Complete Summary

GUIDELINE TITLE

American Gastroenterological Association medical position statement: perianal Crohn´s disease.

BIBLIOGRAPHIC SOURCE(S)

American Gastroenterological Association medical position statement: perianal Crohn's disease. Gastroenterology 2003 Nov;125(5):1503-7. [2 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

According to the guideline developer, the Clinical Practice Committee meets three times a year to review all American Gastroenterological Association Institute (AGAI) guidelines. This review includes new literature searches of electronic databases followed by expert committee review of new evidence that has emerged since the original publication date.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse (NGC): This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- July 08, 2008, Fluoroquinolones (ciprofloxacin, norfloxacin, ofloxacin, levofloxacin, moxifloxacin, gemifloxacin): A BOXED WARNING and Medication Guide are to be added to the prescribing information to strengthen existing warnings about the increased risk of developing tendinitis and tendon rupture in patients taking fluoroquinolones for systemic use.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Perianal Crohn´s disease

GUIDELINE CATEGORY

Diagnosis
Management
Treatment

CLINICAL SPECIALTY

Colon and Rectal Surgery
Gastroenterology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To present the official recommendations of the American Gastroenterological Association (AGA) on perianal Crohn´s disease
- To summarize epidemiology, diagnosis, medical and surgical treatments, and approaches to treatment of perianal Crohn´s disease

TARGET POPULATION

Patients who have Crohn´s disease with perianal lesions

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis

1. Classification systems
    - Cardiff classification
    - Crohn´s Disease Activity Index
    - Parks classification
    - Empiric classification (in clinical practice)
    - Simple or complex fistulas
2. Examination/Imaging
    - Examination under anesthesia (EUA)

- Anorectal endoscopic ultrasonography (EUS)
- Pelvic magnetic resonance imaging (MRI)

Medical Treatments

1. Antibiotics: ciprofloxacin; metronidazole
2. Azathioprine and 6-mercaptopurine
3. Infliximab
4. Cyclosporine
5. Tacrolimus

Surgical Treatments

1. Skin tags: excision (not recommended)
2. Hemorrhoids: simple hemorrhoidectomy (usually contraindicated)
3. Anal fissures: fissurectomy (contraindicated); lateral sphincterectomy
4. Anorectal strictures: dilations
5. Perianal abscess: surgical drainage
6. Perianal fistulas:
    - Fistulotomy
    - Noncutting seton
    - Endorectal advancement flap
    - Temporary diverting ileostomy (rarely performed)
7. Rectovaginal fistulas; fistulotomy (rarely indicated); primary closure; advancement flaps
8. Obstetrical surgical procedures: cesarean section recommended during active disease); vaginal delivery and episiotomy

General Treatment of Crohn´s Disease

1. Active proximal luminal disease: budesonide, conventional corticosteroids, azathioprine, 6-mercaptopurine, methotrexate, infliximab, surgical resection
2. Postoperative bile salt diarrhea or steatorrhea: loperamide, diphenoxylate and atropine, codeine, cholestyramine, low-fat diet

MAJOR OUTCOMES CONSIDERED

Diagnosis

Accuracy of examination/imaging studies

Treatment

- Fistula closure
- Healing rate
- Number of draining fistulas
- Quantity of fistula drainage
- Relapse rates
- Adverse events

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

A search of the online bibliographic databases MEDLINE (1966 to August 2002) and Current Contents/ Science Edition (1996 to August 2002) was performed to identify potentially relevant English-language articles. The Medical Subject Heading terms "Crohn´s disease" or "inflammatory bowel disease" or "regional enteritis" AND "fistulas" or "perianal" were used to perform keyword searches of the database. Manual searches of the reference lists from the potentially relevant papers and the proceedings from annual meetings of the American Gastroenterological Association, American College of Gastroenterology, and American Society of Colon and Rectal Surgeons from 1990 to 2003 were performed to identify additional studies that may have been missed using the computer-assisted search strategy.

Studies selected were retrospective or prospective studies reporting on the classification, epidemiology, diagnosis with magnetic resonance imaging (MRI) or anorectal endoscopic ultrasonography (EUS), treatment with medical therapy, and surgical treatment of perianal Crohn´s disease. This technical review is not based solely on level 1 studies (population-based natural history studies and randomized, double-blind, placebo-controlled trials of diagnostic modalities and therapeutic interventions), because only 5 level 1 studies were identified and they do not provide a sufficient basis for an "evidence-based" technical review and medical position statement.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The paper was approved by the Committee on May 18, 2003, and by the American Gastroenterological Association (AGA) Governing Board on July 25, 2003.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Diagnosis

To plan appropriate medical or surgical therapy, patients with perianal Crohn´s disease must be classified as having simple or complex perianal disease (refer to the original guideline document for details). Diagnosis of simple fistulas or complex perianal disease by physical examination and rectosigmoid endoscopy may be sufficient for many patients when medical therapy is the initial treatment strategy. Additional diagnostic evaluation by examination under anesthesia (EUA) and either anorectal endoscopic ultrasonography (EUS) or pelvic magnetic resonance imaging (MRI) is indicated in those patients with pain, fluctuation, or stricture on digital rectal examination, in those patients in whom surgical therapy is the initial treatment strategy (because up to 10% of patients with perianal fistulas will be misclassified by EUA alone and fistulotomy of a high fistula misclassified as a low fistula may lead to incontinence and/or poor wound-healing and in some instances subsequent proctectomy), and in those failing medical or surgical therapy. It is recognized that this recommendation represents a change in

practice, even for gastroenterologists and colorectal surgeons with great expertise in the management of perianal Crohn´s disease, but acknowledges that EUA is not 100% accurate and that inaccurate diagnosis before surgical intervention may lead to irreversible functional consequences.

General Treatment of Crohn´s Disease

In addition to the specific medical and surgical treatments outlined as follows, any active proximal luminal disease should also be treated as appropriate with budesonide, conventional corticosteroids, azathioprine, 6-mercaptopurine, methotrexate, infliximab, and surgical resection.

Postoperative bile salt diarrhea or steatorrhea should be treated as indicated with loperamide, diphenoxylate and atropine, codeine, cholestyramine, and low-fat diet. These measures are all aimed at reducing stool liquidity, with the goal of decreasing the quantity of fistula drainage.

Treatment of Simple Perianal Fistulas

Potential treatments for simple fistulas include antibiotics, fistulotomy, and possibly azathioprine or 6-mercaptopurine and infliximab. Antibiotics are widely used to treat simple fistulas and are recommended in practice guidelines and previous treatment algorithms but have not been evaluated in placebo-controlled trials. Fistulotomy is widely used by surgeons to treat simple fistulas, resulting in a high rate of healing that is often sustained. The prevailing view among surgeons is that those patients with a simple fistula who do not respond to a short course of antibiotics are best treated with fistulotomy. However, reported surgical series have been small, there are no controlled trials comparing fistulotomy with sham operation or medical therapy, and some patients fail to heal and may require proctectomy. The immunosuppressive medications azathioprine and 6-mercaptopurine can be used to treat simple fistulas and are recommended in practice guidelines but have not been evaluated in placebo-controlled trials in which fistula reduction or closure was the primary end point. These agents are slow acting and thus may be of more utility for maintaining fistula closure than for the initial induction of fistula closure. Infliximab has been proven effective in placebo-controlled trials for the indications of both reduction in the number of draining fistulas and maintenance of that reduction, and a 3-dose induction regimen and a maintenance regimen every 8 weeks are approved by the U.S. Food and Drug Administration (FDA) for treatment of fistulas; however, infliximab is expensive, concomitant immunosuppressive therapy is probably required to counteract the formation of human antichimeric antibodies that may lead to infusion reactions and loss of efficacy, and rarely serious infections may occur. There are insufficient high-quality data (level 1 evidence [population-based natural history studies and randomized, double-blind, placebo-controlled trials of diagnostic modalities and therapeutic interventions]) to make a clear recommendation as to whether antibiotics, fistulotomy, azathioprine or 6-mercaptopurine, or infliximab is the preferred strategy for simple fistulas. Tacrolimus and cyclosporine are not appropriate treatment for simple fistulas because of toxicity.

Treatment of Complex Perianal Fistulas

Potential treatments for complex fistulas include antibiotics, azathioprine and 6-mercaptopurine, infliximab, tacrolimus and cyclosporine, and surgery (dilation of anal strictures, placement of noncutting setons, endorectal advancement flap, repair of rectovaginal fistulas, fecal diversion, and proctectomy). Antibiotics are widely used to treat complex fistulas and are recommended in practice guidelines and treatment algorithms but have not been evaluated in placebo-controlled trials. Relapse rates are high after antibiotic therapy for complex fistulas is discontinued, and their use should probably be adjunctive in combination with other medical agents or surgery in this setting. Similarly, the immunosuppressive medications azathioprine and 6-mercaptopurine are used to treat complex fistulas and are recommended in practice guidelines but have not been evaluated in placebo-controlled trials in which fistula reduction or closure was the primary end point. Furthermore, these agents are slow acting and thus are of more utility for maintaining fistula closure than for the initial reduction in the number of draining fistulas.

In contrast to antibiotics and immunosuppressive medications, infliximab has been proven to be effective in placebo-controlled trials for reduction in the number of draining fistulas and maintenance of that reduction and treatment of fistulas with a 3-dose induction regimen and a maintenance regimen every 8 weeks is approved by the U.S. Food and Drug Administration (FDA). Finally, tacrolimus or cyclosporine can rarely be considered in selected patients who fail multimodality treatment with other medical and surgical therapies, including infliximab. This practice is based on uncontrolled case series with cyclosporine and a single short-term placebo-controlled trial with tacrolimus that showed a reduction in the number of draining fistulas; however, nephrotoxicity and other side effects occur frequently and these agents should be used with caution. The trials examining tacrolimus and cyclosporine have been of short duration, without determining whether maintenance therapy after initial fistula closure is safe and effective.

Surgical therapy for complex perianal disease is largely palliative. Perianal abscesses should be drained and anal strictures dilated. Noncutting setons can be placed in fistula tracts in patients with macroscopic rectal inflammation, and endorectal advancement flap procedures for high perianal fistulas and rectovaginal fistulas can be performed in patients without rectal inflammation. The recurrence rates following removal of noncutting setons and following endorectal advancement flap procedures are both relatively high. Setons can be left in place indefinitely; however, given the alternative of suppressive medical therapy, patients may not prefer this option. Because infliximab therapy can completely close all fistula tracks in many patients with complex fistulas, most gastroenterologists now believe that infliximab is the initial treatment of choice in this setting (it is debated by surgeons whether infliximab or noncutting setons is the initial treatment of choice for the subgroup of patients with complex perianal fistulas who do not have active rectal disease, because there are no data on patient acceptance of long-term noncutting setons versus treatment with infliximab). Azathioprine, 6-mercaptopurine, or methotrexate should be coadministered routinely both to counteract an immunogenic reaction to infliximab and as maintenance of remission therapy. Some patients will require combination maintenance therapy with azathioprine, 6-mercaptopurine, or methotrexate and infliximab. Temporary adjunctive therapy with antibiotics may be considered. Routine EUA and seton placement before initiating infliximab therapy is not mandatory.

Patients with complex fistulas who initially fail treatment with infliximab should undergo anorectal endoscopic ultrasonography or pelvic MRI as well as EUA with placement of setons as indicated while continuing treatment with infliximab, azathioprine or 6-mercaptopurine, and antibiotics. Tacrolimus or cyclosporine can be considered in patients who fail this multimodality approach. As a last resort, fecal diversion or proctectomy may be undertaken.

Specific Treatment of Rectovaginal Fistulas

Potential treatments for rectovaginal fistulas include both medical therapy and surgery. 6-Mercaptopurine, infliximab, cyclosporine, and tacrolimus have all been used to treat rectovaginal fistulas in uncontrolled series. A controlled trial of maintenance infliximab infusions in patients with fistulas who responded to infliximab included a subgroup of patients with rectovaginal fistulas. Surgical treatment of rectovaginal fistulas can only be performed when there is endoscopic healing of the rectosigmoid mucosa. Standard medical therapy with conventional corticosteroids, azathioprine, 6-mercaptopurine, methotrexate, or infliximab should be administered as indicated to control active luminal inflammatory disease in the rectosigmoid colon. If the rectovaginal fistula persists after the patient has received medical therapy to treat both the fistula itself and the rectosigmoid mucosa, and there is no evidence of an anorectal stricture or active rectal disease, then surgical repair with transanal or transvaginal advancement flaps, or laparotomy with primary closure or sleeve advancement flap can be performed. Advancement flap surgery should be reserved for patients with disabling symptoms because of the risk of worsening symptoms in those patients in whom the operation fails. As a last resort, fecal diversion or proctectomy may be undertaken. Some women may choose to accept residual fistula drainage over proctectomy with an ostomy to optimize their overall quality of life.

CLINICAL ALGORITHM(S)

A treatment algorithm for managing patients with Crohn´s perianal fistulas is provided in the Technical Review that accompanies the guideline (see the "Companion Documents" field).

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence supporting the recommendations is not explicitly stated.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Improved treatment of perianal Crohn´s disease, with greater potential for disease cure; or with reduced need for maintenance therapy and prolonged periods of remission

POTENTIAL HARMS

Medication-related Adverse Events

- Adverse events associated with **metronidazole** include metallic taste, glossitis, nausea, and a distal peripheral sensory neuropathy.
- Adverse events associated with **ciprofloxacin** are uncommon but include headache, nausea, diarrhea, and rash.
- Adverse events associated with **azathioprine and 6-mercaptopurine** include leukopenia, allergic reactions, infection, pancreatitis, drug-induced hepatitis, and possibly non-Hodgkin´s lymphoma. Patients treated with these medications should have regular monitoring of leukocyte counts and liver transaminase levels.
- Adverse events observed in patients treated with **infliximab** include infusion reactions, delayed hypersensitivity reactions, formation of human antichimeric antibodies, formation of antinuclear antibodies and anti-double-stranded deoxyribonucleic acid (DNA) antibodies, and drug-induced lupus. Concomitant immunosuppressive therapy with azathioprine, 6-mercaptopurine, or methotrexate is recommended to reduce the frequency of these reactions, which are largely due to an immunogenic response to the murine component of the chimeric antibody. There is also an increased overall rate of infections and, rarely, serious infections including pneumonia, sepsis, tuberculosis, histoplasmosis, coccidioidomycosis, listeriosis, *Pneumocystis carinii* pneumonia, and aspergillosis occur. It is recommended that patients undergo purified protein derivative skin testing before treatment with infliximab.
- Adverse events observed in patients treated with **cyclosporine** include renal insufficiency, hirsutism, hypertension, paresthesias, headache, seizure, tremor, gingival hyperplasia, hepatotoxicity, and an increased incidence of infection (including *P. carinii* pneumonia).
- Adverse events observed in patients treated with **tacrolimus*** include headache, increased serum creatinine level, insomnia, leg cramps, paresthesias, and tremor, typically resolved with dose reduction. The major toxicity observed in patients treated with tacrolimus* was an increase in serum creatinine level from baseline to a value $\geq$1.5 mg/dL (designated before the study as nephrotoxicity requiring tacrolimus dose reduction), which occurred in 8 of 21 patients (38%) treated with tacrolimus compared with 0 of 25 (0%) placebo-treated patients (P = 0.008).

CONTRAINDICATIONS

CONTRAINDICATIONS

- Simple hemorrhoidectomy, the newer procedure for prolapsing hemorrhoids, or banding of hemorrhoids in patients with Crohn´s disease are usually contraindicated due to the frequent occurrence of postoperative complications, including poor wound healing, anorectal stenosis, and a high rate of proctectomy.
- Fissurectomy is contraindicated.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- The guideline has been developed under the aegis of the Clinical Practice Committee of the American Gastroenterological Association (AGA). It provides preferred approaches to specific medical problems or issues. The statements herein are derived from the data available at the time of their creation and may need to be modified as new information is generated. Unless otherwise stated, these statements are intended for adult patients. The strength of the evidence upon which the statements are based is noted, with prospective, randomized, controlled trials being the strongest. When adequate data are absent, expert consensus may be used and will be identified as such. This document is not to be construed as a standard of care. All decisions regarding the care of a patient should be made by the physician in consideration of all aspects of the patient´s specific medical circumstances.
- Although descriptions of surgical therapy are provided in the accompanying Technical Review, along with the indications, outcomes, and complications of surgical intervention, the reader is cautioned that this review is not meant to provide the details of how to perform the specific individual surgical procedures.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Clinical Algorithm

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

American Gastroenterological Association medical position statement: perianal Crohn's disease. Gastroenterology 2003 Nov;125(5):1503-7. [2 references]
PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2003 Nov

GUIDELINE DEVELOPER(S)

American Gastroenterological Association Institute - Medical Specialty Society

SOURCE(S) OF FUNDING

American Gastroenterological Association Institute

GUIDELINE COMMITTEE

American Gastroenterological Association Clinical Practice Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Not stated

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

According to the guideline developer, the Clinical Practice Committee meets three times a year to review all American Gastroenterological Association Institute (AGAI) guidelines. This review includes new literature searches of electronic databases followed by expert committee review of new evidence that has emerged since the original publication date.

GUIDELINE AVAILABILITY

Electronic copies: Available from the American Gastroenterological Association Institute (AGAI) *Gastroenterology* journal Web site.

Print copies: Available from the American Gastroenterological Association Institute, 4930 Del Ray Avenue, Bethesda, MD 20814.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- W.J. Sandborn, V.W. Fazio, B.G. Feagan, S.B. Hanauer. AGA technical review on perianal Crohn´s disease. Gastroenterology. 2003 Nov;125(5):1508-1530.

Electronic copies: Available from the American Gastroenterological Association Institute (AGAI) Gastroenterology journal Web site.

Print copies: Available from the American Gastroenterological Association Institute, 4930 Del Ray Avenue, Bethesda, MD 20814.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on May 19, 2004. This summary was updated by ECRI on March 15, 2005 following release of a public health advisory from the U.S. Food and Drug Administration regarding the use of Elidel. This summary was updated by ECRI Institute on July 28, 2008 following the U.S. Food and Drug Administration advisory on fluoroquinolone antimicrobial drugs.

COPYRIGHT STATEMENT

DISCLAIMER

NGC DISCLAIMER

The National Guideline Clearinghouse™ (NGC) does not develop, produce, approve, or endorse the guidelines represented on this site.

All guidelines summarized by NGC and hosted on our site are produced under the auspices of medical specialty societies, relevant professional associations, public or private organizations, other government agencies, health care organizations or plans, and similar entities.

Guidelines represented on the NGC Web site are submitted by guideline developers, and are screened solely to determine that they meet the NGC Inclusion Criteria which may be found at http://www.guideline.gov/about/inclusion.aspx .

NGC, AHRQ, and its contractor ECRI Institute make no warranties concerning the content or clinical efficacy or effectiveness of the clinical practice guidelines and related materials represented on this site. Moreover, the views and opinions of developers or authors of guidelines represented on this site do not necessarily state or reflect those of NGC, AHRQ, or its contractor ECRI Institute, and inclusion or hosting of guidelines in NGC may not be used for advertising or commercial endorsement purposes.

Readers with questions regarding guideline content are directed to contact the guideline developer.

Date Modified: 11/3/2008