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# Combined Medical and Surgical Approach Improves Healing of Septic Perianal Crohn's Disease



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- BACKGROUND:** Septic perianal Crohn's disease (SPCD) is a treatment challenge in spite of tumor necrosis factor antagonists (anti-TNF). Our aim was to define the success of SPCD management with a combined medical and surgical approach and to identify clinical and genetic factors predictive of healing.
- STUDY DESIGN:** A retrospective chart review of patients with SPCD treated at the Penn State Milton S Hershey Medical Center was done. Primary end point was complete healing (ie normal clinical exam and no pain for at least 6 months). Genetic analysis of 185 single nucleotide polymorphisms associated with Crohn's disease was performed in 78 patients.
- RESULTS:** One hundred and thirty-five episodes of SPCD were identified in 114 patients with a mean follow-up of  $77 \pm 7.4$  months. Overall, 80 of 135 episodes healed (59.3%) and did not differ between those receiving anti-TNF and not (60.4% vs 56.8%). There appeared to be a consistent improved heal rate in each subcategory of surgically managed patients that received anti-TNF. Female sex was significantly predictive of healing in only those receiving anti-TNF agents (63.6% vs 25.0%;  $p = 0.0005$ ). Twenty-two (19.3%) patients ultimately received a permanent diversion with either a total proctocolectomy or completion proctectomy. Multivariate analysis suggested several single nucleotide polymorphisms in Crohn's disease-associated genes to be possibly associated with healing, but lost significance after Bonferroni correction.
- CONCLUSIONS:** Overall, there is an approximate 60% rate of healing SPCD using a combined medical and surgical approach. About 20% of SPCD patients will require a permanent stoma. There were no clear genetic predictors of healing SPCD. (J Am Coll Surg 2016;223:506–514. © 2016 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)
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Perianal disease occurs in 13% to 43% of patients with Crohn's disease (CD).<sup>1-4</sup> Septic perianal Crohn's disease (SPCD) is a subcategory that includes perianal abscesses

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and/or fistulas, and excludes the more benign manifestations, such as fissure, ulcer, skin tags, and anorectal stricture. The incidence of SPCD is reported to be 23% to 28% or the majority of perianal CD. It is these septic complications that are widely recognized to cause significant morbidity, including significant risk of proctectomy.<sup>1,5</sup> Despite advances in both medical and surgical management of CD, successful healing of SPCD remains notoriously challenging for both the patient and caregiver. The introduction in August 1998 of infliximab, the first tumor necrosis factor antagonist (anti-TNF) agent, marked a new era of medical therapy for CD. Early studies using infliximab to treat CD fistulas described a response rate of up to 60%.<sup>6</sup> However, subsequent longer-term studies found only a 25% rate of continued healing at approximately 1 year.<sup>7-9</sup> As experience with anti-TNF agents is gained, it has become increasingly apparent that a combined medical and surgical approach to SPCD is necessary.<sup>8-10</sup>

### Abbreviations and Acronyms

|          |                                    |
|----------|------------------------------------|
| anti-TNF | = tumor necrosis factor antagonist |
| CD       | = Crohn's disease                  |
| IBD      | = inflammatory bowel disease       |
| RVF      | = rectovaginal fistula             |
| SNP      | = single nucleotide polymorphism   |
| SPCD     | = septic perianal Crohn's disease  |

The Penn State Milton S Hershey Medical Center's colorectal surgery department has developed a care paradigm (Fig. 1) that guides the management of patients with SPCD. One of the goals of the current study was to evaluate the success of this treatment paradigm and specifically evaluate the success of the various combinations of this multimodal management.

Besides anti-TNF therapy, there has been a revolution in the understanding of CD due to the discovery of numerous single nucleotide polymorphisms (SNPs) that are associated with inflammatory bowel disease (IBD).<sup>11</sup> However, the way in which such genetic information can be used for the care of the IBD patient is unclear. Therefore, in this study, we sought to identify not only clinical but possible genetic factors (SNPs) that might be predictive of healing in SPCD.

## METHODS

A retrospective medical chart review was performed to identify patients with SPCD between January 1990 and July 2015 at a single tertiary academic institution. All relevant patient encounters (ie primary care physician, gastroenterologist, and colorectal surgeon) were thoroughly investigated to determine the specific medical and surgical treatments used during the SPCD episode. Crohn's disease patients with a concomitant diagnosis of Fournier's gangrene, hidradenitis suppurativa, adenocarcinoma from a chronic fistula, or a rectovaginal fistula secondary to obstetric complications, were excluded. Patients were identified and stratified by both use of anti-TNF agents and surgical therapy during an SPCD episode.

Demographic characteristics, clinical factors, operations, and medications were retrospectively collected. Clinical factors included age at diagnosis of CD, age at diagnosis of SPCD, smoking status, BMI, diabetes, family history of IBD, anatomic distribution of CD, extraintestinal manifestations, and medications specific to CD treatment. Anti-TNF agents include infliximab, adalimumab, and certolizumab. In addition, patients treated with ustekinumab (anti-interleukin 23/anti-interleukin 12 monoclonal antibody) were also included in the anti-TNF group (3 patients). Additional documented medications included

5-aminosalicylic acid, azathioprine or 6-mercaptopurine, and methotrexate. Timing of medications was abstracted to determine whether such treatment preceded or was instituted as a consequence of an SPCD episode. Wide variability in steroid and antibiotic use prohibited accurate measurement of use and was therefore excluded from clinical analysis. All patients presenting with SPCD, however, received antibiotics before, during, or shortly after drainage.

## Multidisciplinary care paradigm

The institutional paradigm of care is summarized in Figure 1 and has been our routine since the early introduction of anti-TNF agents in 1998.<sup>12-14</sup> When a patient presents with a perianal abscess, surgical drainage is performed concurrently with initiation of antibiotics. The presence of a fistula usually mandates the placement of a noncutting silastic vessel loop seton. However, if the fistula tract is in a favorable location, such as a low intersphincteric, a simple fistulotomy is performed without a seton or anti-TNF administration. Anatomic extent of disease both in the rectum and elsewhere in the gastrointestinal tract can be determined through a staging workup using endoscopic and radiologic studies to define all areas of disease involvement. Subsequent co-management with an IBD gastroenterologist is carried out for the initiation of anti-TNF therapy. The patient is regularly examined by the colorectal surgeon for tightening of the skin around the seton and a decrease in drainage reflecting a response to the anti-TNF agent. If symptomatic improvement with such demonstrable healing occurs, the seton is removed, usually by the third or fourth anti-TNF dose. If such healing is not evident (ie loose seton, continued drainage), additional medical and surgical care can include adjusting medication dosage, adding immunomodulators, and additional debridement or operative drainage and/or repair, depending on the extent and severity of the rectal disease. Failure of medical and surgical management might necessitate proctectomy or permanent diversion.

## Definition of variables

The primary end point was complete healing, defined by a normal physical exam performed by a surgeon and complete cessation of purulent drainage and pain lasting at least 6 months. Episodes were recorded if there was sufficient medical information to meet the criteria defined previously. Additional corrective surgery included the following procedures: complete or partial fistulotomy (after seton placement), flap repair, fistula plug, fistula glue, ligation of intersphincteric fistula tract, and temporary diversion. Proctocolectomy and/or permanent diverting stoma were viewed as definitive, last resort surgical options and not corrective surgery.

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