# ARTICLE IN PRESS

Alimentary Tract

# The use of oral corticosteroids in inflammatory bowel diseases in Italy: An IG-IBD survey

Federica Fascì-Spurio [a], Gianmichele Meucci [b,*], Claudio Papi [c], Simone Saibeni [d], on behalf of IG-IBD (Italian Group for Inflammatory Bowel Disease)

[a] Department of Internal Medicine, Ospedale dell'Angelo, Venezia, Italy
[b] Gastroenterology Unit, San Giuseppe Hospital, Milano, Italy
[c] IBD Unit, S Filippo Neri Hospital, Rome, Italy
[d] Gastroenterology Unit, Rho Hospital, Rho, Italy

## ARTICLE INFO

## ABSTRACT

*Aim:* To evaluate how Italian gastroenterologists use corticosteroids in clinical practice for the treatment of Crohn's disease (CD) and ulcerative colitis (UC).

*Material and methods:* All members of the Italian Group for Inflammatory Bowel Disease (IG-IBD) were invited to fill in a web-based questionnaire.

*Results:* 131/448 (29.2%) members completed the survey. In mild-to-moderate UC and CD relapses, low-bioavailability steroids (LBS) are first-line therapy for 37% and 42% of clinicians, respectively. In case of failure, immediate step-up to biologics or immunosuppressants is considered by 23% and 29%. Regarding conventional corticosteroids (CCS), a fixed starting dose is prescribed by 50%, and a weight-based dose by 22%. Tapering is started after 7–10 days by 41% and after 14 days by 32%. The preferred tapering schedule is 5 mg/week. In case of CCS failure, 47% switch to parenteral steroids before considering shifting to different drug classes. In case of symptoms recurrence during tapering, 14% re-increase the dose and try tapering again. Before prescribing steroids, 72% do not prescribe any specific evaluation whereas during treatment some evaluation is performed by 85%. Vitamin D and calcium supplements are routinely prescribed along with steroids by 38%.

*Conclusions:* Several discrepancies and some deviation from the available guidelines were recorded among Italian gastroenterologists regarding corticosteroids use in IBD patients.

© 2017 Editrice Gastroenterologica Italiana S.r.l. Published by Elsevier Ltd. All rights reserved.

## 1. Introduction

Corticosteroids have been used for the treatment of IBD for more than sixty years, having represented the first major therapeutic breakthrough for these conditions. Indeed, early controlled trials have demonstrated the clear superiority of oral corticosteroids over both placebo and sulphasalazine in inducing clinical remission in both UC and CD [1–4], and optimization of intravenous corticosteroids administration has resulted in a dramatic drop in mortality due to severe UC attacks [5]. As a consequence, corticosteroids have been a mainstay in the treatment of these diseases for decades. In spite of this, very few further controlled trials have been subsequently conducted [6–16] and even less studies (either controlled or observational) have explored the best way of using these drugs in terms of dosage, duration and tapering modalities [17–21]. Therefore, available practice guidelines are generally elusive on these issues and the use of corticosteroids in clinical practice is still quite empirical [22–28]. Paradoxically, the use of newer preparations of oral low-bioavailability steroids (LBS) such as budesonide and beclomethasone dipropionate has been better delineated by clinical trials, case series and systematic reviews [29–43] and better codified in guidelines [22,28,44].

We therefore designed a simple questionnaire aimed at exploring the habits and preferences of Italian IBD physicians in the use of oral steroids in their real-life clinical practice. The fields that were explored included preferences between CCS and LBS oral steroids for mild to severe IBD relapses, therapeutic strategies in case of failure of low-availability steroids, starting dose, length of treatment and tapering modalities for systemic steroids, mode of patients' follow-up during steroid treatment.

* Corresponding author at: Gastroenterology Unit, Ospedale San Giuseppe, Via San Vittore 12, 20123 Milano, Italy.
  *E-mail address:* g.meucci@teletu.it (G. Meucci).

**Table 1**
Features of responding physicians.

| | n.% |
|---|---|
| **Age** | |
| <30 years | 7 (5%) |
| 30–39 years | 47 (36%) |
| 40–49 years | 41 (31%) |
| 50–59 years | 29 (22%) |
| >60 years | 7 (6%) |
| **Affiliated hospitals** | |
| Public, non academic | 59 (45%) |
| Public, academic | 50 (39%) |
| Private, non academic | 12 (8%) |
| Private, academic | 10 (6%) |
| **Number of IBD patients followed** | |
| <100 | 8 (6%) |
| 100–499 | 60 (46%) |
| 500–999 | 18 (14%) |
| 1.000–1499 | 21 (16%) |
| >1500 | 24 (18%) |

## 2. Materials and methods

A 35-item web-based questionnaire was sent to all the 448 members of the Italian Group for Inflammatory Bowel Disease (IG-IBD). Three out of 35 questions were aimed at exploring the demographic characteristics of the participants, 12/35 the habits of Italian gastroenterologists in treating mild to severe relapses of CD and UC, 12/35 explored practical details such as starting dose, length of treatment, tapering modalities, 2/35 the behavior in case of steroid-dependency or resistance and the remaining on the modalities of treatment monitoring.

GraphPad Instat package software (GraphPad Software Inc., San Diego, CA, USA) was used to analyze data by means of Student's t test, Mann–Whitney test, Fisher's exact test and Chi-square test for independence, as appropriate. All the statistical tests were two-tailed and the statistical significance was set at $p = 0.05$.

## 3. Results

One hundred and thirty one gastroenterologists (29.2%) completed the survey. The demographic characteristics of respondents are summarized in Table 1.

### 3.1. Preferences between low-bioavailability and conventional steroids for IBD relapses (see also Figs. 1 and 2)

For mild to moderate CD relapses, 37% of physicians use LBS as first line treatment, whereas 42% do so in patients with mesalazine-refractory mild to moderate UC; the remaining either prefer CCS or decide case by case. These figures were significantly higher among clinicians younger than 40, both in CD (50% vs 22%, $p = 0.021$) and UC (52% vs 35%, $p = 0.043$).

For moderate to severe flares, 85% and 92% start CCS as first line treatment in CD and UC respectively; however, 15% and 8% respectively consider starting with LBS. In case of LBS failure, 72% switch to CCS in both CD and UC patients, whereas 23% and 29% move to another drug class in CD and UC patients, respectively. In patients with UC, 3 percent increase LBS dosage.

### 3.2. Dosage and duration, tapering modalities, length of treatment, patients monitoring during treatment with CCS (Figs. 3 and 4)

When using CCS, 22% of gastroenterologists always determine the starting dose according to patients' weight while 50% used a fixed, predetermined, starting dose (50–60 mg daily in most cases,

see figure). Fifty-nine percent recommend taking the entire dose in the morning while 38% recommend dividing the dose between morning and early afternoon. A significantly higher percentage of academic clinicians recommend taking the entire dose in the morning (71% vs 53% $p = 0,037$). As for as duration of full-dose treatment, 40.5% always follow a standard regime (7–10 days 41%, 2 weeks 32%, 3 weeks 7%, 4 weeks 17%); the remaining tailor the length of full-dose treatment either always or sometimes. Before tapering the dose of steroids, 60% of gastroenterologists regularly re-evaluate patients, 35% re-evaluate patients occasionally and 5% never. Among those who re-evaluate patients before tapering the dose of CCS, 7% did it by means of a phone conversation, 40% by a face to face visit, 47% perform also blood tests and 6% endoscopic or ultrasonographic investigations.

Regarding tapering modalities, 60% of respondents stated they use a standard scheme (65% of them reduced the dose by 5 mg every week), the remaining personalizing according to patients' characteristics either always or sometimes.

Among clinicians stating to personalize (always or sometimes) treatment modalities, factors taken into account include patients' age, BMI, severity of the relapse and comorbidities.

### 3.3. Behaviour in case of steroid resistance or dependency (Fig. 5)

In case of unsatisfactory response to a course of full-dosage treatment with CCS, 35% of gastroenterologists switch to a different class of medications, 47% switch to parenteral administration, and 6% increased dosage. The percentage of in case of symptoms recurrence during the tapering phase, 57% increase the dosage of oral steroids while introducing a second line of treatment (either immunosuppressants or biologics), 25% switch directly to immunosuppressants or biologics, 14% increase the dose of CCS and try a second tapering.

### 3.4. Patients monitoring and prevention of complications

Before starting corticosteroids, 72% of respondents do not routinely perform any clinical or laboratory evaluation. A minority routinely request one or more among ohptalmologic evaluation (4%), chest X-ray 13%, DEXA (9%), tuberculin skin test (14%).

During a CCS course, 60% of respondents said they regularly monitor blood pressure, 60% serum glucose levels, 32% serum electrolytes while 14% do no perform any specific monitoring.

As for ostheoporosis prophylaxis, 38% of respondents prescribe calcium and vitamin D supplements every time, 55% do so only in patients with known risk factors and/or preexisting bone loss, while the remaining never prescribe supplementation. The percentage of clinicians routinely prescribing calcium and vitamin D supplements is significantly higher among those younger than 40 (49% vs 31% in older than 40, $p = 0,037$).

In case of presence of comorbidities ad/or relative contraindications to CCS (diabetes, hypertension, glaucoma, chataract, psychiatric disorders) 22% of respondents said they avoid prescribing corticosteroids whereas 78% proceed with caution monitoring patients strictly and/or consulting the appropriate specialists.

Finally, 44% stated to regularly co-prescribe a proton pump inhibitor along with steroids.

## 4. Discussion

To the best of our knowledge, this is the first study exploring the practical use of corticosteroids by gastroenterologists in patients with IBD. The rate of response to the questionnaire was far from optimal, but similar to that achieved in several previous surveys on different topics [45–47]. However, demographic characteristics of responding clinicians suggest that the responding group is
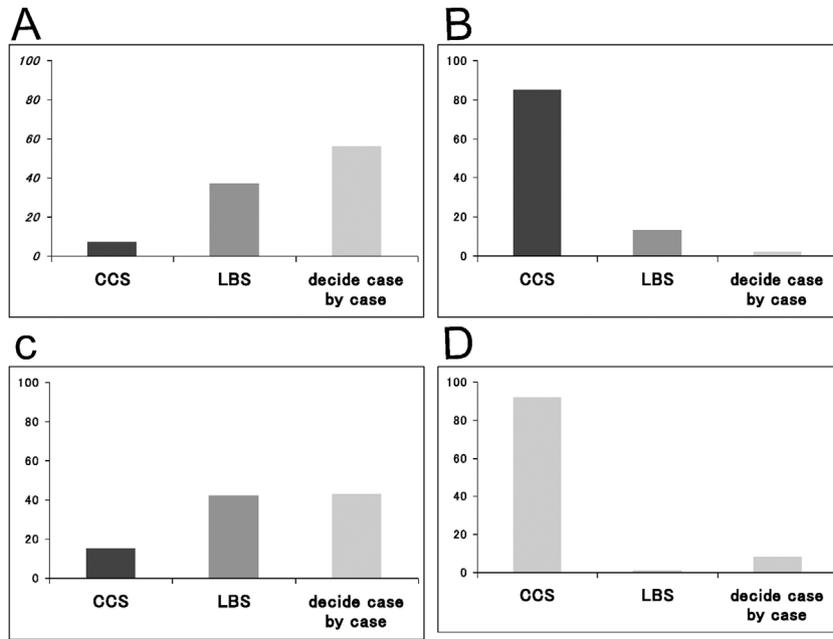
**Fig. 1.** First-line choice for IBD flare. A: mild to moderate CD; B: moderate-severe CD; C: mild to moderate UC; D: moderate to severe UC.
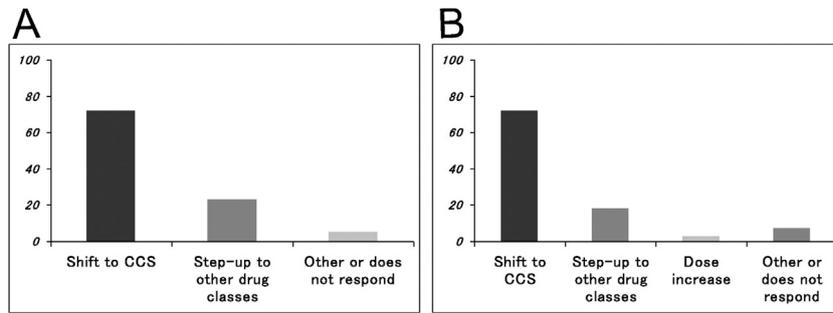CCS: conventional corticosteroids (LBS): low systemic bioavailability corticosteroids.



**Fig. 2.** Behaviour in case of LBS failure. A: mild to moderate CD; B: mild to moderate UC.
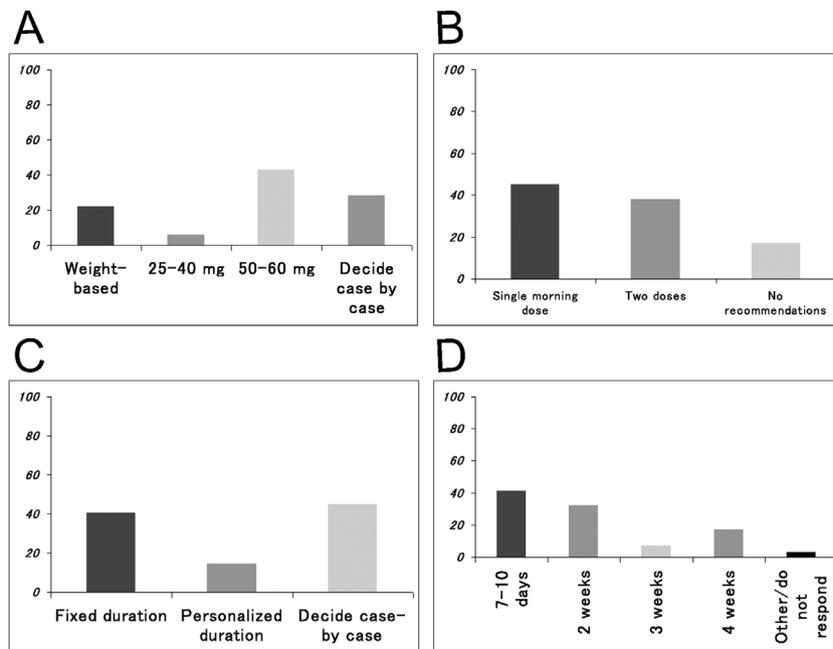CCS: conventional corticosteroids LBS: low systemic bioavailability corticosteroids.



**Fig. 3.** Dosage, number of doses and duration of conventional corticosteroid treatment. A: initial dose; B: number of doses; C and D: duration of full dose treatment.
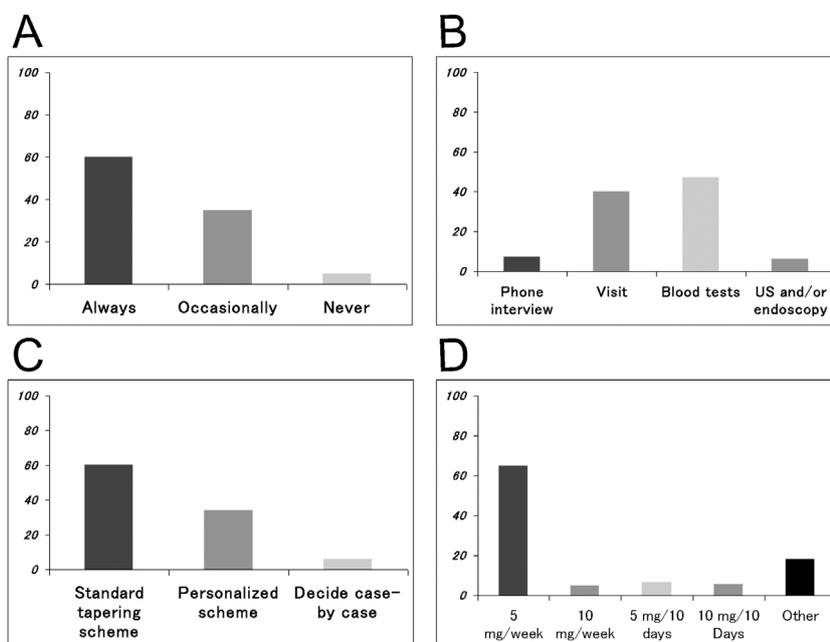
4                                    F. Fascì-Spurio et al. / Digestive and Liver Disease xxx (2017) xxx–xxx



**Fig. 4.** Behaviour about tapering of conventional corticosteroids. A and B evaluations before tapering; C and D: tapering scheme.
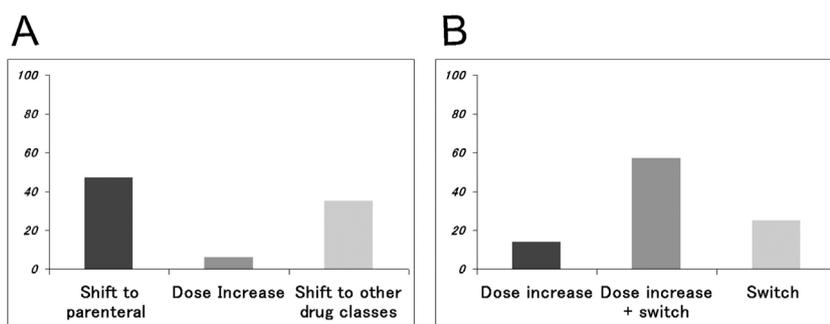


**Fig. 5.** Behaviour in case of resistance (6A) and dependence (6B) to conventional corticosteroids.

fairly representative of Italian gastroenterologists dealing with IBD patients. Several remarks can be made on our results.

1) **Choice of drugs according to disease features.** Only 37% of responders prescribed LBS as first line therapy in mild-to-moderate CD relapse, although most recent guidelines strongly recommend them as the preferred fist-line treatment in mildly active CD flares and as an alternative for CCS in moderate flares [22,28]. On the other hand, it is remarkable that 42% of clinicians used LBS as first-line treatment in mild-to moderate mesalazine refractory UC relapses, and a further 43% decided case by case, thus considering using LBS first in some categories of patients. Although CCS are generally recommended as the preferred treatment of mesalazine-refractory UC flares [22–26], LBS have recently emerged as a possible alternative [40,48] and some recent guidelines indeed mention this possibility [28,44]. It is also interesting to notice that in case of LBS failure, roughly one clinician out of 4 step-up directly to other drugs classes instead of switching to CCS, both in CD and UC patients. This is not currently recommended by any guidelines, but may result convenient in some categories of patients, in order to limit steroid-induced side-effects. Differently, it is quite disappointing that 10–15% of specialists considered LBS in moderate-severe IBD flares – a choice that is universally strongly discouraged [22–28,44] – and even more that 3% of them tried

to increase LBS dosage in case of failure. Another finding that emerged from our study is that younger clinicians tend to prescribe LBS more frequently than their older colleagues.

2) **Treatment dosage and duration.** Very limited evidence-based data are available on this topic. In UC, two older controlled trials had shown that both 40 and 60 mg/die of prednisone are respectively equally effective and significantly more effective than 20 mg/die, and that a single daily dose is as efficacious as divided doses, respectively [17,18]. Conversely, the two pivotal European and American collaborative studies have demonstrated that both metilprednisolone ¼ to ¾ mg/kg/die (according to disease severity) and 48 mg/die are superior than sulphasalazine and placebo in inducing remission in active CD [4,5], whereas lower doses have been shown to be even detrimental in older case series [49]. More recently, higher rates of remission were reported in case series in which up to 1 mg/kg/die of prednisone was administered [19,21]. Finally, no difference was found between a tapering schedule of 4 weeks duration and another of 12 weeks duration in a small controlled trial [20]. Generally, a starting daily dosage of 40–60 mg of prednisone is recommended in patients with UC [24,26,44], and of either 40–60 mg or 0,75–1 mg/kg in patients with CD [26–28]. As for full-dose treatment duration, it is usually recommended to start tapering after 1–3 weeks [26–28] and to complete it within 8–12 weeks [25–28]. Looking at data of our survey, we can notice

that starting dose and treatment duration used by interviewed specialists are in the vast majority of cases in line with such recommendations, only 15% starting treatment at dosages either lower of higher than recommended and 17% commencing tapering after more than 3 weeks. The preferred tapering schedule was 5 mg per week, identical to what suggested by the IBD Ahead Education Program [26], and not much different from the schedule recommended by the AGA [27]. Our data show also that more Italian clinicians prefer a fixed starting dose over a weight-based one, and that 60% recommend taking steroids in a single morning dose, the remaining recommending two divided doses.

3) **Management of steroid-dependent and steroid-refractory patients.** There is nowadays a full consensus that patients not responding to full dosage of corticosteroids and those experiencing symptoms recurrence during CCS tapering must be timely switched to other drug classes [22,28,44]. In this respect, it is somewhat surprising that, in case of resistance to CCS, 47% of responders used to switch to parenteral administration and 6% to increase the dose over that recommended, two conducts that are not supported by any guidelines or expert opinion. On the other hand, the majority stated to timely switch steroid-dependent patients to biologics or immunosuppressants, only 14% increasing steroid dose again and then starting a new tapering.

4) **Patients monitoring before and during treatment.** At present, no specific screening is deemed mandatory before initiating a CCS course, although screening for tuberculosis and/or Clostridium Difficile infection has been sometimes recommended [50,51]. On the other hand, it is generally believed that during CCS treatment some monitoring for complications (mainly ocular disease, diabetes, hypertension and bone loss) is advisable, although very evasive recommendations are reported in published guidelines [25–27]. Our data show that only a minority of Italian gastroenterologists (28%) perform any sort of pretreatment screening, whereas the vast majority (85%) monitored at least blood pressure and/or serum glucose during treatment. Very few respondents said to perform regular ophthalmologic examination, a practice that has sometime been recommended [26]. It is also noteworthy that about 15% of respondents performed TB screening (by means of either X-ray or skin test) before initiating corticosteroids.

5) **Prevention of complications.** It is generally recommended that patients on corticosteroids should receive calcium and vitamin D supplementation and undergo regular DEXA examination [22], although the real effectiveness of these measures in preventing bone loss has not been clearly demonstrated. In our survey, 38% of specialists stated they routinely prescribe calcium and vitamin D supplementation along with corticosteroids, and a further 55% prescribed them only if risk factors and/or pre-existing bone damage were present. This figures appear to be somewhat higher than those reported in a previous Italian survey [52]; noticeably, prescription of supplementation resulted more frequent among younger clinicians. Finally, it is surprising that 44% said to regularly prescribe proton-pump inhibitors along with steroids, since it has been known for a long time that corticosteroids are not per-se a risk factor for peptic disease and co-prescription of anti-secretive dugs has never been recommended in IBD patients on corticosteroids, unless also on NSAIDs [53].

In conclusion, our survey has uncovered some heterogeneities among Italian gastroenterologist regarding the way to prescribe and monitor corticosteroid therapy in IBD patients, as well as some significant deviances from current recommendations. No major differences were found according to age of respondents, the type of institution and the number of followed-up patients, except for a higher rate of LBS prescription and calcium/vitamin D supplementation among younger clinicians. Therefore, some educational intervention appears desirable.

## Submission declaration

The work described in the present paper has not been published previously (except in the form of an abstract) and is not under consideration for publication elsewhere. The publication of the present article was approved by all authors and if accepted, it will not be published elsewhere including electronically in the same form, in English or in any other language, without the written consent of the copyright-holder.

## Conflict of interest

None declared.

## Funding

---

### List of abbreviations

UC, ulcerative colitis; CD, Crohn's disease; IBD, inflammatory bowel disease; IG-IBD, Italian Group for Inflammatory Bowel Disease; LBS, low-bioavailability steroids; CCS, conventional corticosteroids.

---

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.dld.2017.07.005.

## References

[1] Truelove SC, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. Br Med J 1955;29:1041–8.
[2] Lennard-Jones JE, Longmore AJ, Newell AC, et al. An assessment of prednisone, salazopyrin, and topical hydrocortisone hemisuccinate used as out-patient treatment for ulcerative colitis. Gut 1960;1:217–22.
[3] Truelove SC, Jewell DP. Intensive intravenous regimen for severe attacks of ulcerative colitis. Lancet 1974:1067–70.
[4] Summers RW, Switz DM, Sessions Jr JT, et al. National cooperative Crohn's disease study: results of drug treatment. Gastroenterology 1979;77:847–69.
[5] Malchow H, Ewe K, Brandes JW, et al. European cooperative Crohn's disease study (ECCDS): results of drug treatment. Gastroenterology 1984;86:249–66.
[6] Rhodes JM, Robinson R, Beales I, et al. Clinical trial: oral prednisolone metasulfobenzoate (predocol) vs. oral prednisolone for active ulcerative colitis. Aliment Pharmacol Ther 2008;27:228–40.
[7] Borrelli O, Cordischi L, Cirulli M, et al. Polymeric diet alone versus corticosteroids in the treatment of active pediatric Crohn's disease: a randomized controlled open-label trial. Clin Gastroenterol Hepatol 2006;4:744–53.
[8] Herrlinger KR, Witthoeft T, Raedler A, et al. Randomized, double blind controlled trial of subcutaneous recombinant human interleukin-11 versus prednisolone in active Crohn's disease. Am J Gastroenterol 2006;101:793–7.
[9] Hanai H, Watanabe F, Yamada M, et al. Adsorptive granulocyte and monocyte apheresis versus prednisolone in patients with corticosteroid-dependent moderately severe ulcerative colitis. Digestion 2004;70:36–44.
[10] D'Haens G, Lemmens L, Geboes K, et al. Intravenous cyclosporine versus intravenous corticosteroids as single therapy for severe attacks of ulcerative colitis. Gastroenterology 2001;120:1323–9.
[11] Ang YS, Mahmud N, White B, et al. Randomized comparison of unfractionated heparin with corticosteroids in severe active inflammatory bowel disease. Aliment Pharmacol Ther 2000;14:1015–22.

[12] Gorard DA, Hunt JB, Payne-James JJ, et al. Initial response and subsequent course of Crohn's disease treated with elemental diet or prednisolone. Gut 1993;34:1198–202.

[13] Hawthorne AB, Record CO, Holdsworth CD, et al. Double blind trial of oral fluticasone propionate v prednisolone in the treatment of active ulcerative colitis. Gut 1993;34:125–8.

[14] Lindor KD, Fleming CR, Burnes JU, et al. A randomized prospective trial comparing a defined formula diet, corticosteroids, and a defined formula diet plus corticosteroids in active Crohn's disease. Mayo Clin Proc 1992;67:328–33.

[15] Rijk MC, van Hogezand RA, van Lier HJ, et al. Sulphasalazine and prednisone compared with sulphasalazine for treating active Crohn disease. A double-blind, randomized, multicenter trial. Ann Intern Med 1991;114:445–50.

[16] Saverymuttu S, Hodgson HJ, Chadwick VS. Controlled trial comparing prednisolone with an elemental diet plus non-absorbable antibiotics in active Crohn's disease. Gut 1985;26:994–8.

[17] Baron JH, Connell AM, Kanaghinis TG, et al. Out-patient treatment of ulcerative colitis. Comparison between three doses of oral prednisone. Br Med J 1962;18:441–3.

[18] Powell-Tuck J, Bown RL, Lennard-Jones JE. A comparison of oral prednisolone given as single or multiple daily doses for active proctocolitis. Scand Gastroenterol 1978;13:833–7.

[19] Modigliani R, Mary JY, Simon JF, et al. Clinical, biological, and endoscopic picture of attacks of Crohn's disease. Evolution on prednisolone. Groupe d'Etude Thérapeutique des Affections Inflammatoires Digestives. Gastroenterology 1990;98:811–8.

[20] Brignola C, De Simone G, Belloli C, et al. Steroid treatment in active Crohn's disease: a comparison between two regimens of different duration. Aliment Pharmacol Ther 1994;8:465–8.

[21] Munkholm P, Langholz E, Davidsen M, et al. Frequency of glucocorticoid resistance and dependency in Crohn's disease. Gut 1994;35:360–2.

[22] Gomollon F, Dignass A, Annese V, et al. 3rd European evidence-based consensus on the diagnosis and management of Crohn's disease 2016: part 1: diagnosis and medical management. J Crohns Colitis 2017;11:3–25.

[23] Dignass A, Lindsay JO, Sturm A, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. J Crohns Colitis 2012;6:991–1030.

[24] Kornbluth A, Sachar DB, Practice Parameters Committee of the American College of Gastroenterology. Ulcerative colitis practice guidelines in adults: American College Of Gastroenterology Practice Parameters Committee. Am J Gastroenterol 2010;105:501–23.

[25] Mowat C, Cole A, Windsor A, et al. Bloom S guidelines for the management of inflammatory bowel disease in adults. Gut 2011;60:571–607.

[26] Lichtenstein GR, Abreu MT, Cohen R, et al. American Gastroenterological Association Institute medical position statement on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. Gastroenterology 2006;130:935–9.

[27] Ferrante M, Karmiris K, Newnham E, et al. Physician perspectives on unresolved issues in the use of conventional therapy in Crohn's disease: results from an international survey and discussion programme. J Crohns Colitis 2012;6:116–31.

[28] Gionchetti P, Rizzello F, Annese V, et al. Use of corticosteroids and immunosuppressive drugs in inflammatory bowel disease: clinical practice guidelines of the Italian Group for the Study of Inflammatory Bowel Disease. Dig Liver Dis 2017;49:604–17, http://dx.doi.org/10.1016/j.dld.2017.01.161.

[29] D'Haens G. Systematic review: second-generation vs. conventional corticosteroids for induction of remission in ulcerative colitis. Aliment Pharmacol Ther 2016;44:1018–29.

[30] Rezaie A, Kuenzig ME, Benchimol EI, et al. Budesonide for induction of remission in Crohn's disease. Cochrane Database Syst Rev 2015;3:CD000296.

[31] Moja L, Danese S, Fiorino G, et al. Systematic review with network meta-analysis: comparative efficacy and safety of budesonide and mesalazine (mesalamine) for Crohn's disease. Aliment Pharmacol Ther 2015;41:1055–65.

[32] Kuenzig ME, Rezaie A, Seow CH, et al. Budesonide for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev 2014;21:CD002913.

[33] Kane SV, Schoenfeld P, Sandborn WJ, et al. The effectiveness of budesonide therapy for Crohn's disease. Aliment Pharmacol Ther 2002;16:1509–17.

[34] Papi C, Luchetti R, Gili L, et al. Budesonide in the treatment of Crohn's disease: a meta-analysis. Aliment Pharmacol Ther 2000;14:1419–28.

[35] Manguso F, Bennato R, Lombardi G, et al. Efficacy and safety of oral beclomethasone dipropionate in ulcerative colitis: a systematic review and meta-analysis. PLoS One 2016;11:e0166455.

[36] Zhao X, Li N, Ren Y, et al. Efficacy and safety of beclomethasone dipropionate versus 5-aminosalicylic acid in the treatment of ulcerative colitis: a systematic review and meta-analysis. PLoS One 2016;11:e0160500.

[37] Crispino P, Pica R, Unim H, et al. Efficacy of mesalazine or beclomethasone dipropionate enema or their combination in patients with distal active ulcerative colitis. Eur Rev Med Pharmacol Sci 2015;19:2830–7.

[38] Van Assche G, Manguso F, Zibellini M, et al. Oral prolonged release beclomethasone dipropionate and prednisone in the treatment of active ulcerative colitis: results from a double-blind, randomized, parallel group study. Am J Gastroenterol 2015;110:708–15.

[39] Nunes T, Barreiro-de Acosta M, Nos P, et al. Usefulness of oral beclometasone dipropionate in the treatment of active ulcerative colitis in clinical practice: the RECLICU study. J Crohns Colitis 2010;4:629–36.

[40] Papi C, Aratari A, Moretti A, et al. Oral beclomethasone dipropionate as an alternative to systemic steroids in mild to moderate ulcerative colitis not responding to aminosalicylates. Dig Dis Sci 2010;55:2002–7.

[41] Campieri M, Adamo S, Valpiani D, et al. Oral beclometasone dipropionate in the treatment of extensive and left-sided active ulcerative colitis: a multicentre randomised study. Aliment Pharmacol Ther 2003;17:1471–80.

[42] Rizzello F, Gionchetti P, D'Arienzo A, et al. Oral beclometasone dipropionate in the treatment of active ulcerative colitis: a double-blind placebo-controlled study. Aliment Pharmacol Ther 2002;16:1109–16.

[43] Sandborn WJ, Danese S, D'Haens G, et al. Induction of clinical and colonoscopic remission of mild-to-moderate ulcerative colitis with budesonide MMX 9 mg: pooled analysis of two phase 3 studies. Aliment Pharmacol Ther 2015;41:409–18.

[44] Bressler B, Marshall JK, Bernstein CN, et al. Clinical practice guidelines for the medical management of nonhospitalized ulcerative colitis: the Toronto consensus. Gastroenterology 2015;148:1035–58.

[45] Roblin X, Oussalah A, Chevaux JB, et al. Use of thiopurine testing in the management of inflammatory bowel diseases in clinical practice: a worldwide survey of experts. Inflamm Bowel Dis 2011;17:2480–7 [17].

[46] Yip JS, Woodward M, Abreu MT, et al. How are azathioprine and 6-mercaptopurine dosed by gastroenterologists? results of a survey of clinical practice. Inflamm Bowel Dis 2008;14:514–8.

[47] Saibeni S, Kohn A, Meucci G. Papi C on behalf of the Italian Group for Inflammatory Bowel Disease (IG-IBD): how thiopurines are used for the treatment of inflammatory bowel diseases: an Italian survey. Dig Liver Dis 2015;47:170–3.

[48] Danese S, Siegel CA, Peyrin-Biroulet L. Review article: integrating budesonide-MMX into treatment algorithms for mild-to-moderate ulcerative colitis. Aliment Pharmacol Ther 2014;39:1095–103.

[49] Cooke WT, Fielding JF. Corticosteroid or corticotrophin therapy in Crohn's disease (regional enteritis). Gut 1970;11:921–7.

[50] Khanna S, Shin A, Kelly CP. Management of clostridium difficile infection in inflammatory bowel disease: expert review from the clinical practice updates committee of the AGA Institute. Clin Gastroenterol Hepatol 2017;15:166–74.

[51] Dave M, Purohit T, Razonable R, et al. Opportunistic infections due to inflammatory bowel disease therapy. Inflamm Bowel Dis 2014;20:196–212.

[52] Meucci G, AIGO Study Group for IBD. How do Italian gastroenterologists manage bone loss in IBD patients? An AIGO survey. Dig Liver Dis 2008;40S:S61.

[53] Biancone L, Annese V, Ardizzone S, et al. Safety of treatments for inflammatory bowel disease: clinical practice guidelines of the Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD). Dig Liver Dis 2017;49:338–58, http://dx.doi.org/10.1016/j.dld.2017.01.141.