S164–S165.
9. Lutgens M W, van Oijen M G, van der Heijden G J, Vleggaar F P, Siersema P D, Oldenburg B. Declining risk of colorectal cancer in inflammatory bowel disease. *Inflamm Bowel Dis* 2013; **19:** 789–799.
10. Monsén U, Sorstad J, Hellers G JC. Extracolonic diagnoses in ulcerative colitis: an epidemiological study. *Am J Gastroenterol* 1990; **85:** 711–716.
11. Fine K D, Seidel R H, Do K. The prevalence, anatomic distribution, and diagnosis of colonic causes of chronic diarrhoea. *Gastrointest Endosc* 2000; **51:** 318–326.
12. Roggeveen M J, Tismenetsky M, Shapiro R. Best cases from the AFIP: ulcerative colitis. *Radiographics* 2006; **26:** 947–951.

13. Lakatos P-L. Recent trends in the epidemiology of inflammatory bowel diseases: up or down? *World J Gastroenterol* 2006; **12:** 6102–6108.
14. Vind I, Riis L, Jess T *et al.* Increasing incidences of inflammatory bowel disease and decreasing surgery rates in Copenhagen City and County, 2003–2005: a population-based study from the Danish Crohn colitis database. *Am J Gastroenterol* 2006; **101:** 1274–1282.
15. Knights D, Silverberg M S, Weersma R K *et al.* Complex host genetics influence the microbiome in inflammatory bowel disease. *Genome Med* 2014; **6:** 107.
16. Vermeire S. Review article : genetic susceptibility and application of genetic testing in clinical management of inflammatory bowel disease. *Aliment Pharmacol Ther* 2006; **24 Suppl 3:** 2–10.
17. Russell R, Satsangi J. IBD: a family affair. *Best Pract Res Clin Gastroenterol* 2004; **18:** 525–539.
18. Baumgart D C, Carding S R. Gastroenterology 1 Inflammatory bowel disease: cause and immunobiology. *Lancet* 2007; **369:** 1627–1640.
19. Orholm M, Binder V, Sorensen T I, Rasmussen L P, Kyvik K O. Concordance of inflammatory bowel disease among Danish twins. Results of a nationwide study. *Scand J Gastroenterol* 2000; **35:** 1075–1081.
20. Tysk C, Lindberg E, Jarnerot G, Floderus-Myrhed B, Järnerot G, Flodérus-Myrhed B. Ulcerative colitis and Crohn's disease in an unselected population of monozygotic and dizygotic twins. A study of heritability and the influence of smoking. *Gut* 1988; **29:** 990–996.
21. Loftus E V. Clinical epidemiology of inflammatory bowel disease: incidence, prevalence, and environmental influences. *Gastroenterology* 2004; **126:** 1504–1517.
22. Zheng J J, Zhu X S, Huangfu Z, Gao Z X, Guo Z R, Wang Z. Crohn's disease in mainland China: a systematic analysis of 50 years of research. *Chin J Dig Dis* 2005; **6:** 175–181.
23. Burisch J, Pedersen N, Čuković-Čavka S *et al.* East–West gradient in the incidence of inflammatory bowel disease in Europe: the ECCO-EpiCom inception cohort. *Gut* 2014; **63:** 588–597.
24. Sicilia B, Arribas F, Nerín J, López Miguel C, Vicente R, Gomollón F. Risk factors for ulcerative colitis: a population-based, case-control study in Spain. *J Crohns Colitis* 2008; **2:** 158–161.
25. Heide F Van Der, Wassenaar M, Linde K Van Der. Effects of active and passive smoking on Crohn ' s disease and ulcerative colitis in a cohort from a regional hospital. *Eur J Gastroenterol Hepatol* 2011; **23:** 255–261.
26. Ole H, Wolters F, Riis L *et al.* Ulcerative colitis: patient characteristics may predict 10-yr disease recurrence in a European-wide population-based cohort. *Am J Gastroenterol* 2007; **102:** 1692–1701.
27. Boyko E J, Koepsell T D, Perera D R, Inui T S. Risk of ulcerative colitis among former and current cigarette smokers. *N Engl J Med* 1987; **316:** 707–710.
28. Birrenbach, T, Bocher U. Inflammatory bowel disease and smoking. *Inflamm Bowel Dis* 2004; **10:** 848–859.
29. Cosnes J. Tobacco and IBD: relevance in the understanding of disease mechanisms and clinical practice. *Best Pract Res Clin Gastroenterol* 2004; **18:** 481–496.
30. Koutroubakis I E, Vlachonikolis I G, Kouroumalis E A. Role of appendicitis and appendectomy in the pathogenesis of ulcerative colitis: a critical review. *Inflamm Bowel Dis* 2002; **8:** 277–286.
31. Radford-Smith G L, Edwards J E, Purdie D M *et al.* Protective role of appendicectomy on onset and severity of ulcerative colitis and Crohn's disease. *Gut* 2002; **51:** 808–813.
32. Cosnes J, Carbonnel F, Beaugerie L, Blain A, Reijasse D, Gendre JP. Effects of appendicectomy on the course of ulcerative colitis. *Gut* 2002; **51:** 803–807.
33. Dignass A, Eliakim R, Magro F *et al.* Second European evidence-based consensus on the diagnosis and management of ulcerative colitis Part 1: Definitions and diagnosis. *J Crohns Colitis* 2012; **6:** 965–990.
34. Marshall J K, Thabane M, Steinhart a H, Newman J R, Anand A, Irvine E J. Rectal 5aminosalicylic acid for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2010; CD004115.
35. Regueiro M, Loftus E V, Steinhart a H, Cohen R D. Medical management of left-sided ulcerative colitis and ulcerative proctitis: critical evaluation of therapeutic trials. *Inflamm Bowel Dis* 2006; **12:** 979–994.
36. Chapman R W, Selby W S, Jewell D P. Controlled trial of intravenous metronidazole as an adjunct to corticosteroids in severe ulcerative colitis. *Gut* 1986; **27:** 1210–1212.
37. Reinisch W, Olson A, Johanns J *et al.* Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005; **353:** 2462–2476.
38. Laharie D, Bourreille A, Branche J *et al.* Ciclosporin *versus* infliximab in patients with severe ulcerative colitis refractory to intravenous steroids: a parallel, open-label randomised controlled trial. *Lancet* 2012; **380:** 1909–1915.
39. Sutherland L, Macdonald J K. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2006; CD000544.
40. Timmer A, McDonald J W, Tsoulis D J, Macdonald J K. Azathioprine and 6mercaptopurine for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2012; CD000478.
41. Sandborn W J, Van Assche G, Reinisch W *et al.* Adalimumab induces and maintains clinical remission in patients with moderatetosevere ulcerative colitis. *Gastroenterology* 2012; **142:** 257–265.e1-3.
42. Sandborn W J, Feagan B G, Rutgeerts P *et al.* Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2013; **369:** 711–721.
43. Dignass A, Van Assche G, Lindsay J O *et al.* The second European evidence-based consensus on the diagnosis and management of Crohn's disease: Current management. *J Crohns Colitis* 2010; **4:** 28–62.
44. Hoie O, Wolters F L, Riis L *et al.* Low colectomy rates in ulcerative colitis in an unselected European cohort followed for 10 years. *Gastroenterology* 2007; **132:** 507–515.
45. Oresland T, Bemelman W A, Sampietro G M *et al.* European evidence based consensus on surgery for ulcerative colitis. *J Crohns Colitis* 2015; **9:** 4–25.
46. Elahi M, Telkabadi M, Samadi V, Vakili H. Association of oral manifestations with ulcerative colitis. *Gastroenterol Hepatol Bed Bench* 2012; **5:** 155–160.
47. Lisciandrano D, Ranzi T, Carrassi A *et al.* Prevalence of oral lesions in inflammatory bowel disease. *Am J Gastroenterol* 1996; **91:** 7–10.
48. Katz J, Shenkman A, Stavropoulos F, Melzer E. Oral signs and symptoms in relation to disease activity and site of involvement in patients with inflammatory bowel disease. *Oral Dis* 2003; **9:** 34–40.
49. McCarthy F P. Pyostomatitis vegetans; report of three cases. *Arch Derm Syphilol* 1949; **60:** 750–764.
50. Field E A, Llan R B A. Review article: oral ulceration – aetiopathogenesis, clinical diagnosis and management in the gastrointestinal clinic. *Aliment Pharmacol Ther* 2003; **18:** 949–962.
51. Fatahzadeh M, Schwartz R A, Kapila R, Rochford C. Orofacial Crohn's Disease : an oral enigma. *Acta Dermatovenerol Croat* 2009; **17:** 289–300.
52. Jurge S, Hegarty A M, Hodgson T. Orofacial manifestations of gastrointestinal disorders. *Br J Hosp Med (Lond)* 2014; **75:** 497–501.
53. Lankarani K B, Sivandzadeh G R, Hassanpour S. Oral manifestation in inflammatory bowel disease: a review. *World J Gastroenterol* 2013; **19:** 8571–8579.
54. Ruiz-Roca J A, Berini-Aytés L, Gay-Escoda C. Pyostomatitis vegetans. Report of two cases and review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005; **99:** 447–454.
55. Mijandrusić-Sincić B, Licul V, Gorup L, Brncić N, Glazar I, Lucin K. Pyostomatitis vegetans associated with inflammatory bowel diseasereport of two cases. *Coll Antropol* 2010; **34 Suppl 2:** 279–282.
56. Markiewicz M, Suresh L, Margarone J, Aguirre A, Brass C. Pyostomatitis Vegetans: a clinical marker of silent ulcerative colitis. *J Oral Maxillofac Surg* 2007; **65:** 346–348.
57. Hegarty A M, Barrett A W, Scully C. Pyostomatitis vegetans. *Clin Exp Dermatol* 2004; **29:** 1-7.
58. Chaudhry S I, Philpot N S, Odell E W, Challacombe S J, Shirlaw P J. Pyostomatitis vegetans associated with asymptomatic ulcerative colitis: a case report. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1999; **87:** 327–330.
59. Calobrisi S D, Mutasim D F, Mcdonald J S. Pyostomatitis vegetans associated with ulcerative colitis. Temporary clearance with fluocinonide gel and complete remission after colectomy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1995; **79:** 452-454
60. Daley T D, Armstrong J E. Oral manifestations of gastrointestinal diseases. *Can J Gastroenterol* 2007; **21:** 241–244.
61. Femiano F, Lanza A, Buonaiuto C, Perillo L, Dell'Ermo A, Cirillo N. Pyostomatitis vegetans: a review of the literature. *Med Oral Patol Oral Cir Bucal* 2009; **14:** 5–8.
62. Chan S W, Scully C, Prime S S, Eveson J. Pyostomatitis vegetans: oral manifestation of ulcerative colitis. *Oral Surg Oral Med Oral Pathol* 1991; **72:** 689–692.
63. Trost L B, McDonnell J K. Important cutaneous manifestations of inflammatory bowel disease. *Postgrad Med J* 2005; **81:** 580–585.
64. Lourenço S V, Hussein T P, Bologna S B, Sipahi A M, Nico M M. Oral manifestations of inflammatory bowel disease: a review based on the observation of six cases. *J Eur Acad Dermatol Venereol* 2010; **24:** 204–207.
65. Thrash B, Patel M, Shah K R, Boland C R, Menter A. Cutaneous manifestations of gastrointestinal disease: part II. *J Am Acad Dermatol* 2013; **68:** 211.e1–33; quiz 244–246.
66. Veloso F T. Extraintestinal manifestations of inflammatory bowel disease: do they influence treatment and outcome? *World J Gastroenterol* 2011; **17:** 2702–2707.
67. Brito F, de Barros F C, Zaltman C *et al.* Prevalence of periodontitis and DMFT index in patients with Crohn's disease and ulcerative colitis. *J Clin Periodontol* 2008; **35:** 555–560.
68. Grössner-Schreiber B, Fetter T, Hedderich J *et al*. Prevalence of dental caries and periodontal disease in patients with inflammatory bowel disease: a case-control study. *J Clin Periodontol* 2006; **33:** 478–484.
69. Habashneh R A, Khader Y S, Alhumouz M K, Jadallah K, Ajlouni Y. The association between inflammatory bowel disease and periodontitis among Jordanians: a case-control study. *J Periodontal Res* 2012; **47:** 293–298.
70. Mancheno-Franch A, Jimenez-Soriano Y, Sarrion-Perez M. Dental management of patients with inflammatory bowel disease. *J Clin Exp Dent* 2010; **2:** e191–e195.