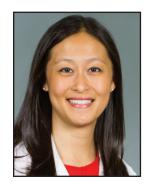
Seymour Katz, M.D., Series Editor

Management of the Ileal Pouch-Anal Anastomosis in the Elderly



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The ileal pouch-anal anastomosis (IPAA) has become standard of care in maintaining fecal continence after colectomy. Elderly patients are able to undergo IPAA surgery safely with similar functional outcomes compared to those of younger patients. Overall, elderly patients with IPAA report satisfaction and high quality-of-life scores. When caring for the elderly patient with IPAA, many of the medications prescribed for management of pouchitis or diarrhea should be used with caution, with or without dose adjustments. Other special considerations in the elderly population include history or use of radiation therapy, dysplasia surveillance, and sphincter dysfunction.

INTRODUCTION

he ileal pouch-anal anastomosis (IPAA) is the surgery of choice for patients requiring total proctocolectomy who wish to maintain continence. First described in the 1970s by Drs. Parks and Nicholls, multiple types of "pouches" may be fashioned including the "J," "S," "W" and "K" pouches. The most frequently created pouch is the "J-pouch," irrespective of the indication for total proctocolectomy (eg, medically refractory ulcerative colitis or intermediate colitis, familial adenomatous polyposis syndrome (FAP), dysplasia or malignancy in inflammatory bowel disease). The creation of a pouch allows patients to

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maintain fecal continence and avoids the need for a permanent ileostomy.

Select elderly patients are now candidates for IPAA surgery. In this article, we review the medical management and functionality of pouches in the elderly population.

Pouch Creation in the Elderly

Initially, the IPAA surgery was reserved for younger patients, with the belief that older patients would have poorer surgical outcomes. However, recent studies demonstrate that postoperative complications from pouch formation are not specifically linked to age at the time of surgery,¹ with safety, functionality, and improvement in quality of life demonstrated even in patients over the age of 70 years.²

The age that defines "elderly" in the medical

literature is highly variable, with age cutoffs ranging from 45 to 65 years of age. 1,3-7 Given evidence of successful IPAA formation in the elderly, end ileostomies are decreasing in patients ages 61 to 70.4 We suggest that age alone should not constitute an absolute contraindication to pouch surgery. Rather, the overall health, functional status, and sphincter function of the patient should be considered. Detailed specific preoperative discussions regarding expectations of quality of life after IPAA should focus on risks of surgery, postoperative bowel frequency, risk of pouchitis, and potential incontinence.

Pouch Function Over Time

Up to 30 years after pouch creation, 93% of patients with pouches report continued functionality, defined based on daytime and nocturnal bowel movements. However, there may be slight changes in pouch functioning over time. For example, patients report an increased number of bowel movements per day, with an average of 5.7 daily bowel movements at 1 year increasing slightly to 6.2 daily bowel movements at 30 years. Nocturnal bowel

movements also increase in frequency, on average, from 1.5 to 2.1 bowel movements. Stool quality changes, with higher numbers of patients reporting liquid stools. These changes may occur within the initial 5 years after pouch formation but stabilize thereafter. Despite these changes in bowel frequency and consistency, quality-of-life scores remain stable over time, as most patients remain satisfied with their pouch. As patients with pouches age, small changes in bowel habits are expected with preservation of overall pouch function. Any significant changes in pouch function should prompt an evaluation for infection, pouchitis, mechanical disorders, or sphincter dysfunction.

Pouchitis

Pouchitis, an inflammatory condition of the pouch, is the most commonly reported complication after pouch creation. Patients often present with a constellation of nonspecific symptoms such as increased stool frequency, liquid stool, tenesmus, abdominal cramps, and pelvic pressure. The pathogenesis of pouchitis has not been fully elucidated but likely relates to an aberrant

Table 1. Adjustments to Antibiotics for Pouchitis in the Elderly

Antibiotic	Conventional Dosing	Renal Impairment	Hepatic Impairment	Caution When Used in the Elderly
Ciprofloxacin	500 mg BID	CrCl 30-50 ml/min: 250-500 q12h CrCl <30ml/min: 250-500 q18h ESRD: give after dialysis	No adjustments necessary	Risk of tendinopathy, Clostridium difficile infection
Metronidazole	500 mg every 8 hours	No adjustments necessary.	Severe hepatic impairment (Child-Pugh Class C): use of extended-release tablets not recommended; immediate-release: reduce dose by 50%	Risk of peripheral neuropathy, nausea, vomiting, seizures, encephalopathy, dysguesia, headache, dizziness
Tinidazole	2 g daily	ESRD: Give additional 50% dose after dialysis	No adjustments necessary	Risk of dysguesia, nausea, vomiting, fatigue, seizures, peripheral neuropathy
Rifaximin	400 mg TID	No adjustments necessary	Severe hepatic impairment (Child-Pugh Class C): use with caution	

CrCl=creatinine clearance; ESRD=End Stage Renal Disease; BID=twice daily; TID= three times daily; QD=daily

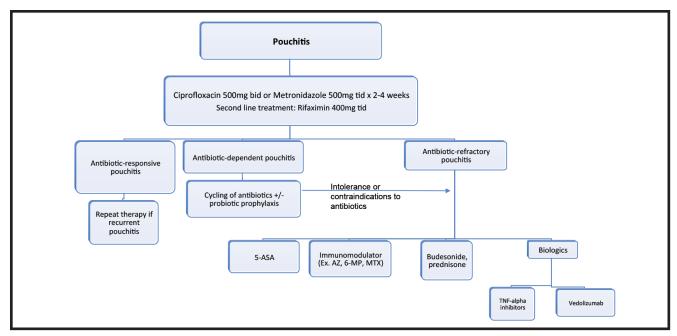


Figure 1. Treatment Algorithm of Pouchitis

AZA=azathioprine; 6-MP = 6-mercaptopurine

immune response to changes in mucosal bacteria.

There is a reported lifetime risk of 80.2% of developing pouchitis after IPAA.8 Interestingly, patients who have a pouch and diagnosis of FAP have less pouchitis than patients with underlying autoimmune diseases such as ulcerative colitis. Most patients with pouchitis will have self-limited episodes. However, a small number of patients will progress to chronic pouchitis, requiring long-term therapy.

Differentiating pouchitis from other infectious or inflammatory conditions is of paramount importance. Clostridium difficile infection should be ruled out when patients present with symptoms suspicious for pouchitis.

The mainstay of initial treatment for acute pouchitis includes antibiotics, most commonly ciprofloxacin (500 mg by mouth twice daily), metronidazole (500 mg by mouth every 8 hours), or dual therapy with ciprofloxacin and metronidazole (Table 1). Common side effects of metronidazole include nausea, vomiting, dysgeusia, headache, and occasionally dizziness. Tinidazole, also a nitroimidazole, may be better tolerated than metronidazole. Rifaximin and tinidazole are utilized as second-line treatment for pouchitis, partially due to insurance obstacles or high co-pay and need for prior authorization. For patients with recurrent antibiotic-dependent pouchitis, treatment with mesalamines (5-ASAs), thiopurines such as 6-mercaptopurine (6MP) or azathioprine, or biologics may be necessary,

though there is very limited high-quality data available (Figure 1). The highest quality evidence in one report supports use of probiotics such as VSL#3 for secondary prophylaxis.⁹

Medical Management of IPAA in the Elderly Patient with Common Medical Comorbidities

Elderly patients commonly take medications that may need to be adjusted in the setting of common medical comorbidities such as cardiac arrhythmias, heart failure, renal insufficiency, hepatic impairment, malignancy, and neurologic conditions. We review different medications used in patients with pouches, focusing on potential dosing adjustments and contraindications for the elderly(Tables 1, 2, and 3).

Treatment of Pouchitis in the Elderly

Adjustments to pouchitis treatment regimens may be necessary in the elderly patient. Moreover, potential side effects of medications may be more pronounced in the elderly. Close monitoring for polypharmacy (stopping medications that may be superfluous) is necessary. Elderly patients with renal or hepatic dysfunction require adjustments to antibiotics dosing (Table 1). Ciprofloxacin dosing should be adjusted in patients with renal impairment. In patients with end-stage renal disease (ESRD), ciprofloxacin should be given after dialysis. Additionally, ciprofloxacin is known to cause

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tendinopathy and tendon rupture and must be used with caution in the elderly population. Ciprofloxacin may also predispose patients to Clostridium difficile infection. Elderly patients may suffer from particularly virulent strains of Clostridium difficile.¹⁰

Metronidazole metabolites accumulate in patients with ESRD, and therefore patients should be monitored for adverse events, including headache, nausea, as well as rare adverse reactions, including central nervous system, gastrointestinal, genitourinary and pulmonary side effects. For patients with severe hepatic impairment (Child-Pugh Class C), the use of extended-release metronidazole is not recommended. Furthermore, metronidazole may cause peripheral neuropathy, a particularly hazardous side effect in an elderly population already prone to neuropathy and gait disturbances. While the neuropathy associated with metronidazole is often reversible with discontinuation of the drug, it may take years for complete reversal of symptoms.¹¹

Rifaximin requires no adjustments for renal impairment. In patients with severe hepatic impairment (Child-Pugh Class C), rifaximin has increased systemic exposure and therefore should be used with caution. However, no dose adjustments are recommended as rifaximin is presumed to act locally. Also of note, rifaximin is commonly used for treatment of portosystemic encephalopathy in cirrhotic patients.

When pouchitis is refractory to antibiotic therapy or patients develop a contraindication (eg, Clostridium difficile infection) or intolerance to antibiotics, current treatment options for pouchitis revert back to the conventional medications used to treat IBD (Figure 1). Mesalamines (5-ASAs), immunomodulators (azathioprine, 6-mercaptopurine), corticosteroids, or biologic therapy have all been used with limited evidence and success in antibiotic-refractory pouchitis. Adjustments to IBD medications may be warranted in elderly patients who have had IPAA and have renal disease, hepatic impairment, or with concomitant medications (Table 2).

Oral and topical 5-ASAs have been shown in limited small studies to improve symptoms of pouchitis. ¹² However, the topical use of mesalamine enemas and suppositories may be more challenging for the elderly patient with decreased dexterity, impaired mobility, or sphincter dysfunction. Renal function should be monitored while on 5-ASAs given the risk of interstitial

nephritis (Table 2).

Immunomodulators, such as azathioprine and 6-mercaptopurine (6MP), have been shown in small studies to improve symptoms of pouchitis as well as facilitating tapering of steroids. 12 Thiopurine methyltransferase (TPMT) activity should be checked before initiation of a thiopurine to gauge risk of leukopenia and hepatotoxicity. After starting a thiopurine, a complete blood count (CBC) and hepatic panel should be checked twice monthly for the first several months. Doses of both immunomodulators should be decreased based on creatinine clearance. If the patient suffers from gout and is taking allopurinol or febuxostat, two inhibitors of xanthine oxidase, the dose of azathioprine or 6MP should be decreased by 50 to 75% to avoid myelosuppression. Potential serious risks of pancreatitis, skin cancer, and lymphoproliferative disorders or more common side effects of nausea, vomiting, malaise, and photosensitivity should be taken into account before starting an elderly patient on an immunomodulator.

Biologic medications can be used in cases of antibiotic-refractory pouchitis, particularly if an underlying autoimmune process is suspected to be driving the symptoms. As the tumor necrosis factor alpha inhibitors (anti-TNF's) have been in use longer than the anti-integrin vedolizumab, there is more data available regarding the use of TNFs for antibiotic-refractory pouchitis, ¹³ but vedolizumab also has reported efficacy in pouchitis with a good safety profile. ^{14,15}

Anti-TNF medications, while safe for use in the elderly, should be used with caution. Patients taking anti-TNFs may develop a severe infection, a complication that is increased fivefold in the elderly. Anti-TNFs should be avoided in patients with advanced heart failure (New York Heart Association Class III or IV) and in those with demyelinating disorders.

Vedolizumab, approved for IBD in 2014, appears safe in elderly patients,¹⁷ though studies promoting its use in the elderly have been limited in numbers.¹⁸ However, there appear to be no signals for increased risk of infection or malignancy associated with vedolizumab. Adverse events with vedolizumab may include nasopharyngitis, headache, arthralgias.

Medical Management of Diarrhea with IPAA

A major function of the colon is water reabsorption, and as such, the stool of patients with IPAA typically will

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Table 2. Adjustments to IBD Medications for Treatment of Pouchitis in the Elderly

	Renal Impairment	Hepatic Impairment	Potential Drug- Drug Interactions	Considerations When Used in the Elderly
ASA	US labeling: no adjustments Canadian labeling: contraindicated in GFR<30	US Labeling: no adjustments necessary Canadian Labeling: contraindicated in severe hepatic impairment	NSAIDS: risk of nephrotoxicity	Difficult administration of topical 5-ASA therapy if sphincter dysfunction, poor dexterity Risk of idiosyncratic interstitial nephritis
Azathioprine	CrCl 10-50ml/min: administer 75% of dose ³⁴ CrCl <10ml/min: administer 50% of dose	No adjustments necessary	ACE-inhibitors: increased risk of leukopenia. Allopurinol: risk of toxicity, decrease azathioprine dose by 50-75% Febuxostat: risk of toxicity; decrease dose by 50-75%	Risk of lymphoma Risk of non- melanoma skin cancer
6-mercaptopurine	CrCl 10-50ml/min: administer 75% of dose ³⁴ CrCl <10ml/min: administer 50% of dose	Consider starting at lower dose	Allopurinol: risk of toxicity, decrease dose by 50-75% Febuxostat: risk of toxicity; decrease dose by 50-75%	Risk of lymphoma Risk of non- melanoma skin cancer
Anti-TNFs (infliximab, adalimumab, golimumab, certolizumab)	No adjustments necessary	No adjustments necessary		Risk of infection Avoid in advanced heart failure (NYHA Class III-IV) Avoid in demyelinating disease May cause lupus-like reaction
Vedolizumab	No adjustments necessary	No adjustments necessary		Risk of nasopharyngitis, headache, arthralgias

CrCI=Creatinine clearance; CBC=complete blood count; LFT=liver function test; ESRD = End State Renal Disease; ULN=upper limit of normal; NSAIDs=nonsteroidal anti-inflammatory drugs (continued on page 46)

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be watery or soft. Several over-the-counter medications for diarrhea are routinely used to manage the frequency and consistency of bowel movements in patients after IPAA. These medications are relatively safe but must be used with caution in the elderly (Table 3).

Loperamide, a frequently used anti-diarrheal medication, is a locally acting opioid receptor agonist that inhibits peristalsis and has been reported to increase internal sphincter tone. ¹⁹ Though rarely reported, loperamide may cause cardiac conduction abnormalities, including both QRS and QT prolongation, at very high doses. ²⁰ Providers should monitor the patient's QT interval, particularly if the elderly patient is known to have a prolonged QT interval or is taking other QT-prolonging medications.

Diphenoxylate-atropine, another anti-diarrheal agent, is a centrally acting opioid. The anticholinergic effects of atropine can cause side effects including dizziness, nausea, palpitations. Anticholinergic side effects are augmented in the elderly.²¹

Cholestyramine, a bile-acid sequestrant, may bind medications intraluminally and decrease serum concentrations of certain medications (e.g. atorvastatin, furosemide, propranolol).

Tincture of opium, another anti-diarrheal agent containing morphine, inhibits gastrointestinal motility and decreases digestive secretions. Tincture of opium should be used cautiously in the elderly, as it may cause central nervous system depression and hypotension, specifically in patients with cardiovascular disease.²²

Other Potential Concerns in the Elderly Radiation and Pouch Function

Elderly patients are more likely than younger patients to have a history of radiation therapy. Radiation therapy, commonly part of treatment for prostate and endometrial cancer, is associated with acute and chronic toxicity to the gastrointestinal tract.²³ Pelvic radiation therapy alters pouch function, irrespective of whether radiation therapy preceded or came after pouch surgery. In patients who have had radiation after pouch formation, studies have demonstrated decreased pouch capacity and compliance, worsened pouch function, and increased potential for radiation-related pouchitis.^{23,24} Among patients who receive radiation therapy prior to pouch formation, there is increased risk for chronic pouchitis and pouch failure. 25,26 While these findings do not represent a contraindication for the combination of pouch formation and radiation therapy, we do recommend an informed discussion to address the potential deterioration of pouch function that may occur with radiation therapy.

Sphincter Dysfunction

Aging may be associated with incontinence or fecal seepage. Some of the proposed mechanisms for worsening anorectal function in the elderly include thinning and atrophy of the anal sphincters, decreased rectal sensation, and decreased length of anal sphincter.²⁷ Additionally, the decreased volume of skeletal muscle predisposes elderly women to pelvic floor dysfunction and prolapse, as the remaining tissue fails to support the pelvic and abdominal organs.²⁸

Table 3. Anti-Diarrheal Medications and Concerns in the Elderly

Medication	Concerns in the Elderly	
Loperamide	May prolong QRS and QT interval Dizziness	
Diphenoxylate-atropine	Dizziness Nausea Palpitations Dry mouth	
Cholestyramine	May decrease absorption of oral medications; should be taken separately from other oral medications	
Tincture of opium	Hypotension CNS depression	

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The IPAA surgery itself has been associated with decreased anal sphincter pressure.²⁹ As such, patients with suspected anal sphincter dysfunction, pelvic floor dysfunction, or patients with a history of obstetrical complications, are at risk for partial or complete incontinence after pouch surgery. In cases of mild incontinence despite control of pouchitis symptoms, patients can be referred for anorectal manometry and possible biofeedback therapy.

Dysplasia Surveillance

The role of dysplasia and malignancy screening in patients who have undergone IPAA remains controversial. Neoplasia may develop in the retained rectal "cuff" or anal transition zone (ATZ), as well as within the pouch itself. The rate of colitis-associated dysplasia or cancer after IPAA is low. At 25 years after IPAA creation, the cumulative incidence of pouch neoplasia (dysplasia or malignancy) either at the anal transition zone (ATZ) or pouch body has been reported to be 5.1%, with an increased risk of pouch neoplasia in patients with a preoperative diagnosis of cancer or dysplasia.³⁰ However as patients' pouch lifespans extend into the third and fourth decades, it remains to be seen whether the incidence of pouch neoplasia will increase. Current recommendations for dysplasia screening in patients with IPAA range from no screening at all to routine screening with stool DNA markers and imaging enhanced endoscopy.³⁰⁻³³ It is our practice to do surveillance pouchoscopy yearly in patients with a history of neoplasia.

CONCLUSION

Despite the risk of potential complications, elderly patients with IPAA have reported a similar acceptable quality of life compared with younger patients with IPAA. However, in contrast to the less complicated, younger patient, elderly patients with IPAA are a special subset of patients who require extra consideration. Elderly patients frequently have more comorbidities and are at risk for polypharmacy and drug-drug interactions. Attention to the selection of medications and modification of traditional doses in elderly patients is needed to avoid adverse events. Prior history of the use of radiation therapy or sphincter dysfunction may further complicate treatment decisions. Patients with an IPAA and a history of dysplasia should undergo routine pouchoscopy surveillance.

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