# **Steroid use and misuse- a key performance indicator in the management of IBD**

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# **Abstract**

Corticosteroids remain an important tool for inducing remission in Inflammatory Bowel Disease (IBD) but they have no role in maintenance of remission. The significant adverse side-effect profile of these drugs means their use should be avoided where possible or measures taken to reduce their risk. Despite an expanding array of alternative therapies corticosteroid dependency and excess remain common. Appropriate steroid use is now regarded a key performance indicator in the management of Inflammatory Bowel Disease. This article aims to outline indications for corticosteroid use in Inflammatory Bowel Disease, their risks and strategies to reduce their use and misuse.

# **Introduction and history of Corticosteroid use**

Truelove and Witts were the first to trial cortisone, referred to as “the special tablets”, to induce remission in ulcerative colitis (UC). 1 Two thirds in the treatment arm either improved or entered full clinical remission compared with about one third of those treated with the standard medical therapy of the time.1 Later corticosteroids were reported to be efficacious for the induction of remission in Crohn’s disease (CD) with three quarters of patients initially improving.2 However, it became apparent that the long-term benefits of corticosteroids for patients with IBD were less favourable and associated with a wide range of significant side effects.3,4Despite an expanding array of new therapies now available, corticosteroids remain an important tool in the management of inflammatory bowel disease (IBD) but must be used judiciously.

# **Indications for Corticosteroids in IBD**

# **Induction of remission in ulcerative colitis**

Corticosteroids are effective agents for inducing remission in UC. A meta-analysis found patients treated with systemic corticosteroids were twice as likely to enter remission compared to patients who received a placebo.4 Oral steroids are also superior to 5-ASA in this context, with higher rates of clinical remission (76% vs 52%, p<0.05) and improvement in endoscopic appearances (78% vs 43%, p<0.05), though due to corticosteroids’ side-effect profile 5-ASA remains the first-line therapy for mild to moderate UC.5 In patients with severe UC, corticosteroids are recommended first-line either orally or, in the case of acute severe ulcerative colitis (ASUC), intravenously. BSG guidelines recommend either Hydrocortisone 100mg IV 6 hourly or Methylprednisolone 60-80mg IV daily as the initial treatment for ASUC.6 Methylprednisolone has less mineralocorticoid potency than hydrocortisone, so may be preferred in patients with hypokalaemia.7 One in three patients with ASUC will not respond adequately to parenteral corticosteroids and normally on the third day of admission patients should be reassessed and considered for rescue therapy with infliximab or ciclosporin, as appropriate, or colectomy as the clinical picture dictates.8–10 BSG recommendations suggest that, provided colectomy does not take place, parenteral corticosteroids should be continued until the patient is passing less than 4 stools per day with no blood for two consecutive days. Once this threshold is reached parenteral corticosteroids can be switched to oral Prednisolone 40mg daily, which should then be appropriately tapered. If colectomy is undertaken an appropriately prompt steroid taper should be closely supervised post-operatively.11,12

## **Induction of remission in Crohn’s Disease**

Guidelines recommend the use of corticosteroids for inducing remission in ileocolonic CD.6 Budesonide (Budenofalk™ and Entocort™) formulated to release in the ileum and proximal colon, taken orally 9mg daily for 8 weeks is recommended as the first line agent in mild-to-moderate ileocaecal CD, marginally less effective than systemic steroids but with a significantly better side-effect profile.6,13,14 Systemic corticosteroids still have a place for inducing remission in more severe ileal or ileocaecal and colonic disease (Table 1).14,15

# **Misuse of Steroids**

Corticosteroids have no role in the maintenance of remission for either CD or UC as there is clear evidence they lack of efficacy in this respect.16,17 In spite of this, one in four individuals in the UK with CD and one in eight with UC have prolonged steroid exposure for greater than 6 months (Figure 1) within the first five years of diagnosis and this is mirrored in Europe, Canada and the USA.18–22 This carries with it a substantial burden of corticosteroid related side-effects, including increased rates of infection, adrenal suppression, osteoporosis, diabetes, cardiovascular events, mood disorders and all-cause mortality - a more detailed description of common side effects can be found below.23–26 BSG guidelines state that prolonged steroid use is harmful and should be avoided, similarly the Crohn’s and Colitis Foundation of America regard steroid-free remission as a treatment target.6,27

European Crohn’s and Colitis Organisation (ECCO) and BSG guidelines define steroid dependency as an inability to wean prednisolone below 10mg per day within 3 months without recurrent active disease, or symptomatic relapse of IBD within 3 months of stopping steroids requiring recommencement.6,28 Early escalation of treatment with the introduction of steroid sparing agents such as immunomodulators like azathioprine or a biologic agent is advocated in such patients.6,27,29–31

A multicentre audit of 1176 UK patients with IBD examined rates of steroid dependency or excess, where excess was defined as more than one course of steroids in a 12 month period.32 It found that in the course of a year 14.9% of patients met the definition of steroid dependency or excess, half of which was deemed to be avoidable. Where corticosteroids had been prescribed in primary care 91% of steroid dependency or excess was deemed avoidable, although it should be noted that primary care prescriptions only accounted for a minority of the total burden of steroid excess. Self-medication may also contribute to steroid dependency and around 15% of IBD patients report self-medicating with corticosteroids.33,34 Steroid dependency continues to be a significant issue and although prescription rates may have begun to decline amongst CD patients, in UC their use has continued to rise (figure 1).18,32,35–38

Elderly patients with IBD appear to be at particular risk of steroid misuse. In a study of 20 hospitals in Pennsylvania a third of patients 65 years or older received prednisone for more than 6 months.39 The same study found steroid use rose from 36.3% in the era 1991-2000 to 63.7% in the era 2001-2010. Likewise, another study at a tertiary IBD clinic found 24% of elderly patients in clinical remission or with mild disease activity were maintained on long-term corticosteroids.40 This might be explained by the fact steroid sparing therapies such as thiopurines and anti-TNF therapy are used much less frequently in the elderly IBD population.39,40 Among elderly IBD patients receiving corticosteroids only 37% received thiopurines and just 21% were treated with a biologic agent.40 The reluctance to use thiopurines and biologics in elderly patients likely stems from concerns about the safety of these medications in this population, notably the risk of infection and malignancy. However avoiding these drugs and employing corticosteroids as an alternative is likely to be particularly deleterious in the elderly since corticosteroid related infection, osteoporosis, diabetes mellitus, and depression are significantly increased in this age group.41,42

**Reducing steroid use and misuse**

Suitable alternatives to steroids should always be considered. Guidelines recommend 5-ASA should be used first-line before corticosteroids for inducing remission in mild to moderate UC, reserving corticosteroids for refractory cases.6 Before starting corticosteroids the addition of a 5-ASA enema to oral 5-ASA should also be considered as this increases rates of mucosal healing and reduces time to the resolution of symptoms, regardless of UC disease extent.43,44 In proctitis, first-line treatment is topical 5-ASA as it is both better tolerated and more effective than steroid enemas, which are a second line alternative before the introduction of oral steroids.45,46 Combination therapy of topical 5-ASA and topical corticosteroids *may* offer a benefit over monotherapy; a study of 60 patients with proctitis found the combination of 2g 5-ASA enemas and 3mg beclomethasone diproprionate (BPD) enemas daily for 28 days was superior to either therapy alone for achieving clinical improvement (5-ASA/BPD 100% vs BPD 70% vs 5-ASA 76%).47 However, this finding was not replicated in a recent large, well-performed randomized control trial comparing Budesonide and 5-ASA suppositories as combination or monotherapy for treating proctitis.48 Budesonide foam has a low incidence of adverse events, similar to patients receiving placebo.49 In particular serum cortisol concentrations do not appear to be significantly affected. However, whether there is an advantage to using this second-generation topical corticosteroid instead of cheaper hydrocortisone foam remains unclear, as both appear to have similar efficacy and safety profiles.50

In CD exclusive enteral nutrition is effective, if tolerated, for the induction of remission as an alternative to steroids particularly if surgery is being contemplated.6,51

Where steroid use is unavoidable in ileal and ileocaecal CD, budesonide (Entocort™ or Budenofalk™) is indicated for mild to moderate disease.52 Likewise in UC it may be appropriate to prescribe budesonide MMX (Cortiment™) or beclomethasone (Clipper™) to induce remission.53,54 These agents have a low systemic bioavailability and therefore a more favourable side-effect profile compared to conventional steroids.55,56 However, budesonide is under-utilised with only 11% of individuals diagnosed with CD being prescribed Budesonide within 3 years of diagnosis, despite an estimated one third of patients fulfilling the criteria for its use.57 In some healthcare systems the relative cost of second-generation corticosteroids compared with prednisolone may be a barrier to their use,58 for example one study in the USA found less than 1% of IBD patients were prescribed budesonide between 2001-2010.39 Set against this is the considerable health-economic burden of treating side-effects from long-term systemic steroids.59,60

Maintenance therapy with anti-TNF has been associated with reduced steroid excess in CD (OR 0.61, 95%CI 0.24-0.95), however, an equivalent benefit in UC was not found, although the study was potentially underpowered in this regard.61 Akin to this finding from the UK, a nationally representative study from the USA of 8,502 patients with IBD found one in five anti-TNF users were concomitantly using steroids for 6 months or more.62 When initiating maintenance therapy clinicians should be aware that timely induction of some faster onset agents, such as anti-TNF agents, may not necessarily require bridging steroids while others with a slower onset of action, for example thiopurines, will do.

An increasing array of therapies have demonstrated steroid-sparing potential in IBD, including thiopurines, anti-TNF agents, vedolizumab, ustekinumab and tofacitinib.63–72 However timely escalation, when a patient is either corticosteroid refractory or dependent, is not carried out in significant proportion of cases, leading to inappropriate steroid excess.32 The choice of therapy should be made on an individual basis and take into account the side-effect profile with particular consideration given to risk of malignancy or infection or other recognised contraindications, route of administration, risk of immunogenicity and cost.6

Organisational factors are also important determinants of the risk of steroid excess. In a study of twenty hospitals, 11 introduced quality improvement projects to educate patients and clinicians regarding steroid use and improve access to specialist advice through telephone helplines and rapid access clinics. Patients attending hospitals where the intervention was implemented were less likely to use steroids to excess (11.5% vs 17.1%, p<0.001).61 There is also evidence that dedicated IBD clinics are associated with less excessive use of steroids in UC.32 Likewise, a dedicated IBD multi-disciplinary meeting is key to reducing inappropriate steroid excess in both CD (OR 0.37, 95%CI 0.15-0.83) and UC (OR 0.24, 95%CI 0.07-0.73).61

The recently published UK IBD Standards state that steroid use should be audited regularly, ideally on an annual basis, and a dedicated online steroid assessment tool is available for this purpose.73 This simple tool can easily be used `live’ in clinic. The introduction of the IBD benchmarking tool may also act as a stimulus to IBD services to monitor steroid use more closely and take measures to reduce steroid misuse. Recently the UK IBD registry has also started to evaluate steroid use in their annual report.35 A specific target for rates of steroid dependency and excess has yet to be fully defined and this may vary between different patient populations.61 By annually auditing steroid use, individual services can determine the local burden of inappropriate steroid excess and take steps to reduce it.

Barriers to specialist advice are likely to contribute to high rates of avoidable steroid excess in primary care. Aside from support via through IBD advice lines and rapid access clinics, education may also play a role in reducing steroid misuse in IBD.74 The IBD Spotlight Project, is a collaboration between Crohn’s and Colitis UK, The Royal College of General Practitioners and the BSG. It has developed an IBD toolkit and e-learning module to guide primary care physicians’ management of IBD ([*www.rcgp.org.uk/ibd*](http://www.rcgp.org.uk/ibd)*).*75This includes IBD flare-pathways for both CD and UC and IBD services should signpost primary care clinicians to these resources.

# Management of common side-effects

Several steps can be taken to reduce the significant side-effect profile of corticosteroids. Adrenal insufficiency occurs in roughly a third of patients receiving corticosteroids, particularly but not exclusively, in those exposed to high dose and long courses of corticosteroids.76,77 Guidelines recommend tapering corticosteroids in IBD, but practice varies greatly.6,78–80 BSG guidelines recommend moderate to severe UC should be treated with 40mg Prednisolone tapered over 6-8 weeks, whereas the American College of Gastroenterology guidelines state that the optimal tapering regimen has not been established but suggest reducing the dose of corticosteroids over 8-12 weeks.6,80 Similar regimens have been employed for inducing remission in CD.6,13 The dose of corticosteroids can be adjusted according to disease severity and patient tolerance, but there is no evidence to suggest a benefit from doses greater than 60mg Prednisolone per day, the optimal starting dose may be 40mg, smaller doses are probably inferior.4 It is also important to note that slow or very slow tapering regimes may be required for patients who have been on long-term steroids to avoid withdrawal side effects particularly if there is adreno-cortical insufficiency as indicated by an abnormal short synacthen test.59

Loss of bone density may occur as a result of IBD even before diagnosis.82 Corticosteroids compound this problem, with between 17-41% of IBD patients having osteoporosis.83 It is recommended that all IBD patients taking corticosteroids should have 800-1000 mg of calcium and 80 IU of vitamin D per day, either through diet or oral supplementation. The BSG guidelines outline an algorithm for determining the risk of a fracture and recommend patients at high risk should also be started on a bisphosphonate.6

Corticosteroids stimulate gluconeogenesis within the liver and result in hyperglycaemia.84 Patients using oral corticosteroids are more than twice as likely to require hypoglycaemic therapy compared with non-users (RR 2.23, 95% CI 1.92-2.59).85 This may affect both patients with and without previous diabetes mellitus and all patients receiving courses of corticosteroids for longer than 3 months should have their glycaemic control monitored and be considered for hypoglycaemic therapy.

The association between corticosteroids and peptic ulcer disease remains controversial.25 In experimental models corticosteroids impair ulcer healing86,87 however a meta-analysis found the risk of developing a peptic ulcer with corticosteroid use was similar to placebo.88 Therefore NICE does not recommend proton pump inhibitors (PPI) as routine prophylaxis of peptic ulceration in people taking oral corticosteroids.89

Cataracts occur in almost a third of patients on long-term corticosteroids.90 The risk appears to increase with both the dose and duration of steroid treatment, once again highlighting the importance of minimising corticosteroid dependency in IBD.91

Corticosteroids increase the risk of septicaemia, cellulitis, varicella, herpes zoster, and scabies and patients are at particular risk of lower respiratory tract infections and candidiasis in the first weeks of treatment.41 Recent data also suggest that high dose corticosteroids (≥40mg prednisolone or equivalent per day) increase the risk Hepatitis B reactivation, although this has not yet been studied in an IBD population.92,93

A discussion of the full range of side-effects from corticosteroids is beyond the scope of this article however particular thought should be given to the risk of avascular necrosis of the femoral head, which presents with hip pain.94 If suspected, steroids should be discontinued immediately until an MRI has excluded the condition. Clinicians should also be aware that 5.7% of individuals using steroids experience severe psychiatric symptoms and should therefore screen for depression and the less common steroid-induced psychosis, which if present warrants corticosteroids withdrawal .95,96

# Conclusion

Corticosteroids remain a potent tool in the expanding array of treatments for IBD in the 21st century however they need to be used carefully since their misuse can lead to challenging sometimes life threatening side effects. Their use and misuse, is a key performance indicator and a benchmark of the quality of an IBD service and should be regularly audited. The decision to initiate steroids should always be considered carefully and ideally wherever possible by an IBD MDT.

## **Key Points**

* Steroids have wide ranging and sometimes devastating side effects
* Steroids have no place in maintenance therapy for IBD
* Steroid dependency and excess are common and often avoidable in IBD.
* Alternatives to systemic corticosteroids, including 5-ASA, budesonide and beclomethasone, should be explored and timely introduction of an immunomodulator and/or biologic is essential.
* Dedicated IBD clinics, telephone helplines and MDTs can reduce steroid excess. IBD services should audit corticosteroid use on a regular basis.
* IBD services should signpost primary care physicians to the IBD toolkit and flare pathways ([*www.rcgp.org.uk/ibd*](http://www.rcgp.org.uk/ibd)*)* to support the management of IBD out of hours in the community.
* Steroids should be tapered appropriately to minimise the risk of adrenal insufficiency.
* All IBD patients on steroids should have adequate calcium and vitamin D supplementation for bone protection and be considered for bisphosphonates where appropriate.

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# Table 1

Indications and suggested regimens for corticosteroids in IBD.

|  |  |  |  |
| --- | --- | --- | --- |
| **Type** | **Target** | **Indication** | **Suggested Dose** |
|  |  |  |  |
| Hydrocortisone 10% Foam Enema | Rectum, Sigmoid | Proctitis, Proctosigmoiditis | 1-2 metered applications (equivalent of 90mg) per day for 2-3 weeks, then once daily alternate days |
| Budesonide Rectal Foam | Rectum, Sigmoid | Proctitis, Proctosigmoiditis | 1 metered application (equivalent of 2mg) once daily for up to 8 weeks |
| BudesonidepH-dependent | Ileum, Right Colon | Mild to moderate ileocaecal CD | 9mg daily for 8 weeks, taper over 1-2 weeks |
| BudesonideMMX | Colon | Mild to moderate UC | 9mg daily for 8 weeks |
| Beclamethasone dipropionate | Colon | Mild to moderate UC | 5mg daily for 4 weeks, followed by 5mg every other day for 4 weeks |
| Prednisolone | Systemic | Moderate to severe UCModerate to severe CD (not penetrating) | 40mg daily, tapering over 6-8 weeks |
| Hydrocortisone | Systemic | Acute Severe UC | 100mg IV 6 hourly, switch to 40mg Prednisolone OD after 2 days of passing <4 stools per day with no blood |
| Methylprednisolone | Systemic | Acute Severe UC | 60-80mg IV daily, switch to 40mg Prednisolone OD after 2 days of passing <4 stools per day with no blood |