presence of any active infection should be treated and resolved before attempting repair. After fistula excision the treatment with a mucosal advancement flap can then be performed. In a similar manner, enterovesical or colovesical fistulas may be treated with immunomodulator therapy or anti-TNF antibodies, or both, but the occurrence of recurrent symptomatic urinary tract infection is a relative indication for surgery (especially if associated with pyelonephritis). Surgery usually involves resection of involved inflamed bowel and closure of the bladder defect.

Finally, enteroenteric fistulas (such as ileum to ileum) may be present and asymptomatic. As these fistulas are asymptomatic they do not require surgical management; however, treatment with immunomodulator therapy or anti-TNF antibodies, or both, might be initiated. Major symptomatic internal fistulas, such as gastrocolic and coloduodenal fistulas, may cause symptoms as they bypass part of the intestine. If medical management fails or if an abscess develops, surgical intervention is recommended.

A variety of different medications have been used to treat fistulas in patients with CD. Mesalamine and corticosteroids are ineffective treatments for fistulizing CD.

Although poorly studied, antibiotics may heal simple, superficial perianal fistulas, with minimal penetration of sphincter musculature, and play an adjunctive role in treating perianal sepsis associated with more complex fistulas. Simple fistulas respond well to medical therapy. Metronidazole and ciprofloxacin have been evaluated in the management of perianal CD (263–266). Typical initial medical therapy might include therapy with metronidazole (10 to 20 mg/kg/day orally for 4 to 8 weeks) and/or ciprofloxacin (500 mg orally twice daily for 4 to 8 weeks) or levofloxacin (500–750 mg once daily for 4 to 8 weeks) for the fistula and treatment of concurrent mucosal disease. Antibiotics (e.g., metronidazole, ciprofloxacin, and levofloxacin) improve fistula symptoms and may be associated with healing of simple fistulas. Metronidazole and ciprofloxacin have not been effective at healing complex perianal fistulas, but may improve symptoms related to the fistula (249). Antibiotics are most commonly administered for active infection, but rarely replace the need for surgical drainage of an abscess. There have been recent warnings for the occurrence of tendonitis, tendon rupture, and neuropathy when using the fluoroquinolones.

Thiopurines, although poorly studied, may also lead to reduction of the symptoms of perianal fistulas, but can be slow in onset of effect. Azathioprine and 6-mercaptopurine have been shown to be effective for treating fistulizing CD. Tacrolimus is effective for short-term treatment of fistulizing CD; however, significant toxicity precludes long-term therapy with this agent

The anti-TNFs are effective for closure of perianal fistula, but only infliximab has been studied in a prospective, randomized controlled trial. In the initial study, infliximab 5 mg/kg at 0, 2, and 6 weeks led to cessation of all drainage of perianal fistula on 2 consecutive visits 1 month apart, defined as complete closure, in the majority of patients.(244) A subsequent, large randomized controlled trial confirmed the efficacy of infliximab for induction of closure of perianal fistula, but also every 8 week dosing at 5 mg/kg for maintenance of complete closure and response, defined as >50% closure on clinical assessment (245). Infliximab may also be effective at maintaining response of rectovaginal fistula closure (246). Subsequent studies from clinical practice cohorts have replicated the efficacy of infliximab for the induction of perianal fistula closure and maintenance of response (267,268). Although not as thoroughly studied, adalimumab may also be effective in treating signs and symptoms of perianal fistulas. Perianal fistula closure was not a primary end point of any of the adalimumab or certolizumab studies. On *post hoc* analysis from two adalimumab CD studies, there was no benefit over placebo for fistula closure (269,270). In a large maintenance study of adalimumab for CD, fistula response and remission was a secondary end point that was achieved in a higher percentage of patients compared with placebo (218,220,271,272). A small open-label trial of adalimumab also suggested a benefit for fistula induction of remission and maintenance of closure (272). Similarly, there is a suggestion of efficacy based upon *post hoc* analysis of certolizumab pegol, vedolizumab, and ustekinumab trials, but no controlled studies indicating unequivocal benefit in fistulizing CD (220,273,274). In addition, the use of combination therapy with anti-TNF therapy and antibiotics may be more beneficial than each agent individually. Combination therapy with ciprofloxacin and infliximab or ciprofloxacin and adalimumab has been shown to be more effective than monotherapy for each anti-TNF agent to treat fistulas and is effective in reduction of fistula drainage.

## MAINTENANCE THERAPY OF LUMINAL CROHN'S DISEASE

*No maintenance treatment is a treatment option for some patients with asymptomatic (silent), mild Crohn's disease (Summary Statement).*

*Surgery may be considered for patients with symptomatic Crohn's disease localized to a short segment of bowel* (*Summary Statement).*

***Recommendations***

44. Once remission is induced with corticosteroids, a thiopurine or methotrexate should be considered (strong recommendation, moderate level of evidence).
45. Patients who are steroid dependent should be started on thiopurines or methotrexate with or without anti-TNF therapy (strong recommendation, moderate level of evidence).

Corticosteroids are not indicated for long-term treatment of CD because of lack of efficacy for maintenance of remission and adverse effects (275). There are three scenarios by which a thiopurine is used after corticosteroid induction of remission. One scenario is to initiate the thiopurine at the time of the first course of corticosteroid, the second is after repeated courses of corticosteroids or in patients who are corticosteroid dependent (i.e., unable to taper the steroid without CD relapse), and the third is as a concomitant medication to an anti-TNF. The efficacy of 6-mercaptopurine 1.5 mg/kg/day as a maintenance medication when administered in combination with the first course of corticosteroid for newly diagnosed pediatric CD is good (276). Presumably, the same efficacy