Published in final edited form as:
Dis Colon Rectum. 2009 April ; 52(4): 726–739. doi:10.1007/DCR.0b013e31819ed571.

Prevalence and Outcome of Anemia After Restorative Proctocolectomy: A Clinical Literature Review

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Abstract

PURPOSE—Iron and/or vitamin B_{12} deficiency anemias, which have adverse effects on patients' quality of life, are commonly observed and often overlooked complications after restorative proctocolectomy. We performed a systematic review of publications on the prevalence of anemia as well as on the impact of anemia on a range of clinical, functional, quality of life, and economic outcomes in restorative proctocolectomy patients. This information is important to help healthcare providers through a comprehensive overview to increase awareness about a condition that could require therapy to improve patient healthcare and quality of life.

METHODS—We reviewed the English language publications on the incidence of anemia and its adverse effect after restorative proctocolectomy The United States National Library of Medicine database (MEDLINE), the Excerpta Medica database (EMBASE), the Cochran Library, and the Google® search engine were searched for published articles on the prevalence and impact of anemia in post-restorative proctocolectomy surgical patients.

RESULTS—The long-term complication most frequently described after RPC is pouchitis. Pouchitis is significantly associated with iron deficiency anemia caused by pouch mucosal bleeding. Other causes are insufficient and/or impaired iron absorption. It has also been observed, however, that restorative proctocolectomy patients with underlying familial adenomatous polyposis rarely develop pouchitis yet show higher rates of iron deficiency anemia compared to those patients with underlying ulcerative colitis. Other causes shown as independent risk factors for iron deficiency anemia in restorative proctocolectomy patients are malignancy, desmoid tumors, and J-pouch configuration. Vitamin B_{12} deficiency anemia is also common after

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Presented at the Congress of the European Society for Surgical Research (ESSR), Corfu, Greece, May 18 to 21, 1997, at XVII Biennial Congress of the International Society of University Colon and Surgeons (ISUCRS), Malmö, Sweden, June 7 to 11, 1998, and at Dissertation meeting, Karolinska Institute and University Hospital, Stockholm, Sweden, November 8, 2001.

restorative proctocolectomy. About one-third of restorative proctocolectomy patients show abnormal Schilling test and 5 percent have low referenced serum cobalamin. It has been observed that the degree resection of the terminal-ileum, malabsorption, bacterial overgrowth, and dietary factors are among the known causes of cobalamin deficiency. Folate deficiency has not been reported in restorative proctocolectomy patients. Describing restorative proctocolectomy surgery and its outcomes, in patients without anemia, the quality of life is reported excellent regardless of operative technique.

CONCLUSIONS—Anemia is not uncommon following restorative proctocolectomy and has been shown to have negative effects on the patient's quality of life and the economy and may substantially increase healthcare costs. The treatment of anemia and its underlying causes is important to improving clinical and economic outcomes.

Keywords

Restorative proctocolectomy; Ulcerative colitis; Familial adenomatous polyposis; Anemia; Desmoids tumors; Patient's quality of life; Economic outcomes

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The restorative proctocolectomy (RPC) or proctocolectomy with ileal pouch-anal anastomosis (IPAA) was first performed three decades ago and is currently the criterion standard surgical management for patients with ulcerative colitis (UC) and familial adenomatous polyposis (FAP).[1,2] The operative technique has been modified during the years,[3–5] which involves utilization of the terminal ileum to construct an ileal pouch that is anastomosed to the anal canal after resection of the colon and rectum (with or without creation of a temporary diverting loop ileostomy).[1,5,6] The clinical, functional, and quality of life (QoL) outcomes are excellent and remain stable for over 20 years after this operation[7,8] although a deterioration in fecal continence has been noted and attributed to the effects of aging on continence.[9,10] The advantages of the RPC include avoidance of a permanent stoma and “curing” the underlying disease while disadvantages include complexity of the procedure and a high complication risk, including pouchitis – an inflammatory condition of the pouch occurring in ≤60 percent of UC-RPC patients.[6,7,11,12] Pouchitis is a rare reported complication in RPC patients with underlying FAP[13–21] seen in only 0 to 11 percent. However, after RPC, FAP patients are at higher risk, compared to UC, of systemic iron deficiency anemia and developing adenomas (and occasional adenocarcinomas), either in the anal canal (10–31 percent) or in the ileal pouch itself (8–62 percent), thus requiring lifelong endoscopic monitoring.[16,19–22]

Because one of the terminal ileal functions is absorption of VB_{12} (cobalamin, an essential building block for red cell formation among other things), it is unclear what the creation of an ileal pouch might do to this function - especially in the presence of pouchitis. Therefore, assessments for pernicious anemia (as the result of vitamin B_{12} insufficiency) as well as other types of anemia should be considered after RPC. Unfortunately, this has not been systematically evaluated.

The goal of this study was to systematically identify and review the literature on the prevalence of anemia after RPC. Additionally, the impact of anemia on a range of (i) clinical factors (*e.g.*, morbidity, mortality, hospitalization, transfusion requirements, responsiveness

to treatment, *etc.*), (ii) functional factors (functional status, cognitive function, psychosocial function, patient QoL *etc*., (III) patient satisfaction, and (iv) economic factors (direct and indirect costs of care).

METHODS

We reviewed the English language publications on the incidence of anemia after RPC as well as on the impact of anemia on a range of clinical, functional, and economic (direct and indirect costs of care) outcomes as well as QoL after RPC.

The United States National Library of Medicine database (MEDLINE), the Excerpta Medica database (EMBASE), the Cochran Library, and the Google® search engine were searched for published articles on the prevalence and impact of anemia in RPC surgical patients. The initial search covered from January 1975 through December 2007. A second search was performed in February 2008 to update the initial search. The search excluded foreign language and nonhuman studies as well as editorials. Searched key words literature that included “ulcerative colitis,” “familial adenomatous polyposis,” “colectomy,” “restorative proctocolectomy,” “pouchitis,” “anemia,” “iron deficiency,” “vitamin B_{12},” and “folate deficiency.” Additional articles were identified by cross-referencing from papers retrieved in the initial search. Papers were included on the basis of most recent available evidence for each specific point of interest. Final and conclusive agreement was assessed with the *k*-statistic during the title review and abstract review. If the *k*-value was ≤0.6 the titles were reviewed divided into 2 sets; each was reviewed by only 1 of the 2 researchers. If the *k*-value was <0.6 reviewers discussed discrepancies followed by other assessments of agreement. Similar process for abstract review like the title review was done, with an increased *k*-value of 0.7 for acceptance.

The same team of researchers involved in the original title, abstract, and article review process conducted hand searches of bibliography from accepted articles and review articles. These hand searches resulted in retrieval of a limited number of additional articles for review.

RESULTS

Anemia

Anemia is defined as a pathologic condition in which the blood is deficient in either red blood cells (RBC), in hemoglobin (Hb), in total volume, and/or deficient in VB_{12} or folic acid.[23–25] Anemia was defined according to World Health Organization (WHO) criteria hemoglobin (Hb) less than 13.0 g/dL in men and less than 12.0 g/dL in women with hematocrit levels less than 38 percent in men and less than 33 percent in women.

Anemia, which is known to cause adverse impact on patient's health related QoL[26–28] is frequently observed in RPC patients with a prevalence of 5 to 56 percent.[7,29–31] There have only been four studies with over 100 patients that assessed hematologic outcomes after RPC[7,29,32,33] and were designed specifically to address the prevalence and possible causes of post-RPC anemia. The identification of the underlying causes of anemia in RPC can be

challenging.[33] Anemia may require blood transfusion perioperatively and/or postoperatively.[29,34] A Cleveland Clinic assessment[34] of risk factors associated with anemia and the use of perioperative allogeneic blood transfusion and the effect of transfusion on infectious complications after RPC highlighted vital clinical information. They reported that preoperative anemia is a significant risk factor for perioperative transfusion with significant increase in postoperative infectious complications and anastomotic complications after RPC.[34] The study recommended that strategies to correct preoperative anemia, refine indications for transfusion, and define the use of blood salvage techniques may be helpful in decreasing this risk. Another intriguing study from the same institution[35] reports that an intraoperative blood transfusion had a negative impact on fertility in women patients who tried to conceive both before and after RPC.

Larger sized benchmark hematologic evaluation and performance improvements from Karolinska University,[36] before and after RPC of functionally acceptable pouches following closure of diverting loop ileostomy is depicted in Tables 1 and 2. Table 3 depicts the differing definition of anemia and the assessment experiences from different countries.[7,29–34,37–44]

Iron Deficiency Anemia

Iron is a critical element required for the normal functioning of all cells, and is necessary for basic metabolic processes such as oxygen transport, DNA synthesis, cyto-chrome P450 enzyme oxidative metabolism, and electron transport. Fortunately, humans are able to maintain appropriate levels of available iron in the body, even if our iron consumption does not always match the body's iron loss.[23] Physiologically, most stored iron is bound by ferritin molecules; the largest amount of ferritin-bound iron is found in hepatocytes, the bone marrow, and the spleen. The liver's stores of ferritin are the primary physiologic source of reserve iron in the body. Ferritin is the key to this important control of the amount of iron available to the body. Hence, the body has a “buffer” against iron deficiency (if the blood has too little iron, ferritin can release more) and, to a lesser extent, iron overload (if the blood and tissues of the body have too much iron, ferritin can help to store the excess iron). Iron is stored in the Fe (III) oxidation state. To release iron when the body needs it, the iron must be changed from the Fe (III) to the Fe (II) oxidation state.

Mean serum transferrin saturation was noted to be insignificantly increased and was above the referenced level in 6 percent to 14 percent after colectomy during the manipulative period with terminal ileostomy and diverting loop ileostomy.[36] During functionally acceptable pouches, 21 percent of the patients were reported to have had serum transferrin lower than the referenced level.[29,36] The deprivation of systematic transferrin in these patients corresponded with iron deficiency anemia.[7,36] Other researchers[40,41] have observed normal referenced transferrin values during the same phases.

Until recently, iron-deficiency anemia has not been included as a possible long-term complication[31,33,37] after RPC. Iron deficiency anemia is seen in about 6 to 21 percent of patients with functionally acceptable pouches.[7,29–31,33,36,37] Oikonomou *et al*.[33] showed a higher rate of iron deficiency anemia in RPC patients with underlying FAP compared to RPC for UC. In their study, the multivariable analysis showed that the presence of

malignancy or desmoid tumor and the J-pouch configuration were the only independent risk factors associated with iron deficiency anemia in 75 percent of cases. One-fourth of the RPC patient population with anemia showed unclear etiology. Other possible factors observed leading to iron-deficiency anemia include insufficient iron intake, impaired absorption and increased requirements and/or chronic blood loss.[29,31,33,37] A recent Puerto Rican trial[37] evaluated RPC-patients who presented with iron-deficiency anemia. They used clinical, serologic and histologic, and endoscopic data and found that more than half of the patients developed iron-deficiency anemia during long-term follow-up. They noted Iron deficiency anemia in 55.5 percent (10/18) of patients and pouchitis was found in 77 percent (14/18). All ten patients with anemia had pouchitis, suggesting that chronic blood loss because of hemorrhagic mucosal pouchitis as the cause of the anemia; whereas only four of the eight without anemia had pouchitis. Interestingly, in half of the anemic patients, their pouchitis was asymptomatic.[37] These observations are in accordance with other reports that the identified leading cause of iron-deficiency anemia in RPC patients to be prolonged pouchitis.[7,38] Currently, there is an argument among clinician-scientists suggesting that iron-deficiency anemia in RPC patients may be a presenting clinical sign of active pouchitis and that hemoglobin and hematocrit levels should be considered as surveillance tools for pouchitis.[37] Obviously, studies to exclude other possibilities that might cause anemia are required including evaluation of iron intake, absorption, transport, storage, serum iron levels, total binding globulins, ferrin levels, percentage of iron saturation, stool for occult blood, and ferrin receptor levels.

Nicholls and associates[6] carried out a metabolic and physiologic assessment in RPC patients and found that a significant number of their patients (5 out of 14) had low serum iron levels. Tulchinsky *et al*.[39] had similar results and reports iron-deficiency anemia in 22 percent of their RPC patients. Kuisma *et al*.[38] observed that of 34 of their RPC-patients, 10 (29.4 percent) had hypohemoglobinemia. In both studies, patients were treated and responded well with oral or intravenous iron supplements. Controversially, they found no correlation between pouchitis and iron deficiency anemia.[29,31,33,36,45] Tiainen *et al*.[31] described the prevalence of iron deficiency anemia after long-term follow-up after RPC; but no clear correlation or further investigational assessments have been reported. Among females, the etiology of iron deficiency anemia could not be attributed to a past history of excessive bleeding or metrorrhagia.[33] These studies raise concern that RPC-patients may be at risk of developing iron deficiency anemia, which (if undetected) may ultimately result in other clinical and economic outcome complications.[31,33,37]

Vitamin B_{12} Deficiency Anemia

VB_{12}, also known as cobalamin, was first isolated in 1948 and obviously shown to be effective in the treatment of pernicious anemia.[24] In recent years, an interest in VB_{12} has been renewed because of the recognition that cobalamin deficiency occurs in 3 percent to 40 percent of the general population[27] (compared to 25 percent to 53 percent in pouch recipients). The distribution of VB_{12} deficiency in the general population is roughly 2:1 female:male, but is not the case in RPC patients, in which 53 percent of those patients with low B_{12} levels were females. The reason for this difference is uncertain, but with a median age of 40, this was not a relatively young study group. Looking at an older population,

Lindenbaum *et al*.[27] found that 15 percent of normal subjects over 60 years of age have undiagnosed VB_{12} deficiency attributed to food-cobalamin malabsorption as the probable main cause.

Absorption of VB_{12} from foods is complex and a defect in any step can lead to deficiency.[25] In the stomach, gastric acid and pepsin release cobalamin from proteins, and it binds preferentially to salivary R protein. In the upper small intestine, pancreatic enzymes and an alkaline pH digest the R protein-cobalamin complex then binds to intrinsic factor (IF) to form an IF-cobalamin complex. Endogenous VB_{12}, excreted in bile, also binds to IF. The IF-cobalamin complex attaches to membrane receptors in the ileum and is absorbed through endocytosis. Absorption of VB_{12} by this process is limited (< 3 micrograms per meal). About 1 percent of the VB_{12} dose is absorbed by passive diffusion even in the absence of IF.[25]

The liver stores most of the body's cobalamin (about 1.5 mg), followed by the kidneys, heart, spleen, and brain. Normal body stores of VB_{12} range from 2 to 10 mg while daily losses are 2 to 5 micrograms. Over 75 percent of the cobalamin excreted in bile is reabsorbed. Urinary excretion of cobalamin is usually low.[46] Because of this efficient enterohepatic circulation, in normal circumstances, VB_{12} deficiency typically takes a long time to develop. At least 2 to 5 years must elapse from an event until there is noted to be a serum cobalamine decrease.[47]

Patients that have undergone RPC are often reported to develop VB_{12} deficiency anemia. One Swedish trial reported more than one-third of RPC-patients to have had abnormal Schilling tests and 5 percent had serum VB_{12} below referenced levels (Table 2).[29] Another similar trial from Ireland[32] also observed abnormally low serum VB_{12} in 25 percent of their RPC-patients. About 40 percent of their RPC patients had three or more sequential VB_{12} measurements, and of these, 66 percent showed steadily declining VB_{12} levels. Surprisingly, 94 percent of these patients with low serum VB_{12} had a normal Schilling test and were negative for bacterial overgrowth.[32] Kuisma *et al*.[38] observed VB_{12} deficiency in approximately 5 percent of their 34 RPC-patients. Hylander *et al*.[42] reported VB_{12} malabsorption in 32 percent of their RPC-patients. Studies on Kock's original pouch and continent ileostomy patients showed abnormal Schilling tests and abnormal absorption of VB_{12}.[48,49] Gadacz *et al*.[50] studied patients that had undergone the same procedure and found abnormal Schilling test in three out of four patients. They also observed that VB_{12} was poorly absorbed when a solution containing VB_{12} without IF, was instilled directly into the pouch. However, they found indirect evidence of active absorption of VB_{12} by the pouch, since patients who had IF given with VB_{12} solution directly into the pouch, demonstrated cobalamin absorption. Substitution therapy with VB_{12} was necessary in about one-third of the patients. Controversially, one Canadian study found no RPC-patients with low serum VB_{12} levels at a long-term follow-up, and Schilling tests were normal in all of their 38 patients tested.[51] Similarly, observations from St. Mark's Hospital in London[6] and the Mayo Clinic[52] also reported that they found no VB_{12} abnormalities, though the earlier study noted four patients to have had marginally low values.

There are three described possible causes for VB_{12} deficiency observed in patients who have undergone RPC. First, patients may have had the absorptive capacity for VB_{12} reduced because of resection of the distal ileum.[53,54] The exact minimum length of terminal ileum required for adequate VB_{12} absorption is unclear, but has been reported to be between 13-36 cm.[53,54] Thompson *et al*.[55] concluded that VB_{12} malabsorption was likely if more than 60 cm of terminal ileum was resected. Another group[56] discovered receptors for the VB_{12}-IF complex over, “the entire lower 3/5 of the human small intestine,” supporting the fact that excising small amount of terminal ileum does not remove the entire area capable of absorbing VB_{12}. Since the ileocecal valve is removed in RPC procedure, changes in transit time may play a factor. Hagedorn *et al*.[56] also stated that it is possible that only certain parts of the ileum contain the complete absorption system, rather than just the VB_{12}-IF receptor necessary to transport VB_{12} from receptor into enterocyte and that there may be additional intracellular factors to be defined that may be only located in the terminal ileum.

Some researchers[32] argue that the short length of ileal resection and the fact that all but one patient with a sub-normal VB_{12} had a normal Schilling test suggests that removal of the terminal ileum segment was not the cause of the falling VB_{12} levels. This is despite the fact that the manipulated terminal ileum for creation of the pouch is the only known active part for the absorption of VB_{12} in humans.[57–59] The question of whether or not the surface of the defunctionalized intestinal segment during temporary diverting loop ileostomy is sufficient for the cause of malabsorption of VB_{12} has been widely discussed.[5,60–62] It has been repeatedly confirmed that cobalamin in sufficient amounts cannot be absorbed in the absence of the terminal ileum.[63,64] A reversible absorptive loss of ileal capacity was demonstrated in the case of VB_{12} deficiency, and it was suggested that a depletion of VB_{12} further impairs the absorption of VB_{12}.[65] The pouch design with use of a diverting loop ileostomy leads to temporary bypassing the terminal ileum of about a mean length of ≤120 cm (range, 45Some researchers212 cm, including the pouch).[2,5,29] Despite the fact that patients with terminal ileal exclusion less than 20 cm are not at risk of developing VB_{12} deficiency,[58] the stasis of small bowel contents predis-poses to bacterial overgrowth in both the ileal reservoir and the more proximal ileum until closure of the loop ileostomy.[32] For predicting pernicious anemia in patients with resections of 20 to 60 cm of terminal ileum, options include doing a Schilling test and treating those with abnormal results, empirically treating patients on the presumption that they are at high risk of developing deficiency, or monitoring for biochemical evidence of deficiency. Duerksen *et al*.[58] and Behrend *et al*.[61] differ from other studies and showed that patients with ileal resections less than 20 cm had a 38 percent chance of having an abnormal Schilling test result. They found that there were no abnormal test findings if patients had a resection less than 20 cm.[58] Possible reasons for this difference vs. the previously mentioned studies may relate to the patient population studied (all patients in the study by Behrend *et al*.[61] had ileorectal anastomoses), inadequate urine collections, or there could have been active ileal disease at the time of the Schilling test. Other studies have attempted to correlate length of ileal resection with risk of developing VB_{12} deficiency. Ooi *et al*.[66] showed that, over time, VB_{12} absorption may normalize in patients who have had ileal resections because of intestinal adaptation. This has been shown in pediatric populations but not in adult patients,[67] *e.g*., repeat testing in 35 patients did not demonstrate any normalization of previously abnormal test results.[61] However, this latter

study also demonstrated that in a few cases the Schilling test repeated in the same individual varied between a normal and abnormal result over time. In a long-term follow-up study of a pediatric population with ileal resections of 3 to 45 cm for necrotizing enterocolitis in infancy, only one patient developed VB_{12} deficiency after a follow-up at a median of 7.2 years.[68]

Despite these controversies, clinicians are left with the dilemma of how to manage VB_{12} in patients who have had ileal resections. The literature appears consistent that resections more than 60 cm have a high likelihood of causing VB_{12} deficiency and therefore these patients should empirically be treated with VB_{12} supplementation.[55,61,67] However, further studies are needed to determine whether oral VB_{12} supplementation is effective enough in these patients.

Second, there may be “competition” for VB_{12} within the pouch secondary to the recognized bacterial over-growth.[69] Using a quantitative method, O'Connell *et al*.[70] found evidence of ileal bacterial overgrowth in all 20 of their study RPC-patients. They stated that, rather than bacterial overgrowth, it is an increase in anaerobic bacteria in the pouch that reduces VB_{12} absorption by binding the vitamin in its free and IF-complex states, thereby reducing absorption without altering the processes by which it occurs. While some studies[71,72] concluded that bacterial overgrowth of the small bowel may have lead to VB_{12} deficiency, Riordan *et al*.[73] found that serum VB_{12} levels were not significantly different in subjects with or without such bacterial overgrowth. Other studies[73,74] have shown that while the proportion of aerobic bacteria is relatively high within ileostomy flora, the pouch is colonized by a bacterial population with a composition comparable to the physiologic colonic flora, with anaerobic bacteria outnumbering the aerobic flora by several orders of magnitude. Despite the fact that absolute counts of bacteria are lower in pouch contents (10^{10}/g) than in the normal large intestine, metabolic activity is comparable. [74–77] In two other studies[78,79] hydrogen breath tests were performed after the patients were given lactulose which causes fermentation of colonic bacteria with the subsequent release of hydrogen. Using this technique, bacterial overgrowth was reported in 53 to 68 percent of the RPC-patients respectively. In contrast, Coull *et al*. study[32] found no evidence of bacterial overgrowth using the hydrogen breath test, but no quantitive studies of the bacterial flora were undertaken. Since their RPC-patients were not given lactulose in the study[21] it may explain the discrepancy in their results. Further studies of the effect of the bacterial flora on VB_{12} absorption in pouch patients would be required to determine the role of bacterial overgrowth.

Finally, patients with UC often report dietary intolerances.[80,81] RPC largely improves preoperative dietary intolerances in 67 percent[82] but in 25 percent remain unchanged while in 18 percent show exacerbated. Some RPC-patients however, are at risk for onset of new dietary intolerances[82,83] and in some a concomitant worsening of a preoperative dietary intolerance.[82] There was, however, a 20 to 40 percent incidence of post-RPC dietary intolerance across all dietary intolerance categories examined.[82] However, patients with UC appear to be more susceptible to developing persistent dietary intolerance after RPC than other patient populations undergoing RPC.[82] The observed VB_{12} deficiency in RPC-patients may simply because of dietary restriction[82,83] since little is known about the long-term

nutritional consequences of ileal pouch surgery. Clinicians, however, are aware that RPC-patients avoid foods that increase bowel frequency. It is of interest that patients, who have an end ileostomy without a pouch, have also been shown to develop VB_{12} deficiency.[77] In these patients, a shortened intestinal transit time has been suggested as a contributory or alternative explanation for B_{12} malabsorption. Another likely dietary cause of cobalamin deficiency in RPC patients is food-cobalamin malabsorption secondary to achlorhydria/hypochlorhydria which could be confirmed by testing for abnormal absorption of protein-bound cyanocobalamin.[84,85]

Although the exact cause of low VB_{12} levels in RPC-patients has not been determined, it has been observed to be possible to correct low serum VB_{12} levels by giving oral cyanocobalamin. All VB_{12} deficient RPC-patients who were given oral VB_{12} had their deficiency corrected.[32] Oral VB_{12} replacements is as effective as intramuscular injections, even in patients with pernicious anemia or ileal disease. This suggests that the absorption mechanism is normal and may point to either an inadequate dietary intake or a competitive bacteriologic environment for VB_{12} within the pouch, despite the fact that the breath test was observed to be normal.[32] Andres *et al*.[86] reported that all of their patients with subnormal VB_{12} levels had normal VB_{12} levels within two months of treatment with oral cyanocobalamin (500–1000 2g/day).

Based on the results of the aforementioned studies, the risk of developing VB_{12} deficiency in RPC-patients is much greater than has previously been recognized. It is assumed that the higher incidence in some studies is related to a longer period of follow-up.[32] Combining the above studies as the global pouch community (GPC) has shown that one-quarter of patients who have undergone RPC have subnormal VB_{12} levels.[32] These levels progressively fall in up to two-thirds of patients. Since this may have serious clinical consequences, VB_{12} levels should be monitored in RPC-patients, and dietary advice should be given as most RPC-patients suffer dietary restrictions, forcing them to adopt a fixed dietary regimen,[87] such as being vegetarian.[29,88] Cobalamine - folate interrelationships and the effects of folate deficiency on VB_{12} are presented below.

FOLATE DEFICIENCY ANEMIA

Folic acid or folate deficiency anemia has not been reported in RPC population. Folate works closely with VB_{12}.[89–92] Cobalamin is needed to free folate from an inactive to an active state.[93] There is a concern, though rare, that high intakes of folate supplements might mask the macrocytic anemia of VB_{12} deficiency, thereby eliminating an important diagnostic sign.[94] One of folate's key functions is to allow for complete development of healthy red blood cells (erythrocytes) and deoxyribonucleic acid (DNA).[95] When body folic acid is deficient, the red blood cells cannot develop properly[93–95] and as a result small size/volume hypochromic erythrocytes are produced.

In two studies from Karolinska University[29,88] that followed RPC-patients 6:36 months after closure of their diverting loop ileostomy, observed a significantly increase of mean serum folate retentions compared to preoperative saturation (Table 2). Preoperatively, 12 percent of the studied cases (n=42) showed serum folate concentration below referenced level. These

patients were prescribed with the anti-inflammatory drug sulfasalazine preoperatively in triple therapy scheme (sulfasalazine, corticosteroid, and total parental nutrition) to treat fulminant UC. One common known side effect of sulfasalazine is depletion in the body's supply of folate.[96–98] Postoperatively, no patient received sulfasalazine and none was noted to have folate lower than the referenced level [29,41,43,88] even after 20 years of having a functional pouch.[7] Similar observations were noted by others.[38,40] Nicholls *et al*.[6] reported that of their 14 RPC-patients, 2 (14.5 percent) cases showed folate concentration below referenced level, but all had normal red cell folate values. There was, therefore, no evidence for folate deficiency anemia despite having a low serum level of folate and perhaps there was not enough time to become symptomatic.

POUCHITIS

Publications from the Mayo Clinic,[8,45,52] Karolinska Institute,[7,29,36,99] Cleveland Clinic Foundation,[100] and St. Mark's Hospital[1,4,6,11,101] extensively describe the clinical results of patients after RPC. Among the described complications is pouchitis, the most common long-term complication of RPC in UC patients (≤ 60 percent).[7,11,12,29–33,37,45,101] Pouchitis is defined as a clinical syndrome of watery, frequent, and (at times), bloody stool accompanied by urgency, incontinence, abdominal cramps, malaise, and fever.[101] Moskowitz *et al*.[11] defined pouchitis applying more specific diagnostic criteria as a triad of diarrhea, endoscopic findings, and a minimum grade of 4 in a 6-point histopathologic index. In 1994, the Pouchitis Disease Activity Index (PDAI) was developed incorporating these two definitions.[52,102] The PDAI provided a standardized definition of pouchitis based on clinical, endoscopic, and histologic markers, with pouchitis defined as a score ≥ 7 points.[11,52] Diagnosis based on the modified pouchitis disease activity index (mPDAI) is seen to offer similar sensitivity and specificity when compared with the PDAI for patients with acute or acute relapsing pouchitis.[103] Pouchitis and anemia has been frequently observed to occur concomitantly.

Quality of Life (QoL) After RPC

The most important goal of RPC operation is to cure the disease and improve QoL of the patients.[8,104–107] QoL evaluation included physical function, physical status, corporal pain, general health, vitality, social function, emotional status, employment, and mental health. The studies show that RPC is a safe and effective procedure and that QoL remains at or above population norms regardless of surgical technique.[104,108,109] However, the presence of stoma and fecal incontinence are factors that contribute to deterioration of QoL after RPC.[110] Approximately 87.5 percent of patients consider that their health status has improved during the first year postoperatively.[110] Ninety-two percent of post-RPC patients retained their employment.[8]

Economic Burden of RPC Patients With Anemia

Inflammatory bowel disease (IBD) carries with it a high incidence of anemia as a result of gastrointestinal blood loss.[111–113] Surgical intervention in selected patients has had an important effect on well-being despite the fact that post-RPC anemia is an issue for many IBD patients.[7,31–33,37,48,61,88] A retrospective cohort study used to estimate the effects, the

differences, and the impact in health-care costs between anemic and nonanemic IBD patients is depicted in Table 4. Although cost analyses of IBD in the United States, Canada, the United Kingdom, Germany, and Sweden have been published, there are no such studies focused specifically for anemia in RPC patients per se. The prevalence of anemia in patients with IBD ranges from 8.8 percent to 73.7 percent depending on the patient subpopulation.[111] Because of the long disease duration, IBD is responsible for high use of health services and high lifetime costs for medical care.[114–117] Even in times of remission, patients with IBD regularly need outpatient care for monitoring the course of disease and drug therapy.[118] The cost includes physician costs, laboratory costs, and costs for diagnostic procedures following the visit. The average annual medical cost per patient with UC in the United States was estimated at $2,801[119] with an overall annual health care cost for IBD of more than $1.7 billion.[120,121] In Germany the mean cost of one outpatient visit in 2004 was $252.[118] Based on the statistics of the Association of German Pension Insurance Institutes (VDR), and total of 840 patients with IBD were unable to work and retired at a mean age of 42 years (female) and 46 years (male), which is approximately 15 to 20 years before the official age for retirement.[122] Over a decade ago, Blomqvist and Ekbom[116] reported direct annual health-care costs of patients with IBD of $44.7 million for Sweden. According to a Swedish analysis, the indirect costs as a result of morbidity were approximately double the direct costs.[116] Indirect costs to society caused by morbidity are estimated to be as high as $94.8 million. The authors also analyzed the distribution of outpatient (OPD) care because of IBD. They found that only 10 percent of the visits took place in primary care, whereas 90 percent of the visits occurred in the OPD of hospitals (66 percent to internal medicine and 21 percent to surgery). Ershler *et al*.[123] reported about the economic burden of patients with anemia in IBD. Their results for unadjusted direct costs of the anemic and nonanemic populations and the differences as well as the budget impact in a model of hypothetical population of one million members are depicted in Table 4.[123] Hay *et al*.[119] concluded that approximately 5 to 10 percent of IBD patients experience work disability annually. Thus, the annual morbidity-related loss of productivity would be in the range of $0.8–1.55 billion.[124] The costs are likely to continue to increase.

DISCUSSION

Anemia is common in the RPC patient population,[7,31–33,37] but the prevalence varies dramatically. It has been reported to range from as low as 5 percent to as high as 56 percent. Interpretation of this range of results is complicated both by the definition of anemia and by the variety of possible causes and the onset of clinical manifestations. A large study relied on the presence of The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-10-CM) codes in a discharge database to identify patients with anemia.[125] This classification method, of course, is likely to underestimate the true anemia prevalence because anemia may not be coded reliably in the hospital record. Because mild anemia is the most likely to be undercoded, such a study population may be skewed toward patients with more severe anemia and thus is unlikely to underestimate the true incidence of anemia.

Iron and/or Vitamin B_{12} deficiency anemia is an important frequent extraintestinal post-RPC complication that is commonly overlooked despite its impact on QoL in RPC patients. It is a

commonly undetected complication as both medical as well as a surgical problem. In this review, most studies demonstrate that some patients are at higher risk of developing anemia after RPC than others often as the result of recurrent bleeding from the pelvic pouch mucosa and with chronic pouchitis.[31,33,37,38] Metabolic consequences after RPC are commonly associated with pouchitis,[7,37,38,52,126] grade of villous atrophy,[69,127,128] and extent of inflammation[30,102,129] in the remaining ileum. The impacts of these post-RPC sequelae on anemia are not clearly understood. Patients with active chronic pouch inflammation therefore need long-term follow-up[7,8,31,38,45,51,99] since some patients run a risk of significant anemia. Follow-up should include blood tests.[7,31,33] A report suggesting that iron-deficiency anemia may be a clinical sign of active pouchitis, and that hemoglobin and hematocrit levels may serve as surveillance tools for pouchitis, should be considered when pouchitis is a concern. This would need to be confirmed with larger prospective, multi-institutional studies. One recent study from Cleveland Clinic[33] reported that there is a higher rate of iron deficiency anemia in RPC patients with underlying FAP compared to those patients with UC. They also found that multivariable analysis showed that the presence of malignancy or desmoid tumor and the J-pouch configuration were the only independent risk factors associated with iron deficiency anemia.

The mechanism for post-RPC vitamin B_{12} deficiency is unknown but often requires the exogenous addition of this vitamin.[57–59] A possible explanation for this complication in RPC patients may be because of changes in bacterial flora in the neoterminal ileum and pouch,[32,69] degree of ileal resection,[55,58] and/or even dietary.[39,77] A likely dietary cause of cobalamin deficiency in RPC patients is food-cobalamin malabsorption secondary to achlorhydria/hypochlorhydria which could be confirmed by testing for abnormal absorption of protein-bound cyanocobalamin.[84,85] This would be strengthened by analyzing gastric biopsies to test for achlorhydria/hypochlorhydria and fecal elastase tests to exclude chronic pancreatitis. Folic acid deficiency, which has not been reported in RPC population, may result in falsely low serum vitamin B_{12} levels.[93]

This review emphasizes that 25 percent of RPC patients develop cobalamin deficiency thus encouraging vitamin B_{12} levels be checked if an RPC-patient is anemic. It should be understood that vitamin B_{12} levels may start to fall preoperatively during the stage of active colitis. Normal Schilling test in vitamin B_{12}-deficient RPC-patients suggest that the terminal ileal resection alone may not be the cause (and also that backwash ileitis is an unlikely cause). Pouchitis may be a contributory factor and that the increasing usage of probiotics to treat pouchitis may have a beneficial influence on declining vitamin B_{12} levels.

Anemia has shown to have a negative impact on the economy.[116–124] Direct and indirect medical and other costs of anemia (after adjusting for differences in demographics) in IBD patients was substantially higher than in the nonanemic.[123] Nonanemic patients incurred higher average annual income costs because they could manage to return to work, compared to anemic patients who had higher absent records and therefore had negative impact on work productivity among IBD patients. [116–124]

SUMMARY

If one has to weigh the risk of symptoms of preoperative chronic colonic disease, patient QoL improved significantly after successful RPC. Patients after RPC may develop iron and/or vitamin B_{12} deficiency anemia while having functionally acceptable pouches. Folic acid deficiency anemia has not been reported in RPC-patients. Pouchitis, which corresponds significantly with anemia, continues to be a challenging and frequent complication. Pouchitis with pouch mucosal bleeding and malabsorption are observed to be associated with iron deficiency anemia. Iron deficiency anemia is being considered as a possible indicator of active pouchitis. Presence of malignancy, desmoid tumors and J-shaped pouch are seen associated with iron deficiency anemia. Vitamin B_{12} deficiency anemia after RPC is attributed to the degree of terminal ileal resection, malabsorption, bacterial overgrowth, and dietary intolerance factors.

Anemia may substantially increase healthcare costs at a level that is economically very relevant. Treatment of anemia and the underlying cause is critical as this has the potential to improve clinical and economic outcomes.

CONCLUSION

Both Iron and vitamin B_{12} deficiency anemia are not uncommon after RPC surgery. Given its high prevalence, patients undergoing RPC surgery should, therefore, undergo high index suspicion hematologic laboratory evaluation, unless reliable and satisfying, on long-term surveillances. Delays in diagnosis and treatment of anemia may result in irreversible complications. In patients that are shown to be intolerant of oral iron replacement therapy or their anemia were refractory to such supplementation, correction of such anemias through the administration of intravenous iron saccharate or supplemental erythropoietin has shown to improve patient hematologic indices and QoL.[111,130] In the case of vitamin B_{12} deficiency anemia oral vitamin B_{12} supplement have equally shown to be as effective as intramuscular injections. Timely screening and treatment of anemia makes a difference.

Acknowledgments

We are grateful to Vanderbilt University Medical Center, Department of Surgery, Division of General Surgery, and the Colon and Rectal Program. We acknowledge all the scientists who made contributions to the areas of research that are reviewed here but were not cited owing to space constraints. We are grateful to Dr. Robert Matusik, Ph.D., for critical reading of the manuscript.

REFERENCES

1. Parks AG, Nicholls RJ. Proctocolectomy without ileostomy for ulcerative colitis. Br Med J. 1978; 2:85–8. [PubMed: 667572]
2. Utsunomiya J, Iwama T, Imajo M, et al. Total colectomy, mucosal proctectomy, and ileoanal anastomosis. Dis Colon Rectum. 1980; 23:459–66. [PubMed: 6777128]
3. M'Koma AE, Wise PE, Muldoon RL, Schwartz DA, Washington MK, Herline AJ. Evolution of the restorative proctocolectomy and its effects on gastrointestinal hormones. Int J Colorectal Dis. 2007; 22:1143–63. [PubMed: 17576578]
4. Nicholls RJ, Pezim ME. Restorative proctocolectomy with ileal reservoir for ulcerative colitis and familial adenomatous polyposis: a comparison of three reservoir designs. Br J Surg. 1985; 72:470–4. [PubMed: 4016516]

5. Remzi FH, Fazio VW, Gorgun E, et al. The outcome after restorative proctocolectomy with or without defunctioning ileostomy. Dis Colon Rectum. 2006; 49:470–7. [PubMed: 16518581]
6. Nicholls RJ, Belliveau P, Neill M, Wilks M, Tabaqchali S. Restorative proctocolectomy with ileal reservoir: a patho-physiological assessment. Gut. 1981; 22:462–8. [PubMed: 7262623]
7. M'Koma AE. Serum biochemical evaluation of patients with functional pouches ten to 20 years after restorative proctocolectomy. Int J Colorectal Dis. 2006; 21:711–20. [PubMed: 16437210]
8. Hahnloser D, Pemberton JH, Wolff BG, Larson DR, Crownhart BS, Dozois RR. Results at up to 20 years after ileal pouch-anal anastomosis for chronic ulcerative colitis. Br J Surg. 2007; 94:333–40. [PubMed: 17225210]
9. Bengtsson J, Borjesson L, Lundstam U, Oresland T. Long-term function and manovolumetric characteristics after ileal pouch-anal anastomosis for ulcerative colitis. Br J Surg. 2007; 94:327–32. [PubMed: 17225209]
10. Chapman JR, Larson DW, Wolff BG, et al. Ileal pouch-anal anastomosis: does age at the time of surgery affect outcome? Arch Surg. 2005; 140:534–9. [PubMed: 15967900]
11. Moskowitz RL, Shepherd NA, Nicholls RJ. An assessment of inflammation in the reservoir after restorative proctocolectomy with ileoanal ileal reservoir. Int J Colorectal Dis. 1986; 1:167–74. [PubMed: 3039030]
12. Mahadevan U, Sandborn WJ. Diagnosis and management of pouchitis. Gastroenterology. 2003; 124:1636–50. [PubMed: 12761722]
13. Kartheuser A, Stangherlin P, Brandt D, Remue C, Sempoux C. Restorative proctocolectomy and ileal pouch-anal anastomosis for familial adenomatous polyposis revisited. Fam Cancer. 2006; 5:241–60. [PubMed: 16998670]
14. Kartheuser AH, Parc R, Penna CP, et al. Ileal pouch-anal anastomosis as the first choice operation in patients with familial adenomatous polyposis: a ten-year experience. Surgery. 1996; 119:615–23. [PubMed: 8650601]
15. Nyam DC, Brillant PT, Dozois RR, Kelly KA, Pemberton JH, Wolff BG. Ileal pouch-anal canal anastomosis for familial adenomatous polyposis: early and late results. Ann Surg. 1997; 226:514–9. [PubMed: 9351719]
16. Parc YR, Olschwang S, Desaint B, Schmitt G, Parc RG, Tiret E. Familial adenomatous polyposis: prevalence of adenomas in the ileal pouch after restorative proctocolectomy. Ann Surg. 2001; 233:360–4. [PubMed: 11224623]
17. Dozois RR, Kelly KA, Welling DR, et al. Ileal pouch-anal anastomosis: comparison of results in familial adenomatous polyposis and chronic ulcerative colitis. Ann Surg. 1989; 210:268–71. [PubMed: 2549890]
18. Becker JM, Stucchi AF. Proctocolectomy with ileoanal anastomosis. J Gastrointest Surg. 2004; 8:376–86. [PubMed: 15120354]
19. Colwell JC, Gray M. What functional outcomes and complications should be taught to the patient with ulcerative colitis or familial adenomatous polyposis who undergoes ileal pouch anal anastomosis? J Wound Ostomy Continence Nurs. 2001; 28:184–9. [PubMed: 11452254]
20. Barton JG, Paden MA, Lane M, Postier RG. Comparison of postoperative outcomes in ulcerative colitis and familial polyposis patients after ileoanal pouch operations. Am J Surg. 2001; 182:616–20. [PubMed: 11839326]
21. Penna C, Tiret E, Kartheuser A, Hannoun L, Nordlinger B, Parc R. Function of ileal J pouch-anal anastomosis in patients with familial adenomatous polyposis. Br J Surg. 1993; 80:765–7. [PubMed: 8392425]
22. Moslein G, Pistorius S, Saeger HD, Schackert HK. Preventive surgery for colon cancer in familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer syndrome. Langenbecks Arch Surg. 2003; 388:9–16. [PubMed: 12690475]
23. Fleming RE, Bacon BR. Orchestration of iron homeostasis. N Engl J Med. 2005; 352:1741–4. [PubMed: 15858181]
24. Herbert, V. Vitamin B12 an overview. Royoal Society of Medicine Press; London: 1999.
25. Schjonsby H. Vitamin B12 absorption and malabsorption. Gut. 1989; 30:1686–91. [PubMed: 2693230]

26. Evans RW, Rader B, Manninen DL. The quality of life of hemodialysis recipients treated with recombinant human erythropoietin. Cooperative Multicenter EPO Clinical Trial Group. JAMA. 1990; 263:825–30. [PubMed: 2404150]
27. Lindenbaun J, Rosenberg IH, Wilson PW, Stabler SP, Allen RH. Prevalence of cobalamin deficiency in the Framingham elderly population. Am J Clin Nutr. 1994; 60:2–11. [PubMed: 8017332]
28. Crawford J, Cella D, Cleeland CS, et al. Relationship between changes in hemoglobin level and quality of life during chemotherapy in anemic cancer patients receiving epoetin alfa therapy. Cancer. 2002; 95:888–95. [PubMed: 12209734]
29. M'Koma AE. Follow-up results of hematology data before and after restorative proctocolectomy. Clinical outcome. Dis Colon Rectum. 1994; 37:932–7. [PubMed: 8076494]
30. Vendrell R, Inesta M, Mera R, et al. Ileal pouch-anal anastomosis for ulcerative colitis: the University of Puerto Rico experience. P R Health Sci J. 2001; 20:221–4. [PubMed: 11776722]
31. Tiainen J, Matikainen M. Long-term clinical outcome and anemia after restorative proctocolectomy for ulcerative colitis. Scand J Gastroenterol. 2000; 35:1170–3. [PubMed: 11145288]
32. Coull DB, Tait RC, Anderson JH, McKee RF, Finlay IG. Vitamin B12 deficiency following restorative proctocolectomy. Colorectal Dis. 2007; 9:562–6. [PubMed: 17509054]
33. Oikonomou IK, Fazio VW, Remzi FH, Lopez R, Lashner BA, Shen B. Risk factors for anemia in patients with ileal pouch-anal anastomosis. Dis Colon Rectum. 2007; 50:69–74. [PubMed: 17115336]
34. Madbouly KM, Senagore AJ, Remzi FH, Delaney CP, Waters J, Fazio VW. Perioperative blood transfusions increase infectious complications after ileoanal pouch procedures (IPAA). Int J Colorectal Dis. 2006; 21:807–13. [PubMed: 16583193]
35. Gorgun E, Remzi FH, Goldberg JM, et al. Fertility is reduced after restorative proctocolectomy with ileal pouch anal anastomosis: a study of 300 patients. Surgery. 2004; 136:795–803. [PubMed: 15467664]
36. M'Koma, AE. Observation on essential biochemical data profile in connection with restorative proctocolectomy in humans, Vitamin B12 and fat absorption cited. Karolinska University Press; Stockholm: 2001. p. 1-126.http://diss.kib.ki.se/2001/91-7349-007-5/
37. Pastrana RJ, Torres EA, Arroyo JM, Rivera CE, Sanchez CJ, Morales L. Iron-deficiency anemia as presentation of pouchitis. J Clin Gastroenterol. 2007; 41:41–4. [PubMed: 17198064]
38. Kuisma J, Nuutinen H, Luukkonen P, Jarvinen H, Kahri A, Farkkila M. Long term metabolic consequences of ileal pouch-anal anastomosis for ulcerative colitis. Am J Gastroenterol. 2001; 96:3110–6. [PubMed: 11721757]
39. Tulchinsky H. Follow-up of restorative proctocolectomy: clinical experience of a specialized pouch clinic. Inflammatory bowel disease and familial adenomatous polyposis. Spring Milan. 2007:293–300.
40. Athanasiadis S. [Restorative proctocolectomy with an ileal pouch. Functional and biochemical results]. Langenbecks Arch Chir. 1983; 360:207–20. [PubMed: 6645731]
41. Fiorentini MT, Locatelli L, Ceccopieri B, et al. Physiology of ileoanal anastomosis with ileal reservoir for ulcerative colitis and adenomatosis coli. Dis Colon Rectum. 1987; 30:267–72. [PubMed: 3030677]
42. Hylander E, Rannem T, Hegnhoj J, Kirkegaard P, Thale M, Jarnum S. Absorption studies after ileal J-pouch anastomosis for ulcerative colitis. A prospective study. Scand J Gastroenterol. 1991; 26:65–72. [PubMed: 2006400]
43. Pironi L, Miglioli M, Ruggeri E, et al. Nutritional status of patients undergoing ileal pouch-anal anastomosis. Clin Nutr. 1991; 10:292–7. [PubMed: 16839934]
44. Bayat M, Brynskov J, Dige-Petersen H, Hippe E, Lonborg-Jensen H. Direct and quantitative vitamin B12 absorption measurement in patients with disorders in the distal part of the bowel. Comparison of stool spot test [SST] with whole body counting in patients with ileal pelvic reservoir, ileostomy or Crohn's disease. Int J Colorectal Dis. 1994; 9:68–72. [PubMed: 8064192]

45. Pemberton JH, Kelly KA, Beart RW Jr, Dozois RR, Wolff BG, Ilstrup DM. Ileal pouch-anal anastomosis for chronic ulcerative colitis. Long-term results. Ann Surg. 1987; 206:504–13. [PubMed: 3662660]
46. Shils JAO, ME.; Shike, M., editors. Modern nutrition in health and disease. Lea and Febiger; Philadelphia: 1994. Herbert V DKC, Folic acid and Vitamin B12.; p. 402-25.
47. Snow CF. Laboratory diagnosis of vitamin B12 and folate deficiency: a guide for the primary care physician. Arch Intern Med. 1999; 159:1289–98. [PubMed: 10386505]
48. Jagenburg R, Kock NG, Philipson B. Vitamin B12 absorption in patients with continent ileostomy. Scand J Gastroenterol. 1975; 10:141–4. [PubMed: 1124347]
49. Kock NG. Intra-abdominal “reservoir” in patients with permanent ileostomy. Preliminary observations on a procedure resulting in fecal “continence” in five ileostomy patients. Arch Surg. 1969; 99:223–31. [PubMed: 5794896]
50. Gadacz TR, Kelly KA, Phillips SF. The continent ileal pouch: absorptive and motor features. Gastroenterology. 1977; 72:1287–91. [PubMed: 870378]
51. Belliveau P, Trudel J, Vasilevsky CA, Stein B, Gordon PH. Ileoanal anastomosis with reservoirs: complications and long-term results. Can J Surg. 1999; 42:345–52. [PubMed: 10526518]
52. Sandborn WJ, Tremaine WJ, Batts KP, Pemberton JH, Phillips SF. Pouchitis after ileal pouch-anal anastomosis: a Pouchitis Disease Activity Index. Mayo Clin Proc. 1994; 69:409–15. [PubMed: 8170189]
53. Payne JH, DeWind LT. Surgical treatment of obesity. Am J Surg. 1969; 118:141–7. [PubMed: 5798387]
54. Dano P, Lenz K. Change of bile acid metabolism and absorption of vitamin B12 after intestinal shunt operation in obesity. A comparison of three types of operation. Scand J Gastroenterol. 1974; 9:159–65. [PubMed: 4594371]
55. Thompson WG, Wrathell E. The relation between ileal re-section and vitamin B12 absorption. Can J Surg. 1977; 20:461–4. [PubMed: 890622]
56. Hagedorn CH, Alpers DH. Distribution of intrinsic factor-vitamin B12 receptors in human intestine. Gastroenterology. 1977; 73:1019–22. [PubMed: 198333]
57. Wolters M, Strohle A, Hahn A. Cobalamin: a critical vitamin in the elderly. Prev Med. 2004; 39:1256–66. [PubMed: 15539065]
58. Duerksen DR, Fallows G, Bernstein CN. Vitamin B12 malabsorption in patients with limited ileal resection. Nutrition. 2006; 22:1210–3. [PubMed: 17095407]
59. Seetharam B, Alpers DH. Absorption and transport of cobalamin (vitamin B12). Annu Rev Nutr. 1982; 2:343–69. [PubMed: 6313022]
60. Coyle JJ, Varco RL, Buchwald H. Vitamin B12 absorption following human intestinal bypass surgery. Am J Dig Dis. 1977; 22:1069–71. [PubMed: 930904]
61. Behrend C, Jeppesen PB, Mortensen PB. Vitamin B12 absorption after ileorectal anastomosis for Crohn's disease: effect of ileal resection and time span after surgery. Eur J Gastroenterol Hepatol. 1995; 7:397–400. [PubMed: 7614100]
62. Hulten L, Kewenter J, Persson E, Ahren C. Vitamin B12-absorption in ileostomy patients after operation for ulcerative colitis. Scand J Gastroenterol. 1970; 5:113–6. [PubMed: 5429871]
63. Fornaro R, Belcastro E, Lo Presti G, Carissimi T, Ferraris R. [The ileocecal valve as a prognostic factor in extensive resection of the small intestine]. Chir Ital. 1991; 43:49–54. [PubMed: 1769094]
64. Headstrom PD, Rulyak SJ, Lee SD. Prevalence of and risk factors for vitamin B12 deficiency in patients with Crohn's disease. Inflamm Bowel Dis. 2008; 14:217–23. [PubMed: 17886286]
65. Herbert V. Transient (reversible) malabsorption of vitamin B12. Br J Haematol. 1969; 17:213–9. [PubMed: 4896717]
66. Ooi BC, Barnes GL, Tauro GP. Normalization of vitamin B12 absorption after ileal resection in children. J Paediatr Child Health. 1992; 28:168–71. [PubMed: 1562369]
67. Lenz K. The effect of the site of lesion and extent of resection on duodenal bile acid concentration and vitamin B12 absorption in Crohn's disease. Scand J Gastroenterol. 1975; 10:241–8. [PubMed: 1138325]

68. Davies BW, Abel G, Puntis JW, et al. Limited ileal resection in infancy: the long-term consequences. J Pediatr Surg. 1999; 34:583–7. [PubMed: 10235328]
69. Philipson B, Brandberg A, Jagenburg R, Kock NG, Lager I, Ahren C. Mucosal morphology, bacteriology, and absorption in intra-abdominal ileostomy reservoir. Scand J Gastroenterol. 1975; 10:145–53. [PubMed: 1124348]
70. O'Connell PR, Rankin DR, Weiland LH, Kelly KA. Enteric bacteriology, absorption, morphology and emptying after ileal pouch-anal anastomosis. Br J Surg. 1986; 73:909–14. [PubMed: 3790923]
71. Brandt LJ, Bernstein LH, Wagle A. Production of vitamin B 12 analogues in patients with small-bowel bacterial over-growth. Ann Intern Med. 1977; 87:546–51. [PubMed: 921081]
72. Welkos SL, Toskes PP, Baer H. Importance of anaerobic bacteria in the cobalamin malabsorption of the experimental rat blind loop syndrome. Gastroenterology. 1981; 80:313–20. [PubMed: 7450422]
73. Riordan SM, McIver CJ, Thomas DH, Duncombe VM, Bolin TD, Thomas MC. Luminal bacteria and small-intestinal permeability. Scand J Gastroenterol. 1997; 32:556–63. [PubMed: 9200287]
74. Nasmyth DG, Godwin PG, Dixon MF, Williams NS, Johnston D. Ileal ecology after pouch-anal anastomosis or ileostomy. A study of mucosal morphology, fecal bacteriology, fecal volatile fatty acids, and their interrelationship. Gastroenterology. 1989; 96:817–24. [PubMed: 2914643]
75. Ambroze WL Jr, Pemberton JH, Phillips SF, Bell AM, Haddad AC. Fecal short-chain fatty acid concentrations and effect on ileal pouch function. Dis Colon Rectum. 1993; 36:235–9. [PubMed: 8449126]
76. Clausen MR, Tvede M, Mortensen PB. Short-chain fatty acids in pouch contents from patients with and without pouchitis after ileal pouch-anal anastomosis. Gastroenterology. 1992; 103:1144–53. [PubMed: 1397871]
77. Floruta CV. Dietary choices of people with ostomies. J Wound Ostomy Continence Nurs. 2001; 28:28–31. [PubMed: 11174459]
78. Bruun E, Meyer JN, Rumessen JJ, Gudmand-Hoyer E. Breath hydrogen analysis in patients with ileoanal pouch anastomosis. Gut. 1995; 37:256–9. [PubMed: 7557577]
79. Santavirta J. Lactulose hydrogen and [14C] xylose breath tests in patients with ileoanal anastomosis. Int J Colorectal Dis. 1991; 6:208–11. [PubMed: 1770288]
80. Hodgson HJ. Inflammatory bowel disease and food intolerance. J R Coll Physicians Lond. 1986; 20:45–8. [PubMed: 3511250]
81. Ballegaard M, Bjergstrom A, Brondum S, Hylander E, Jensen L, Ladefoged K. Self-reported food intolerance in chronic inflammatory bowel disease. Scand J Gastroenterol. 1997; 32:569–71. [PubMed: 9200289]
82. Schmidt CM, Wiesenauer CA, Sitzmann JV. Long-term effects on diet after proctocolectomy for ulcerative colitis. Am J Surg. 2008; 195:353–7. [PubMed: 18207132]
83. Provenzale D, Shearin M, Phillips-Bute BG, et al. Health-related quality of life after ileoanal pull-through evaluation and assessment of new health status measures. Gastroenterology. 1997; 113:7–14. [PubMed: 9207256]
84. Saltzman JR, Kemp JA, Golner BB, Pedrosa MC, Dallal GE, Russell RM. Effect of hypochlorhydria due to omeprazole treatment or atrophic gastritis on protein-bound vitamin B12 absorption. J Am Coll Nutr. 1994; 13:584–91. [PubMed: 7706591]
85. Junca J, de Soria PL, Granada ML, Flores A, Marquez E. Detection of early abnormalities in gastric function in first-degree relatives of patients with pernicious anemia. Eur J Haematol. 2006; 77:518–22. [PubMed: 17042761]
86. Andres E, Perrin AE, Demangeat C, et al. The syndrome of food-cobalamin malabsorption revisited in a department of internal medicine. A monocentric cohort study of 80 patients. Eur J Intern Med. 2003; 14:221–6. [PubMed: 12919836]
87. Coffey JC, Winter DC, Neary P, Murphy A, Redmond HP, Kirwan WO. Quality of life after ileal pouch-anal anastomosis: an evaluation of diet and other factors using the Cleveland Global Quality of Life instrument. Dis Colon Rectum. 2002; 45:30–8. [PubMed: 11786761]
88. M'Koma AE, Lindquist K, Liljeqvist L. Biochemical laboratory data in patients before and after restorative proctocolectomy. A study on 83 patients with a follow-up of 36 months. Ann Chir. 1994; 48:525–34. [PubMed: 7847701]

89. Chanarin I, Deacon R, Lumb M, Muir M, Perry J. Cobalamin-folate interrelations: a critical review. Blood. 1985; 66:479–89. [PubMed: 2862932]

90. Chanarin I. Folate and cobalamin. Clin Haematol. 1985; 14:629–41. [PubMed: 3907912]

91. Chanarin I. Megaloblastic anaemia, cobalamin, and folate. J Clin Pathol. 1987; 40:978–84. [PubMed: 3312306]

92. Chanarin I. Megaloblastic anaemiaYa perspective. Rinsho Ketsueki. 1988; 29:1950–9. [PubMed: 3070069]

93. Steinberg SE. Mechanisms of folate homeostasis. Am J Physiol. 1984; 246:G319–24. [PubMed: 6202150]

94. Brody, TB.; Stokstad, EL. Folic Acid. Marcel Dekker; New York: 1984.

95. Morris MS, Jacques PF, Rosenberg IH, Selhub J. Folate and vitamin B12 status in relation to anemia, macrocytosis, and cognitive impairment in older Americans in the age of folic acid fortification. Am J Clin Nutr. 2007; 85:193–200. [PubMed: 17209196]

96. Lakatos L, Lakatos PL. [Medical therapy of inflammatory bowel diseases: ulcerative colitis]. Orv Hetil. 2007; 148:1163–70. [PubMed: 17573252]

97. Hanauer SB. Review article: high-dose aminosalicylates to induce and maintain remissions in ulcerative colitis. Aliment Pharmacol Ther. 2006; 24(Suppl 3):37–40. [PubMed: 16961743]

98. Pierik M, Rutgeerts P, Vlietinck R, Vermeire S. Pharmacogenetics in inflammatory bowel disease. World J Gastroenterol. 2006; 12:3657–67. [PubMed: 16773681]

99. Weinryb RM, Liljeqvist L, Poppen B, Gustavsson JP. A longitudinal study of long-term quality of life after ileal pouch-anal anastomosis. Am J Surg. 2003; 185:333–8. [PubMed: 12657385]

100. Fazio VW, Ziv Y, Church JM, et al. Ileal pouch-anal anastomoses complications and function in 1005 patients. Ann Surg. 1995; 222:120–7. [PubMed: 7639579]

101. Nicholls RJ. Review article: ulcerative colitisYsurgical indications and treatment. Aliment Pharmacol Ther. 2002; 16(Suppl 4):25–8. [PubMed: 12047256]

102. Sandborn WJ. Pouchitis following ileal pouch-anal anastomosis: definition, pathogenesis, and treatment. Gastroenterology. 1994; 107:1856–60. [PubMed: 7958702]

103. Shen B, Achkar JP, Connor JT, et al. Modified pouchitis disease activity index: a simplified approach to the diagnosis of pouchitis. Dis Colon Rectum. 2003; 46:748–53. [PubMed: 12794576]

104. Larson DW, Davies MM, Dozois EJ, et al. Sexual function, body image, and quality of life after laparoscopic and open ileal pouch-anal anastomosis. Dis Colon Rectum. 2008; 51:392–6. [PubMed: 18213489]

105. Berndtsson I, Lindholm E, Oresland T, Borjesson L. Long-term outcome after ileal pouch-anal anastomosis: function and health-related quality of life. Dis Colon Rectum. 2007; 50:1545–52. [PubMed: 17762968]

106. Bach SP, Mortensen NJ. Revolution and evolution: 30 years of ileoanal pouch surgery. Inflamm Bowel Dis. 2006; 12:131–45. [PubMed: 16432378]

107. Shen B, Fazio VW, Remzi FH, et al. Risk factors for diseases of ileal pouch-anal anastomosis after restorative proctocolectomy for ulcerative colitis. Clin Gastroenterol Hepatol. 2006; 4:81–9. [PubMed: 16431309]

108. Dunker MS, Bemelman WA, Slors JF, van Duijvendijk P, Gouma DJ. Functional outcome, quality of life, body image, and cosmesis in patients after laparoscopic-assisted and conventional restorative proctocolectomy: a comparative study. Dis Colon Rectum. 2001; 44:1800–7. [PubMed: 11742165]

109. Larson DW, Dozois EJ, Piotrowicz K, Cima RR, Wolff BG, Young-Fadok TM. Laparoscopic-assisted vs. open ileal pouch-anal anastomosis: functional outcome in a case-matched series. Dis Colon Rectum. 2005; 48:1845–50. [PubMed: 16175324]

110. Sierra-Montenegro E, Fernandez-Rivero JM, Villanueva-Saenz E, Pena-Ruiz Esparza JP, Martinez-Hernandez Magro P, Solo-Quirino R. [Quality of life after restorative proctocolectomy with ileo-anal J pouch in patients with ulcerative colitis.]. Cir Cir. 2007; 75:449–52. [PubMed: 18177566]

111. Wilson A, Reyes E, Ofman J. Prevalence and outcomes of anemia in inflammatory bowel disease: a systematic review of the literature. Am J Med. 2004; 116(Suppl 7A):44–9. [PubMed: 14706665]

112. Gasche C. Anemia in IBD: the overlooked villain. Inflamm Bowel Dis. 2000; 6:142–50. [PubMed: 10833075]

113. Cronin CC, Shanahan F. Anemia in patients with chronic inflammatory bowel disease. Am J Gastroenterol. 2001; 96:2296–8. [PubMed: 11513165]

114. de Boer AG, Sprangers MA, Bartelsman JF, de Haes HC. Predictors of health care utilization in patients with inflammatory bowel disease: a longitudinal study. Eur J Gastroenterol Hepatol. 1998; 10:783–9. [PubMed: 9831274]

115. Feagan BG, Vreeland MG, Larson LR, Bala MV. Annual cost of care for Crohn's disease: a payor perspective. Am J Gastroenterol. 2000; 95:1955–60. [PubMed: 10950042]

116. Blomqvist P, Ekbom A. Inflammatory bowel diseases: health care and costs in Sweden in 1994. Scand J Gastroenterol. 1997; 32:1134–9. [PubMed: 9399395]

117. Silverstein MD, Loftus EV, Sandborn WJ, et al. Clinical course and costs of care for Crohn's disease: Markov model analysis of a population-based cohort. Gastroenterology. 1999; 117:49–57. [PubMed: 10381909]

118. Ebinger M, Leidl R, Thomas S, et al. Cost of outpatient care in patients with inflammatory bowel disease in a German University Hospital. J Gastroenterol Hepatol. 2004; 19:192–9. [PubMed: 14731130]

119. Hay JW, Hay AR. Inflammatory bowel disease: costs-of-illness. J Clin Gastroenterol. 1992; 14:309–17. [PubMed: 1607607]

120. Sandler RS, Everhart JE, Donowitz M, et al. The burden of selected digestive diseases in the United States. Gastroenterology. 2002; 122:1500–11. [PubMed: 11984534]

121. Baldassano RN, Piccoli DA. Inflammatory bowel disease in pediatric and adolescent patients. Gastroenterol Clin North Am. 1999; 28:445–58. [PubMed: 10372276]

122. Ebinger M, Leidl R, Thomas S, Von Tirpitz C, et al. Cost of outpatient care in patients with inflammatory bowel disease in Germany University Hospital. J Gastroenterol Hepatol. 2004; 19:192–9. [PubMed: 14731130]

123. Ershler WB, Chen K, Reyes EB, Dubois R. Economic burden of patients with anemia in selected diseases. Value Health. 2005; 8:629–38. [PubMed: 16283863]

124. Germany Morbus Crohn's and Colitis association (DCCV). [December 2001] Homepage of the DCCV. 2001. available from URL: http://www.dccv.de/home/index.ht

125. Statistics NCfH. About the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM). 2007.

126. Thompson-Fawcett MW, Marcus V, Redston M, Cohen Z, McLeod RS. Risk of dysplasia in long-term ileal pouches and pouches with chronic pouchitis. Gastroenterology. 2001; 121:275–81. [PubMed: 11487537]

127. Veress B, Reinholt FP, Lindquist K, Liljeqvist L. Different types of mucosal adaptation in the ileal reservoir after restorative proctocolectomy. A two-year follow-up study. APMIS. 1990; 98:786–96. [PubMed: 2223035]

128. Veress B, Reinholt FP, Lindquist K, Lofberg R, Liljeqvist L. Long-term histomorphological surveillance of the pelvic ileal pouch: dysplasia develops in a subgroup of patients. Gastroenterology. 1995; 109:1090–7. [PubMed: 7557073]

129. Marcello PW, Schoetz DJ Jr, Roberts PL, et al. Evolutionary changes in the pathologic diagnosis after the ileoanal pouch procedure. Dis Colon Rectum. 1997; 40:263–9. [PubMed: 9118738]

130. Schreiber S, Howaldt S, Schnoor M, et al. Recombinant erythropoietin for the treatment of anemia in inflammatory bowel disease. N Engl J Med. 1996; 334:619–23. [PubMed: 8592524]

TABLE 1

Serum hemoglobin, iron and transferrin levels before and after restorative proctocolectomy (RPC)

Point of control	Parameter	n	% below normal vs. ref value	% above normal vs. ref value	Mean ± SEM	P value vs. precolectomy	Reference level
Precolectomy	Hemoglobin	63	44	5	123.46 ± 2.85 g/L		130–165 g/L (Men)
Ileostomy	Hemoglobin	48	18	4	137.96 ± 2.34 g/L	*0.004*	*115*–145 g/L (Women)
Loop ileostomy	Hemoglobin	76	12	5	138.84 ± 1.56 g/L	*0.0001*	
6 months	Hemoglobin	75	11	5	139.27 ± 1.85 g/L	*0.0001*	
12 months	Hemoglobin	65	11	9	141.74 ± 1.77 g/L	*0.0001*	
18 months	Hemoglobin	55	7	5.5	140.16 ± 2.0 g/L	*0.0001*	
24 months	Hemoglobin	50	12	2	140.6 ± 2.09 g/L	*0.0001*	
36 months	Hemoglobin	30	14	7	140.2 ± 3.01 g/L	*0.001*	
Precolectomy	Iron (Fe)	55	49	0	10.78 ± 0.99 μmol/L		9–38 μmol/L (Men)
Ileostomy	Iron (Fe)	37	23	0	12.95 ± 1.03 μmol/L	*0.33*	*5–35* μmol/L (Women)
Loop ileostomy	Iron (Fe)	57	16	4	17.54 ± 1.53 μmol/L	*0.0003*	
6 months	Iron (Fe)	68	15	0	15.57 ± 1.05 μmol/L	*0.005*	
12 months	Iron (Fe)	61	11	0	16.34 ± 1.04 μmol/L	*0.0005*	
18 months	Iron (Fe)	49	21	0	15.47 ± 1.04 μmol/L	*0.005*	
24 months	Iron (Fe)	46	18	0	15.07 ± 1.11 μmol/L	*0.01*	
36 months	Iron (Fe)	31	16	0	17.45 ± 1.40 μmol/L	*0.01*	
Precolectomy	Transferrin	15	0	0	2.53 ± 0.35 g/L		2.1–3.60 g/L
Ileostomy	Transferrin	16	0	6	2.9 ± 0.26 g/L	*0.34*	
Loop ileostomy	Transferrin	14	0	14	3.55 ± 0.41 g/L	*0.66*	
6 months	Transferrin	14	0	0	2.58 ± 0.48 g/L	*0.34*	
12 months	Transferrin	16	0	0	2.3 ± 0.32 g/L	*0.32*	
18 months	Transferrin	15	0	0	2.82 ± 0.16 g/L	*0.33*	
24 months	Transferrin	12	0	0	3.0 ± 0.6 g/L	*0.70*	
36 months	Transferrin	11	0	0	2.4 ± 0.25 g/L	*0.35*	

Precolectomy, levels the night prior to total colectomy and ileostomy; Ileostomy, levels night prior to pouch construction; Loop ileostomy, levels prior to closure of diverting loop ileostomy; months, levels of functional pouch after diverting loop ileostomy closure.

Adapted and published (2001) with permission from the Karolinska Institute data base[36]

TABLE 2

Serum vitamin B_{12} levels and absorption test (by Schilling test) and folate levels before and after restorative proctocolectomy (RPC)

Point of control	Parameter	n	% below normal vs. ref value	% above normal vs. ref value	Mean ± SEM	P value vs. precolectomy	Reference level
Precolectomy	Vitamin B_{12}	41	8	10	433 ± 31.45 pmol/L		40–840 pmol/L
Ileostomy	Vitamin B_{12}	43	7	2	353 ± 32.27 pmol/L	*0.17*	
Loop ileostomy	Vitamin B_{12}	61	8	3	326 ± 30.78 pmol/L	*0.28*	
6 months	Vitamin B_{12}	69	7	3	335 ± 26.81 pmol/L	*0.33*	
12 months	Vitamin B_{12}	58	3	5	349 ± 27.73 pmol/L	*0.19*	
18 months	Vitamin B_{12}	53	6	2	319 ± 23.24 pmol/L	*0.03*	
24 months	Vitamin B_{12}	51	6	4	380 ± 36.1 pmol/L	*0.50*	
36 months	Vitamin B_{12}	28	11	0	350 ± 27.22 pmol/L	*0.09*	
Precolectomy	Schl-with-IF	16	38	12	17 ± 2.48 %		12–30% with IF
	Schl-without-IF	17	35	12	16 ± 2.41 %		11–28% without IF
12 months	Schl-with-IF	67	30	6	16 ± 1.09 %	*0.87*	
	Schl-without-IF	67	31	6	15 ± 0.99 %	*0.42*	
36 months	Schl-with-IF	35	37	0	15 ± 1.22 %	*0.23*	
	Schl-without-IF	36	36	0	15 ± 1.23 %	*0.13*	
Precolectomy	Folate	42	12	0	14.99 ± 1.83 nmol/L		>4nmol/L
Ileostomy	Folate	43	0	0	16.16 ± 1.71 nmol/L	*0.01*	
Loop ileostomy	Folate	61	0	0	16.78 ± 1.76 nmol/L	*0.01*	
6 months	Folate	66	0	0	16.20 ± 1.13 nmol/L	*0.01*	
12 months	Folate	56	0	0	16.10 ± 1.40 nmol/L	*0.002*	
18 months	Folate	51	0	0	16.90 ± 1.67 nmol/L	*0.001*	
24 months	Folate	44	0	0	16.51 ± 1.77 nmol/L	*0.005*	
36 months	Folate	25	0	0	19.22 ± 2.44 nmol/L	*0.001*	

Precolectomy, levels the night prior to total colectomy and ileostomy; Ileostomy, levels night prior to pouch construction; Loop ileostomy, levels prior to closure of diverting loop ileostomy; months, levels of functional pouch after diverting loop ileostomy closure; IF, intrinsic factor (vitamin B_{12} intrinsic factor).

Adapted and published (2001) with permission from the Karolinska Institue database.[36]

TABLE 3

The differing definition of anemia in patients' status postrestorative proctocolectomy (RPC) in different countries

Author	Location	Definition of anemia	n	Prevalence in RPC population (%)
Oikonomou *et al.*, 2007[33]	USA	Hemoglobin: < 13.5 g/dL (men), < 12 g/dL (Women)	389	17
M'Koma *et al.*, 199 4 [29], [88]	Sweden	Hemoglobin: < 130.0 g/L (men), < 115.0 g/L (Women)	75	15
		Iron: < 9 μmol/L (men) (< 5 μmol/L (Women)	68	15
		Vitamin B_{12}: < 140 pmol/L	69	7
		Folate: < 4 nmol/L	66	0
		Transferrin: < 2.1 g/L	16	0
		Schilling test: without intrinsic factor (IF), < 11%	67	30
		Schilling test: with intrinsic factor (IF), < 12%	67	31
M'Koma *et al.*, 2006[7]	Sweden & USA	Iron: < 9 μmol/L (men) (< 5 μmol/L (Women)		10.4
Coull *et al.*, 2007[32]	Ireland	Vitamin B_{12}: < 387 pg/mL	171	22.2
		Schilling test: < 11%		0
Nicholls *et al.*, 1981[6]	UK	Iron: < 35 μg/L	18	29
		Vitamin B_{12}:< 370 nmol/L	14	7
		Folate: < 4 nmol/L	14	14.5
		Schilling test: < 11%	14	29
		Transferrin: < 2.1 g/L	14	21
Bayat *et al.* 1994,[44]	Denmark	Schilling test: < 11%		3
Hylander *et al.*, 1991[42]		Schilling test: < 11%	17	30
Tiainen *et al.*, 2000[31]	Finland	Iron: < 9 μmol/L (men), < 6 μmol/L (women)	64	10.4
		Hemoglobin: < 130 g/L (men), < 120 g/L (women)	64	20.8
		Vitamin B_{12}: < 170 pmol/L	64	4.1
		Folate: < 320 nmol/L	64	0
Kuisma *et al.*, 2001[38]		Hemoglobin: < 135 g/L (men), < 125 g/L (women)	34	29.4
		Vitamin B_{12}: < 170 pmol/L)	34	21
		Schilling test: < 11%	34	20
		Folate: < 4 nmol/L	34	0
Pastrana *et al.*, 2007[37]	Puerto Rico	Hemoglobin: < 14 gm/dL (men), < 12 gm/dL (women)	18	
		Iron: < 9 μmol/L	18	55.5
Athanasiadis, 1983[40]	German	Folate: < 4 nmol/L	7	0
		Schilling test: < 11%	7	28.5
		Iron: < 9 μmol/L	7	0
		Transferrin: < 2.1 g/L	7	0
Piron *et al.*, 1991[43]	Italy	Folate: < 320 nmol/L	36	0
Fiorentini *et al.*, 1987[41]		Folate: < 320 nmol/L	8	0
		Vitamin B_{12}: < 370 nmol/L	8	0
		Schilling test: < 11%	8	12.5

Author	Location	Definition of anemia	n	Prevalence in RPC population (%)
		Hemoglobin: < 13.8 gm/dl (men), <12.1 gm/dl	8	0
		Iron: < 9 μmol/L	8	0
		Transferrin: < 2.1 g/L	8	0
		Schilling test: < 11%	34	20
		Folate: < 4 nmol/L	34	0
Tulchinsky *et al.*, 2007[39]		Iron: < 9 μmol/L (men), < 6 μmol/L (women)		22

TABLE 4

Economic burden of inflammatory bowel disease patients with anemia

Average hospitalization and average direct cost by severity			
Disease severity level	Number of patients	Number of hospitalization/year	Direct cost $
Total patients	7,200		
Mild	89.1 percent	0.29	10,687
Moderate/ severe	10.9 percent	1.50	37,925
Adjusted and unadjusted direct/indirect costs per patient			
Unadjusted costs			
Anemic population $	Nonanemic population $	Difference in unadjusted cost $	Difference in adjusted cost $
Direct costs			
28,014	11,187	16,827	7,406
Indirect costs			
2,808	3,017	–209	–145
Budget impact model for a hypothetical population of one million members of similar population			
Anemia associated direct costs $	Anemia associated indirect costs $	Total anemia associated costs $	
3,064,528	–44,942	3,064,528	

The data was published in 2005 by the Institute for Advanced Studies in Aging and Geriatric Medicine, Washington, DC and Cerner Health Insights, Beverly Hills, CA.[123]