Systematic Review of Cyanoacrylate Embolization for Refractory Gastrointestinal Fistulae: A Promising Therapy
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What is This?
Systematic Review of Cyanoacrylate Embolization for Refractory Gastrointestinal Fistulae: A Promising Therapy

Julio López, MD¹, Karime Rodríguez, MD¹, Eduardo M. Targarona, MD, PhD², Heber Guzman, MD³, Iván Corral, MD⁴, Rene Gameros, MD⁵, and Arturo Reyes, MD⁵

Abstract

Background. Surgical management of gastrointestinal fistulae has been reported to carry a 30-day morbidity rate up to 82% and a mortality rate ranging from 2% to 4.8%; thus nonoperative alternatives are required. The aim of the present study was to assess the current experience on the use of cyanoacrylates in the management of these fistulae. Methods. A systematic review was carried out on Medline, Embase, The Cochrane database, Academic Search Complete, MedicLatina, and SciELO for English, Spanish, and Portuguese articles dealing with refractory fistulae by means of cyanoacrylate embolization therapy. Publication dates were restricted from 1969 to present. Outcome parameters were study design, number of participants, etiology of the fistula, approach, material used, success rate, complications, and mortality. Results. Electronic search yielded a total of 377 articles. After a meticulous screening, only 14 studies dealing with foregut/midgut fistulae and 6 addressing hindgut fistulae were included. All the included articles were prospective and retrospective case series. Cumulative success rate was 81% (range 0% to 100%) and 3 out of 203 patients (1%) developed minor complications. Conclusion. Cyanoacrylate embolization of nearly all types of refractory gastrointestinal fistulae is a feasible and harmless technique. Prospective controlled studies are required to support the available evidence.

Keywords
gastrointestinal fistula, enterocutaneous, cyanoacrylates, 2-octyl cyanoacrylate, Glubran 2, embolization therapy

Introduction

Gastrointestinal (GI) fistula is defined as an abnormal communication between 2 epithelialized surfaces, with at least one of them pertaining to the GI tract. They are either congenital or acquired in origin. Acquired fistulae are iatrogenic (postoperative) in 75% to 85% of cases, whereas the remaining 15% to 25% are spontaneously occurring fistulae such as those caused by radiation, inflammatory bowel disease, diverticular disease, appendicitis, ischemic bowel, among others.¹

The standard of care for patients with GI tract fistulae, which has evolved from the experience gleaned from several centers down the years, involves a stepwise approach, including (a) control of sepsis and appropriate skin care; (b) nutrition, ideally via the enteral route; (c) definition of the underlying anatomy of the fistula tracts; and (d) definite treatment of the fistula itself. Fistulae that respond to this conservative approach usually close within 6 weeks. Surgical intervention is generally required for those fistulae persisting despite initial nonoperative management.²⁻⁴

Since the surgical management of enterocutaneous fistulae has been reported to carry a 30-day morbidity rate up to 82%² and a mortality rate ranging from 2% to 4.8%,²⁻⁵ it is desirable to find out alternative nonsurgical options to address the problem with the minimum possible damage. Thus the concept of fistulae embolization...
therapy arose, which can be defined as a nonsurgical, minimally invasive procedure that involves the selective occlusion of the tract by purposely introducing emboli.

Cyanoacrylates are a class of synthetic glues applied as monomers, which polymerize in an exothermic reaction when in contact with a weak base such as blood. Two forms of glue are currently used in GI procedures. n-Butyl-2-cyanoacrylate (enbucrilate) is marketed as Indermil (Covidien, Mansfield, MA) and Histoacryl (B. Braun Medical, Bethlehem, PA). Ocrylate (2-octyl cyanoacrylate) is marketed as Dermabond (Johnson & Johnson, New Brunswick, NJ). Glubran 2 (GEM s.r.l., Viareggio, Italy) contains enbucrylate plus methacryloxy sulfolane, which increases polymerization time and reduces heat generation.

Evidence concerning cyanoacrylate embolization therapy limits to small series and case reports, thus the aim of the present study was to assess the current experience on the use of these cyanoacrylates in the management of GI tract fistulae by systematically searching the relevant medical literature.

Methods

The review was written following the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Eligibility Criteria

All studies dealing with GI tract fistulae by means of cyanoacrylate instillation/embolization, alone or in addition to other therapies, either endoscopically or percutaneously were considered eligible for inclusion and pooling of the data. Language of the eligible publications was restricted to English, Spanish, and Portuguese, and studies amenable for inclusion were restricted to published material solely (at least electronically). Publication dates were restricted from January 1969 to present.

The review included participants of any age suffering from GI tract fistulae, and both types of fistulae were considered eligible for inclusion (spontaneous and iatrogenic).

Search Strategy

A systematic search for literature in English, Spanish, and Portuguese languages was conducted in the main biomedical databases: Scopus (which includes 100% Medline coverage, 100% of EMBASE coverage, and 100% of Compendex coverage), The Cochrane database, Academic Search Complete, MedicLatina, and SciELO databases from January 1969 to present. Search terms included in the abstract, title, or medical subject heading (MeSH) were “enterocutaneous,” “fistula,” “cyanoacrylate,” “histoacryl,” “glubran,” either alone or in combination. Last search was run on August 21, 2013. Additionally, the references from each retrieved publication were individually searched for further relevant literature.

Study Selection

Eligibility assessment was performed by 2 of the investigators conducting the review (JLM and KRG). The retrieved records were first screened by reading the title. Abstracts of the articles that went through this initial screening process were then analyzed. They were subsequently excluded for any of the following reasons: (a) treatment of non–GI-related fistulae, (b) fistula management other than cyanoacrylate, (c) single case reports, (d) animal studies, (e) letters to the editor, (f) review articles, and (g) studies published in a language other than the specified above. Finally, the full texts of eligible articles were retrieved for a more comprehensive analysis.

Data Collection and Analysis

A predefined Excel spreadsheet was developed containing the variables considered important for the review and the 2 investigators, as mentioned above, independently extracted data. Data sought from each study included study design, number of participants, etiology of the fistula, approach, material used, success rate, number of sessions required, follow-up, complications, and mortality. Approach was defined as the route by which the fistula tract was managed (eg, percutaneous or endoscopically). Material was defined as the specific type of cyanoacrylate used, either alone or in combination with other therapies. Primary outcome was the success rate for GI fistulae closure. Secondary outcome measure was the complication rate. Success rate was defined as the proportion of closed fistulae.

After extraction of the first data into the spreadsheet, we realized that there was variation among studies concerning the number of sessions required to achieve closure of fistulae, thus we decided to add this outcome parameter as well. Because the included studies were case series solely, quantitative analyses of data were not performed. Articles were classified, however, according to their level of scientific evidence using the Oxford Centre of Evidence-Based Medicine Level of Evidence Scale.

According to the location, 3 major categories of fistulae resulted: foregut, midgut, and hindgut fistulae. Foregut fistulae are defined as those arising in the proximal part of the alimentary tract, from the mouth to the duodenum at the entrance of the bile duct. The origin of fistulae in this region may include esophagus, stomach,
duodenum (proximal half), liver, gallbladder, and pancreas. Midgut fistulae arise all the way down from the opening of the bile duct in the duodenum to about two thirds of the way through the transverse colon. Hindgut fistulae are best defined as those affecting the distal third of the transverse, descending and sigmoid colon, as well as the rectum.

**Results**

Electronic search yielded a total amount of 377 articles, from which 326 were excluded on the basis of title and abstract appraisal because they dealt with non-GI fistulae (196 articles), fistula management was done with a therapy other than cyanoacrylates (102 articles), results of animal studies (11 articles), language publication other than English, Spanish, and Portuguese (11 articles), editorial/letters to the editor (3 articles), and review articles (3 articles). The remaining 51 publications were further screened by reviewing the full text and application of inclusion/exclusion criteria (Figure 1). Articles were subsequently discarded because they were single-case reports (25 articles), and there was no full text available for comprehensive analysis despite all efforts at getting them (6 articles). Finally, 20 articles written in English were included in the systematic review and the clinical and outcome parameters of such studies are summarized in Tables 1 and 2. No studies in Spanish or Portuguese languages were found.

**Foregut Fistulae**

There were 4 studies reporting the use of cyanoacrylates in the management of 28 esophageal fistulae mainly related to congenital and postsurgical atresia repair. Success rate after the embolization procedure ranged from 46% to 100% among studies, with 1.3 sessions (attempts) per patient on average. Median follow-up was 51 months (Table 1).

Four author groups reported their experience dealing with refractory gastric/duodenal fistulae of operative iatrogenic etiology. Twenty-five patients were treated using Glubran 2 + Lipiodol with or without endoscopic clips in the majority of cases (Table 1). The reported success rate was 57% to 100%, with the highest recurrence rate observed in the study of Lukish et al who attempted to close gastrocutaneous fistulae resulting from removal of gastrostomy tube, with instillation of Histoacryl solely. Bègue et al kindly replied to our email request regarding the success rate achieved in their prospective series of patients treated because of bariatric surgery leaks. They claim a 100% success in the entire endoscopic cohort (with and without endoscopic clips). The former authors also responded to our email by stating that all their patients received 3 applications of Histoacryl, 2 weeks apart. If it failed to close the fistula, they underwent surgical closure. Other study reported 1 session per patient to achieve closure. The remaining 2 studies did not provide such information. Similarly, only 2 of these reported a median follow-up of 15.5 months.

Management of biliary fistulae was reported in 3 studies encompassing 20 patients with a cumulative success rate of 78% to 100%, and 1.2 sessions were required to achieve definitive closure of the fistula. Pancreatic fistulae were dealt with in 3 endoscopic retrograde cholangiopancreatography–based studies. Twenty patients underwent embolization of the fistula tract using a combination of Histoacryl + Lipiodol in the majority of cases, with success rates ranging from 67% to 100%. Authors required an average of 1.2 sessions per patient to accomplish closure of the fistula, and follow-up was 16.7 months. Only Vu et al reported spillage of acrylate glue into the main bile duct during the procedure, but no

![Figure 1. Flow diagram of study selection.](image-url)
## Table 1. Summary of Clinical Studies Reporting the Management of Foregut and Midgut Gastrointestinal Fistulae With Cyanoacrylates.

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Year</th>
<th>Study Design (Level of Evidence)</th>
<th>n</th>
<th>Type</th>
<th>Etiology of Fistula</th>
<th>Approach</th>
<th>Material (n)</th>
<th>Success, n (%)</th>
<th>No. of Sessions (Mean)</th>
<th>Follow-up (Months)</th>
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<tbody>
<tr>
<td>Drury and Grundy</td>
<td>1995</td>
<td>Retrospective series (4)</td>
<td>2</td>
<td>Esophageal-pleural</td>
<td>Neumonectomy (1)</td>
<td>Percutaneous</td>
<td>NB2CA + Lipiodol</td>
<td>1 (100)</td>
<td>1</td>
<td>12</td>
</tr>
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<td></td>
<td>Esophageal laceration (1)</td>
<td></td>
<td>NB2CA + Spongostan + Lipiodol</td>
<td>n/a</td>
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<td>n/a</td>
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<tr>
<td>Willets et al</td>
<td>1998</td>
<td>Retrospective series (4)</td>
<td>11</td>
<td>Tracheo-esophageal</td>
<td>Atresia repair</td>
<td>Endoscopic</td>
<td>NB2CA alone (8)</td>
<td>3 (38)</td>
<td>2.5</td>
<td>228 (192-264)</td>
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<td></td>
<td>NB2CA + Sclerosant (2)</td>
<td>2 (100)</td>
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<td>48 (12-84)</td>
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<td>NB2CA + FG (1)</td>
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<td>Congenital (2)</td>
<td>Endoscopic</td>
<td>Diathermy + NB2CA + Lipiodol (10)</td>
<td>9 (90)</td>
<td>1.1</td>
<td>49 (3-108)</td>
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<td>2011</td>
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<td>Tracheo-esophageal</td>
<td>Esophageal atresia</td>
<td>Endoscopic</td>
<td>NB2CA alone (8)</td>
<td>5 (100)</td>
<td>n/a</td>
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<td>Removal of gastrostomy tube</td>
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<td>4 (57)</td>
<td>3</td>
<td>16 (12-20)</td>
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<td>Bariatric surgery leaks</td>
<td>Endoscopic</td>
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<td>9</td>
<td>Biliary</td>
<td>Laparoscopic cholecystectomy (2)</td>
<td>Endoscopic (ERCP)</td>
<td>NB2CA + Lipiodol</td>
<td>7 (78)</td>
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<td>Hepatectomy (3)</td>
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<td>Vu et al</td>
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<td>Biliary</td>
<td>Hepatic lobectomy (4)</td>
<td>Endoscopic (ERCP)</td>
<td>NB2CA + Ethiodol + taumalum (4)</td>
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<td>27 (13-46)</td>
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<td>Chronic pancreatitis (4)</td>
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<td>Pancreatic</td>
<td>Splenectomy (3)</td>
<td>Endoscopic (ERCP)</td>
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<td>4.5 (1-8)</td>
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<td>NB2CA + Lipiodol</td>
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<td>1.3</td>
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<td>Dalton and Woods</td>
<td>2000</td>
<td>Retrospective series (4)</td>
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<td>Gastro-duodenal</td>
<td>Operative iatrogenic</td>
<td>Percutaneous</td>
<td>NB2CA alone</td>
<td>2 (100)</td>
<td>n/a</td>
<td>n/a</td>
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<td>Mouri et al</td>
<td>2013</td>
<td>Prospective series (4)</td>
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<td>Duodenal</td>
<td>Operative iatrogenic</td>
<td>Percutaneous</td>
<td>NB2CA/MS + Lipiodol (2)</td>
<td>2 (100)</td>
<td>n/a</td>
<td>n/a</td>
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<td>Gelfoam + NB2CA/MS + Lipiodol (1)</td>
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Abbreviations: n, number of participants; type, type of fistula; material, type of cyanoacrylic glue used; NB2CA, n-butyl-2-cyanoacrylate (enbucrilate, Histoacryl); FG, fibrin glue; NB2CA/MS, n-butyl-2-cyanoacrylate plus methacryloxy sulpholane (Glubran 2); 2OC, 2-octyl cyanoacrylate (Dermabond); ERCP, endoscopic retrograde cholangiopancreatography; tantalum, tantalum powder; n/a, not available.

*Oxford Centre of Evidence-Based Medicine level of evidence scale.*
Table 2. Summary of Clinical Studies Reporting the Management of Hindgut Gastrointestinal Fistulae With Cyanoacrylates.

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Year</th>
<th>Study Design (Level of Evidence)</th>
<th>n</th>
<th>Type</th>
<th>Etiology of Fistula</th>
<th>Approach</th>
<th>Material (n)</th>
<th>Success, n (%)</th>
<th>No. of Sessions (Mean)</th>
<th>Follow-up (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Billi et al25</td>
<td>1998</td>
<td>Retrospective series (4)</td>
<td>10</td>
<td>Rectovaginal (6)</td>
<td>Crohn’s (5)</td>
<td>Endoscopic</td>
<td>NB2CA alone</td>
<td>2 (67)</td>
<td>2</td>
<td>19 (2-44)</td>
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<td>Duodeno-colonic (1)</td>
<td>Surgery (3)</td>
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<td>Sigmoido-cutaneous (1)</td>
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<td>Ileal pouch-vaginal (1)</td>
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<td>Anastomotic (1)</td>
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<tr>
<td>Cambj-Sapunar et al26</td>
<td>2012</td>
<td>Retrospective series (4)</td>
<td>6</td>
<td>Postsurgical:</td>
<td>Sigmoid diverticulitis (2)</td>
<td>Percutaneous</td>
<td>NB2CA + Lipiodol</td>
<td>6 (100)</td>
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<td>6 (1-18)</td>
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<td>Barillari et al27</td>
<td>2006</td>
<td>Prospective series (4)</td>
<td>21</td>
<td>Anorectal</td>
<td>Cryptoglandular</td>
<td>Percutaneous</td>
<td>NB2CA/MS alone</td>
<td>19 (90)</td>
<td>1.4</td>
<td>18 (6-28)</td>
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<tr>
<td>Jain et al28</td>
<td>2008</td>
<td>Prospective series (4)</td>
<td>20</td>
<td>Anorectal</td>
<td>Cryptoglandular</td>
<td>Percutaneous</td>
<td>NB2CA alone</td>
<td>19 (95)</td>
<td>1.2</td>
<td>6</td>
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<tr>
<td>Queralto et al29</td>
<td>2010</td>
<td>Prospective series (4)</td>
<td>34</td>
<td>Anorectal</td>
<td>Cryptoglandular</td>
<td>Percutaneous</td>
<td>NB2CA/MS alone</td>
<td>23 (68)</td>
<td>1.1</td>
<td>34 (21-43)</td>
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<tr>
<td>Osman et al30</td>
<td>2013</td>
<td>Prospective series (4)</td>
<td>17</td>
<td>Anorectal</td>
<td>Cryptoglandular</td>
<td>Percutaneous</td>
<td>NB2CA + Lipiodol</td>
<td>16 (94)</td>
<td>1.1</td>
<td>18</td>
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</tbody>
</table>

Abbreviations: n, number of participants; type, type of fistula; material, type of cyanoacrylic glue used; NB2CA, n-butyl-2-cyanoacrylate (enbucrilate, Histoacryl); NB2CA/MS, n-butyl-2-cyanoacrylate plus methacryloxy sulfolane (Glubran 2).

*Oxford Centre of Evidence-Based Medicine level of evidence scale.*
clinical effects were observed as result of the incident. All
the remaining authors reported no complications whatso-
ever. Overall, the estimated median follow-up in studies
dealing with foregut fistulae was 22.9 months (range 1-264 months).

**Midgut Fistulae**

Literature search on this type of fistulae addressed by
cyanoacrylate embolization was far more scarce, yielding
1 prospective study reporting the outcome of 2 patients,
one with a jejunal and the other with an ileal postopera-
tive fistulae. Embolization was performed with Glubran 2 + Lipiodol in the jejunal fistula, whereas in the ileal fis-
tula gelfoam was added to the mix. Both procedures were
successful at first attempt. Postprocedural median follow-
up was reported to be 15 months (range 8-22 months).

Another retrospective study of 2 patients with duodenoc-
colic and ileal pouch–vaginal fistulae arising from
Crohn’s disease and colonic malignancy, respectively,
reported a cumulative success rate of 50% (Table 2). The
patient with Crohn’s fistula did not heal with the emboli-
zation therapy. Follow-up was 19 months. No data were
reported concerning the number of glue sessions done.
No complications were observed.

**Hindgut Fistulae**

Colorectal fistulae managed with cyanoacrylates were
reported in 2 retrospective studies including 14
patients. Endoscopic approach was used in one
study, and the percutaneous route was employed in the
other. Overall, 9 fistulae were postsurgical, 4 had Crohn’s
disease as the etiology, and 1 resulted spontaneously due
to rectal cancer. All fistulae approached percutaneously
showed resolution with 1 session, whereas only 3 of the
fistulae treated endoscopically (30%) closed only after 2
attempts in average.

Anorectal fistulae accounted for the vast majority of
GI tract fistulae treated with this minimally invasive tech-
nique. Four prospective studies reporting the outcomes of
92 patients were identified through the electronic
search. All fistulae were cryptoglandular in etiology,
and were percutaneously approached using Histoacryl or
Glubran 2, either alone or in combination with the con-
trast agent Lipiodol. Cumulative success rate reported in
these 4 studies was 84%, ranging from 68% to 95%, and
average number of sessions required to achieve closure of
the fistulae was 1.2. No complications other than itching
of the perianal zone unresponsive to simple analgesia was
reported in 2 patients. Postprocedural median follow-up
in this cohort of patients with hindgut fistulae was 18
months (range 1-43 months). Since only 3 out of 203 patients developed minor com-
plications (one of them without clinical effects), a compi-
lcation rate of 1% was estimated. Concerning the
cumulative success rate, it was estimated at 81% (range
0% to 100%), whereas the median follow-up was 19.3
months per study (range 1-264 months; Table 3).

**Discussion**

The development of a GI fistula following surgery is a
devastating complication for the patient and their family.
It may lead to significant anxiety, loss of self-esteem,
depression, considerable loss of earnings, and financial
hardship. Their management requires attention to the
control of sepsis, fluid and electrolyte balance, mainte-
nance of nutrition, and attention to wound/stoma care. It
is a condition that places a considerable economic burden
on the health care provider. Despite all the medical
advances over the past 2 decades, the management of GI
fistula still remains a significant challenge and carries a
mortality rate of up to 10% to 30%. Other types of GI
fistulae, such as those arising in the anorectum, may not
be life-threatening. Still, they constitute an annoying and
very common problem.

Novel approaches for the management of GI fistulae
include both endoscopic and percutaneous techniques.
Several reports have documented the safe use of gelfoam
for percutaneous embolization of GI fistulae arising from
the small intestine and distal colon. Fecal colocutane-
ous fistulae have also been reported to be successfully
resolved with the use of metal clips. Fibrin glue is prob-
ably the most widely used agent in the management of
this condition. This is another biological component that

<table>
<thead>
<tr>
<th>Outcome Parameter</th>
<th>Foregut (n = 93)</th>
<th>Midgut (n = 4)</th>
<th>Hindgut (n = 106)</th>
<th>Overall (n = 203)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success (n)</td>
<td>75</td>
<td>3</td>
<td>85</td>
<td>163</td>
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<tr>
<td>Percentage</td>
<td>81</td>
<td>75</td>
<td>80</td>
<td>81</td>
</tr>
<tr>
<td>Complications (n)</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Percentage</td>
<td>1.1</td>
<td>—</td>
<td>1.9</td>
<td>1.0</td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>22.9</td>
<td>17</td>
<td>18</td>
<td>—</td>
</tr>
<tr>
<td>Range</td>
<td>1-264</td>
<td>2-44</td>
<td>1-43</td>
<td>—</td>
</tr>
</tbody>
</table>
has been found to achieve closure of low output as well as high output GI fistulae nonoperatively. The main disadvantages of using gelfoam and fibrin glue as embolic agents, according to the experts in the field, are that both lack of the tensile and adhesive strength that cyanoacrylates provide, and this fact might explain the higher failure rate associated with the former ones. Furthermore, fibrin glue is an animal protein with inherent problems of allergy and prion disease transmission. The compound may also be broken down by enzyme-rich fluid secreted in gastric or pancreatic fistulae, thus potentially making it unsuitable for this role. Finally, cyanoacrylates are much less expensive than fibrin glue.

Cyanoacrylates are used widely outside the United States for gastric variceal bleeding and, to a lesser extent, ulcer bleeding and fistula closures. For the time being, their GI endoscopic applications remain an “off-label” use in the United States. The proposed mechanism of action of cyanoacrylates to obliterate fistulous tracts is the solidification of the compound within 30 seconds and induction of an inflammatory response that enhances fibrosis and foreign-body granuloma formation with ultimate epithelization. Mixing cyanoacrylate glues with the lipid-soluble contrast agent Lipiodol enhances radiopacity and retards the rate of solidification, thereby facilitating endoscopic administration via needle injection, while reducing the risk of inadvertent adherence to catheters and endoscopes. Various mixtures of Histoacryl and Lipiodol (range 1:1 to 1:1.6) have been recommended. A mixture that is too concentrated risks premature polymerization, whereas a mixture too diluted increases the risk of embolization. Glubran, by comparison, polymerizes slowly and therefore does not require dilution in order to be needle injected. However, it still needs to be mixed with Lipiodol to be tracked by fluoroscopy. Although Dermabond is weak in polymerization compared with Histoacryl, it requires dilution with Lipiodol too.

Several observations deserve special mention. (a) Complex fistulae (ie, fistulae with multiple tracts, or pleural or bronchial communication) are associated with higher failure rates. (b) Embolization with 2-octyl cyanoacrylate alone yields the highest failure rate as compared with the mixture cyanoacrylate + Lipiodol, or another combination therapy. (c) Although traditionally associated to refractoriness with conventional therapy, Crohn’s fistulae and those related to malignancy were successfully addressed with cyanoacrylate embolization therapy. (d) Embolization should be considered as soon as the fistula is discovered, if at all possible, because patients treated earlier healed more rapidly and required fewer sessions. (e) Median disease-free interval (follow-up) in the entire cohort of patients treated with cyanoacrylate embolization was acceptable compared with that reported in studies dealing with surgical treatment for GI tract fistulae.

The conventional management of GI fistulae requires input from a wide range of personnel including nutritionists, enterostomal therapists, radiologists, psychiatrists/psychotherapists, nurses, internists, surgeons, and other personnel. This multidisciplinary approach is no less important in the embolization therapy, with endoscopists and interventional radiologists playing a crucial role.

Although the evidence available to date consists of only prospective and retrospective case series, the success rate achieved renders this minimally invasive approach an appealing first-line alternative to the cumbersome and complication-related surgical treatment. Although patient population in this systematic review remains heterogeneous in terms of fistula etiology and age of the patients, this provides evidence that supports the use of these synthetic glues in a wide range of clinical scenarios. Furthermore, the absence of serious side effects claimed by virtually all the authors as result of the instillation of cyanoacrylates into the fistulous tracts represents an important feature that is essential to be provided by every new treatment option that is being tested against a “gold standard.”

The costs related to the fistula management are certainly an important issue. In this regard, when comparing the expected costs of surgical management versus the cyanoacrylate embolization therapy, there is no doubt that the latter is a much more cost-effective procedure that can even be performed in an outpatient setting. Cyanoacrylate vials range in price from US$137 (Histoacryl) to US$160 (Glubran 2) whereas a single Lipiodol bottle costs about US$2.99. On the other hand, concerning the estimated costs of surgical treatment for GI fistulae, the data available are scarce. Teixeira et al analyzed the resource utilization of patients who developed enterocutaneous fistulae after trauma laparotomy and found that the development of an enterocutaneous fistulae was associated with significantly increased hospital length of stay as well as hospital charges that averaged US$412 313 or higher. Another study aimed at assessing the effects of fistula on annual costs of health care and resource utilization for patients with Crohn’s disease found that total median cost per patient was US$10 863.

Among the limitations and weaknesses of this review are the types of studies included, which, as mentioned above, were retrospective and prospective case series solely. Also, the number of participants per study was rather low, as was the follow-up provided in most of the studies. Some of the included studies did not mention all of the outcome parameters wanted and, despite every effort at contacting authors of those original publications, the majority of them did not reply to our request. Thus,
some data in the tables summarizing the outcome parameters appear as not available and, therefore, limit the ability of making a more accurate estimation of the size effects.

**Conclusion**

The evidence available to date, although preliminary, suggests that embolization of nearly all types of refractory GI tract fistulae is a feasible and harmless technique. Success rates reported, as well as the minimal morbidity attributed to the procedure, renders it an appealing alternative to surgical treatment. Prospective controlled studies are required to support the available evidence; however, it appears difficult because of the small number of patients and variations in the etiology and pathology of GI fistulae.

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**Authors’ Note**

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**Declaration of Conflicting Interests**

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