Supplementary Material

Supplementary Figure 1. Consensus Process
April 2012
WGO calls for topics

April 2012
IOIBD and ESCP proposes “Perianal Fistulizing Crohn’s disease”
chaired by G D’Haens, B Feagan, JF Colombel

October 2012, UEGW
Co-chairs identify Working Subgroups and Research Committee:
K Gecse, R Khanna, G Bouguen, B Levesque

Classification
G D’Haens
B Feagan
G van Assche
J Stoker
A D’Hoore
J Panes
K Gecse

Diagnosis
J Stoker
B Sands
A Sturm
Siew Ng
A Hart
R Khanna

Medical & Surgical Treatment
WJ Sandborn
JF Colombel
W Bemelman
MA Kamm
D Laharie
Z Liu
B Levesque

October 2012 – February 2013
Research Committee performs systematic literature search, drafts and circulates Statements

February 2013, ECCO
Working Group revises Statements and assigns Grades of Recommendations

February – May 2013
Research Committee drafts and circulates Algorithms

May 2013, DDW
Working Group revises Algorithms

May – August 2013
Voting on Agreement and preparation of supporting text

September 2013
Expert Consensus presented at WCOG 2013
## Supplementary Table 1. Level of Agreement and Grades of Recommendation

### Level of Agreement

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A+</td>
<td>Agree strongly</td>
</tr>
<tr>
<td>A</td>
<td>Agree with minor reservation</td>
</tr>
<tr>
<td>A-</td>
<td>Agree with major reservation</td>
</tr>
<tr>
<td>D</td>
<td>Disagree with minor reservation</td>
</tr>
<tr>
<td>D-</td>
<td>Disagree with major reservation</td>
</tr>
<tr>
<td>D+</td>
<td>Disagree strongly</td>
</tr>
</tbody>
</table>

### Grades of Recommendation

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>Strong recommendation, high-quality evidence</td>
</tr>
<tr>
<td>1B</td>
<td>Strong recommendation, moderate-quality evidence</td>
</tr>
<tr>
<td>1C</td>
<td>Strong recommendation, low-quality or very low-quality evidence</td>
</tr>
<tr>
<td>2A</td>
<td>Weak recommendation, high-quality evidence</td>
</tr>
<tr>
<td>2B</td>
<td>Weak recommendation, moderate-quality evidence</td>
</tr>
<tr>
<td>2C</td>
<td>Weak recommendation, low-quality or very low-quality evidence</td>
</tr>
</tbody>
</table>

Adapted from Guyatt et al. and Bitton et al.
Experimental Therapies

Medical therapies

Uncontrolled case series have reported the efficacy of miscellaneous treatments (MMF [9-12], nutritional therapy[13-17], hyperbaric oxygen[18-23], platelet derived growth factor[24,25] and GM-CSF[26]) for the treatment of fistulizing Crohn’s disease. Controlled trials are needed to support their use in pCD. Of note, a single short and small placebo-controlled trial randomized 57 patients with perianal Crohn’s fistulas to treatment with placebo or oral spherical adsorptive carbon.[27] Upon 8-weeks of follow-up, 8 of 27 patients (29.6%) achieved clinical remission, defined as a closure of all fistulas without any leakage, as compared to 2 of 30 patients (6.7%) in the placebo group.[27] However, a recent RCT including 249 patients failed to confirm the adsorptive carbon.[28] Prospective open-label series and retrospective cohort observed some efficacy of thalidomide particularly after failure of TNF antagonists, however intolerance and side effects to thalidomide were frequent.[29-35] Thus, the evidence level of efficacy of mycophenolate mofetil (MMF), thalidomide, GM-CSF, nutritional therapy and hyperbaric oxygen is low in fistulizing Crohn’s disease. Evidence for oral adsorptive carbon microspheres is contradictory, therefore its use is not recommended.

Surgical and endoscopic treatments

A modification of the loose Seton, called progressive migration technique (daily self rotation of the Seton by 360 degrees) has recently been introduced for high transspincterich fistulas.[36] Although the technique is promising with regard to healing, recurrence and incontinence rates data, especially concerning Crohn’s fistulae, are yet insufficient to recommend standard use.[36] Preliminary data from a recent prospective study showed that flap advancement can be successfully combined with video-assisted anal fistula treatment (VAAFT).[37] The technique involves direct visualization of the fistula tracts, potential side tracts and internal openings by a fistuloscope before performing advancement flap repair.

Local anti-TNF injections have been proposed for patients who are intolerant or unresponsive to systemic therapy. Two open-label studies have examined the effect of this treatment on perianal fistulizing Crohn’s. Perifistular infliximab injection was shown to induce fistula closure in 10 of 15 patients (15-20mg, 3-12 infusions).[38] In another study, of the 11 patients treated with local infliximab (20mg, repeated every 4 weeks) 8
patients achieved clinical response or remission. During follow-up (mean 10.5 months) 4 patients remained in remission.[39] A prospective open-label study showed improvement in all 12 patients and complete cessation of drainage in 9 patients treated with perifistular adalimumab.[40] Combination treatment of fistulectomy and perifistular infliximab injections (20-25mg, every 4-6 weeks until fistula closure, median 5 sessions) resulted in persistent closure in 7 of 8 patients upon 1-year follow-up according to a prospective cohort.[41] Although these reports showed beneficial effect of local biological therapy patient numbers were low and a control group was lacking, therefore further controlled clinical trials are needed to recommend their use in clinical practice.

Carbon dioxide laser ablation. In a prospective, single-arm study including 27 Crohn’s patients carbon dioxide laser ablation significantly improved perianal fistula drainage.[42] The technique was combined with the placement of noncutting Seton for 6 months and complete healing was reached in 11 patients at the final visit (mean 19 months). This treatment remains highly experimental.

Over The Scope Clip (OTSC). The OTSC (Ovesco Endoscopy, Tübingen, Germany) was tested in a porcine model to close internal fistula openings by using a transanal clip applicator.[43] This pilot study demonstrated feasibility, safety and suggested better fistula healing compared to untreated control fistulas. In a single case report on a high transspincteric fistula, healing was observed and the OTSC was removed eight months after clip closure.[44] Further controlled trials are awaited to evaluate the role of this minimally invasive technique.

Figure Legends

Supplementary Figure 1. Systematic Literature Searches of PubMed and Embase were performed by the Research Committee (KG, RK, GB, BL) in conjunction with the Cochrane Review in IBD team at Western University, London, Ontario, Canada, using the following search terms: Crohn*, enteritis regional*, ileitis terminal*, perianal, anal, perineal, fistul*, sinus, sinus*, classsif*, grade, gradi*, index, index*, indice, scale, scale*, scali*, score, score*, scori*, activity, diagnostic, diagnosi*, diagnose, image, image*, ultrasound*, EUS, magnetic resonance, MR, MRI, endoscop*, sigmoidoscop*, proctosigmoidoscop*, computerized tomography, CT, fistulograph*, EUA, examination under anaesthesia, antibiotic, immunomodulat*, immunosuppress*, biologic, anti-TNF, metronidazole,
ciprofloxacin, amoxicillin, 6-mercaptopurine, azathioprine, thioguanine, tioguanine, cyclosporine, tacrolimus, methotrexate, infliximab, adalimumab, certolizumab, oxygen, carbon, nutrition, mycophenolate mofetil, thalidomide, GM-CSF, surgery, surgery*, surgi*, seton, drain*, fistulotomy, fistulectomy, lay-open, flap, LIFT, bioLIFT, plug, glue, stem cell, stoma, proctectomy. Searches were limited to English language and full papers. Additionally, abstracts from Digestive Disease Week (DDW), United European Gastroenterology Week (UEGW), Annual Meeting of the Radiological Society of North America (RSNA) and European Congress of Radiology (ECR) 2012 and 2013 were also screened. The search initially identified 4680 references. Titles and abstracts were downloaded and two independent committee members reached consensus on which references were the most relevant.
References on Experimental Treatment


