Patients With Late-Adult-Onset Ulcerative Colitis Have Better Outcomes Than Those With Early Onset Disease

CHRISTINA Y. HA,*,‡ RODNEY D. NEWBERRY,* CHRISTIAN D. STONE,* and MATTHEW A. CIORBA*

*Division of Gastroenterology, Washington University in St. Louis School of Medicine, St. Louis, Missouri; and ‡Division of Gastroenterology, Mount Sinai School of Medicine, New York, New York

BACKGROUND & AIMS: The influence of age on the presentation, clinical course, and therapeutic response of patients with adult-onset ulcerative colitis (UC) is understudied. Given potential age-related differences in risk factors and immune function, we sought to determine if disease behavior or clinical outcomes differed between patients diagnosed with UC in later versus earlier stages of adulthood. **METHODS:** We performed a retrospective cohort study of 295 patients with UC seen at a tertiary care center from 2001 to 2008. Adult subjects newly diagnosed with UC between the ages of 18 and 30 years were defined as early onset, those newly diagnosed at age 50 or older were defined as late onset. The 2 groups were analyzed for differences in medication use and clinical end points, including disease extent, severity at the time of diagnosis, and steroid-free clinical remission at 1 year after disease onset. **RESULTS:** Disease extent and symptom severity were similar between groups at the time of diagnosis. One year after diagnosis, more patients in the late-onset group achieved steroid-free clinical remission (64% vs 49%; $P = .01$). Among those who required systemic steroid therapy, more late-onset patients achieved steroid-free remission by 1 year (50% vs 32%; $P = .01$). Former smoking status was a more common risk factor in the late-onset cohort ($P < .001$), whereas more early onset patients had a positive family history ($P = .008$). **CONCLUSIONS: Patients with early and late-adult-onset UC have similar initial clinical presentations, but differ in disease risk factors. Late-onset patients have better responses to therapy 1 year after diagnosis.**

Keywords: Ulcerative Colitis; Late-Onset; Age; Therapy; Disease Outcomes.

View this article's video abstract at www.cghjournal.org.

Epidemiologic studies of ulcerative colitis (UC) reveal a bimodal distribution of disease onset with an initial peak in the third decade and a smaller second peak between the ages of 50 and 80. An estimated 12% of all patients diagnosed with UC present during the latter period,[1] although late-onset UC has been defined inconsistently as onset of disease anytime between the ages of 40 and 70.[2–5] With the aging of the population, the incidence of late-onset UC is expected to increase; therefore, an appreciation of the disease features unique to this cohort is essential for optimizing medical management.

The clinical course and therapeutic response in late-onset UC are not well defined because most studies addressing this population predate contemporary treatment paradigms and rarely provide comprehensive details of medication use and outcomes. Reports from the 1970s and 1980s suggested that older individuals tended to have UC limited to the rectum or left colon yet with a more aggressive clinical course, more frequent hospitalizations, and an earlier need for steroids compared with younger patients.[2,3,5–8] Furthermore, mortality was reported to be higher within the first year of diagnosis in these older patients, often attributed to higher rates of fulminant colitis, toxic megacolon, emergency surgery, and postsurgical complications.[3–5,9–13] In contrast, more recent studies have found no differences in clinical behavior and medical responsiveness between older and younger patients presenting with an initial UC flare.[14–17] Some studies have even suggested that older-age colitis may have a more benign clinical course[18–20] and that long-term prognosis is similar to the general UC population.[11,21] These contradictory results may relate to advances in management of UC in recent years, particularly with the increased use of immunomodulators and availability of biologics.

Other age-related factors also may influence the presentation and course of disease differentially in late-onset UC. Other diseases more prevalent in an older population such as diverticulitis, infections, microscopic colitis, ischemia, or neoplasia may present with similar symptoms as colitis, making the initial differential diagnosis more broad.[21] As comorbidities, some of these diseases also may impact subsequent clinical UC management. The behavior of UC also may be affected by the relative immune senescence of aging, an age-related decline and dysfunction in immunity, which is characterized by a less-robust peripheral immune system response and alterations in mucosal barrier function.[22,23] With increasing age, infections of mucosal surfaces become more common because of an age-related decline in immunity. Generation of cell-mediated immune responses to new antigens also is impaired because of a less-robust peripheral immune system.[24,25] The immune dysregulation seen with aging also may lead to a differential response to therapy or contribute to the development of autoimmunity and malignancies.[26,27]

In light of these senescence-associated changes in the immune system and potential age-related differences in disease risk factors and/or response to current medical therapeutics, we sought to determine if disease behavior or clinical outcomes differed between patients diagnosed with UC in later versus earlier adulthood. For this comparison we used a large contemporary cohort of UC patients and examined disease character-

Abbreviations used in this paper: IBD, inflammatory bowel disease; UC, ulcerative colitis.

© 2010 by the AGA Institute
1542-3565/$36.00
doi:10.1016/j.cgh.2010.03.022

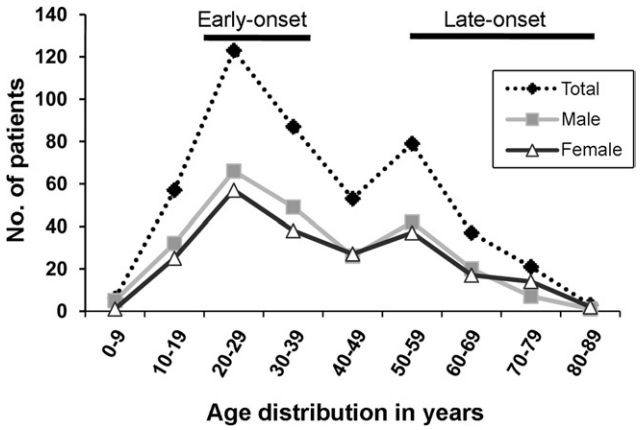

Figure 1. Age at diagnosis of UC study population.

istics at the time of diagnosis, medical therapeutic interventions, and 1-year clinical outcomes.

Methods

Patients with an established diagnosis of UC were identified using a clinical database maintained in the Inflammatory Bowel Disease Clinics at Washington University in St. Louis School of Medicine over a 7-year period from 2001 to 2008. The date of initial UC diagnosis was confirmed by review of initial diagnostic endoscopic data, pathology reports, and radiographic studies. If the diagnosis was not made initially at Washington University in St. Louis School of Medicine, outside hospital records were accessed for confirmation. Additional data sources reviewed included outpatient clinical records, inpatient history and physical examination, hospital discharge summaries, and surgical reports when applicable. Complete medical records for at least 1 year after initial diagnosis was required for inclusion in the study. Patients with indeterminate colitis, Crohn's disease, segmental colitis associated with diverticulosis, ischemic colitis, and primary neoplasia, or patients lost to follow-up evaluation were excluded from the study. Demographic information included sex; smoking history, categorized as current, former, or nonsmoker; family history of inflammatory bowel disease (IBD), defined as having a first- or second-degree relative with a history of IBD; and age of UC diagnosis. All IBD-related medication use, hospitalizations for symptomatic flares of colitis, emergent and elective colectomy, and mortality during the first year of disease were documented.

Disease extent and symptom severity at the time of diagnosis were categorized using the Montreal classification with symptom severity based on the modified Truelove and Witts Severity Index (Supplementary Table 1).[28–30] Clinical remission was defined as an absence of corticosteroids and complete relief of colitis symptoms based on the physician's global assessment and patient report. Age at the date of initial diagnosis was used to categorize patients into early onset and late-onset UC. Patients diagnosed between the ages of 18 and 30 were defined as *early-onset*, whereas those diagnosed at age 50 or older were designated as *late-onset*. The primary clinical end point for comparison between these cohorts was steroid-free clinical remission 1 year after disease onset. Secondary clinical end points included symptom severity at 1 year of disease and medication use during the first year of disease. Medication use was included if prescribed at least once during the first year. Immunomodulator and infliximab therapy were included only when use was documented consistently including blood count monitoring (immunomodulator) or induction doses given (infliximab). Additional clinical comparisons included disease extent and severity at time of diagnosis, hospitalizations, rates of surgery, and 1-year mortality. Unless otherwise specified, we included all UC patients captured during the study periods and excluded from analysis those with incomplete data.

Descriptive statistics are reported as percentages, means, and standard errors of the mean. Categoric data were compared between cohorts using the 2-sided Fisher exact test or the Pearson chi-square test as appropriate. P values of .05 or less were considered significant. The Human Research Protection Office (Institutional Review Board) at the Washington University in St. Louis School of Medicine approved this study.

Results

Patient Demographics

A total of 467 UC patients were identified during the 7-year study period. The age distribution at diagnosis showed a bimodal distribution with the 2 peaks corresponding to the study definitions of early-onset and late-onset UC (Figure 1). Of all patients, 155 (33.2%) fulfilled study criteria for inclusion in the early-onset UC cohort and 140 (30.0%) fulfilled study criteria for inclusion in the late-onset UC cohort. No statistically significant differences in sex or race were present between the early-onset and late-onset groups (Table 1). Patients with early onset UC were more likely to be nonsmokers and have a family history of IBD compared with late-onset patients, whereas more patients with late-onset UC were former smokers. No statistically significant differences were identified in disease extent, symptom severity at diagnosis, remission rates, or medication use between the different smoking categories (former, current, or nonsmokers).

Clinical Comparisons and Primary Outcome

Disease presentation and symptom severity at the time of diagnosis were similar between the early onset and late-onset UC groups (Table 2). There were no gender differences in either cohort. Almost two thirds of patients in the late-onset group achieved steroid-free clinical remission at 1 year compared with half of the early onset patients (P = .0096; Table 3). When

Table 1. Demographics and Patient Characteristics

	Early onset	Late-onset	*P* value
Number of patients	155	140	
Sex, M:F	85:70	70:70	
Mean age, *y*	23.8 ± 0.2	60.2 ± 0.7	
Range, *y*	18–30	50–87	
Ethnicity			
Caucasian	133 (85.8%)	126 (90.0%)	.27
African American	18 (11.6%)	12 (8.6%)	.39
Other	4 (2.6%)	2 (1.4%)	.48
Smoking history			
Current	12 (7.7%)	4 (2.9%)	.06
Never	122 (78.7%)	63 (45.3%)	<.001
Former	21 (13.5%)	72 (51.8%)	<.001
Family history of IBD	33 (21.3%)	14 (10.7%)	.008

Table 2. Disease Behavior at Time of Diagnosis

	Early onset N (%)	Late-onset N (%)	*P* value
Disease extent			
Proctitis	21 (13.6)	11 (8.0)	.12
Left-sided	68 (44.2)	69 (50.3)	.35
Extensive	65 (42.2)	57 (41.6)	.83
Symptom severity			
Mild	34 (22.5)	25 (18.0)	.38
Moderate	98 (64.9)	99 (71.2)	.17
Severe	19 (12.6)	15 (10.5)	.68

NOTE. Disease extent and symptom severity scores based on Montreal Classification (Supplementary Table 1).

stratified by sex, late-onset women were more likely than early-onset women to be in clinical remission at 1 year (74.3% vs 55.7%, respectively; $P = .03$). Remission rates for men trended similarly (57.1% vs 43.5%, respectively; $P = .10$). At 1 year after diagnosis, the trend of more early onset UC patients either having had a colectomy or persistence of severe symptoms (7.8% early vs 3.5% late-onset) was nonsignificant ($P = 0.14$). There were a similar number of UC-related hospitalizations among early onset (n = 57) and late-onset patients (n = 66) during the first year of disease ($P = .09$); this difference became significant only when a later-onset cohort (those diagnosed at age ≥60 y) was considered ($P = .03$). No cases of toxic megacolon or fatalities occurred in either group.

Medication Use During First Year of Disease

Overall, the types of medications used during the first year of disease were similar between the 2 groups (Table 4). However, although common in both groups, more late-onset patients received oral mesalamine therapy. Mesalamines as monotherapy were used to achieve and maintain remission in a similar number of early (42 of 153) and late-onset (41 of 140) patients. An additional 31 early onset and 29 late-onset patients maintained remission at 1 year on mesalamines after a single course of systemic or rectal steroids. These rates were statistically similar.

The majority of early onset (97 of 153; 63.4%) and late-onset (95 of 140; 67.9%) patients required an initial course of oral or intravenous steroid therapy during their first year of disease. However, late-onset patients were more likely to be tapered off steroids successfully and maintain steroid-free clinical remission ($P = .02$) than the early onset patients at 1 year after diagnosis (Table 5).

Immunomodulator (azathioprine and 6-mercaptopurine) and infliximab therapy was used in a similar number of patients in each group. However, of those who used immunomodulators, more late-onset (18 of 41; 43.9%) than early onset patients (7 of 40; 17.5%) maintained clinical remission at 1 year ($P = .016$). Clinical remission rates of those treated with infliximab during the first year were not statistically different between late (3 of 8; 37.5%) and early onset (1 of 7; 14.3%) UC patients.

Table 3. Symptom Severity at 1 Year of Disease

	Early onset N (%) of 153	Late-onset N (%) of 140	*P* value
Clinical remission	75 (49.0)	90 (64.3)	<.01
Mild	18 (11.8)	8 (5.7)	.10
Moderate	48 (31.3)	37 (26.4)	.37
Severe	8 (5.2)	3 (2.1)	.22
Colectomy	4 (2.6)	2 (1.4)	.69

Table 4. Medication Use During First Year of Disease for all Patients

	Early onset N (%)	Late-onset N (%)	*P* value
Mesalamine compounds			
Oral	137 (88.4)	135 (96.4)	.01
Rectal	53 (34.2)	56 (40.0)	.30
Steroids			
Oral	98 (63.2)	94 (67.8)	.48
Rectal	12 (7.7)	19 (13.6)	.10
Intravenous	21 (13.5)	21 (15.0)	.72
Immunomodulators	40 (25.8)	41 (29.3)	.50
Infliximab	7 (4.5)	8 (5.7)	.64

Discussion

In this study, a retrospective cohort analysis was used to compare early versus late-adult-onset UC patients including assessment of disease risk factors, extent, severity, treatment, and outcomes at 1 year. This was a large, US-based study that provided comprehensive comparison using modern patient cohorts inclusive of current treatment paradigms. No significant differences were found between cohorts in terms of disease extent or severity at time of initial diagnosis. However, 1 year after diagnosis, the late-onset cohort showed a better disease profile, with more patients achieving and maintaining steroid-free clinical remission. Even among those requiring systemic steroid therapy, more late-onset patients were in remission at 1 year. Prominent risk factors for UC also differed between age groups. Although family history of IBD was more prevalent in the early onset cohort, former smoking status was significantly more common in the late-onset cohort.

Our study differs from previously published studies in several ways. A validated UC classification system (Montreal) was used for disease extent and severity at diagnosis and disease severity at 1 year.[28] The population was US-based and the cohort size was larger[14,31] and more current[18] than published studies providing similar components of comparison. Earlier studies had reported that older patients were more likely to present with limited disease extent but more severe symptoms at the time of diagnosis.[2,3] In addition, some of their results also suggested that late-onset UC was associated with earlier surgi-

Table 5. Symptom Severity 1 Year After Diagnosis in Patients Requiring Systemic Steroids

	Early onset N (%) of 97	Late-onset N (%) of 95	*P* value
Clinical remission	31 (32.0)	47 (49.5)	.02
Mild	12 (12.4)	6 (6.3)	.22
Moderate	42 (43.3)	37 (38.9)	1.00
Severe	8 (8.2)	3 (3.2)	.21
Colectomy	4 (4.1)	2 (2.1)	.68

cal intervention and higher associated mortality.[3,4,8,9,12] In contrast, our study found more than 90% of late-onset patients presented with left-sided or extensive disease and only 10.5% had symptoms categorized as severe. Furthermore, the overall 1-year outcome was no worse in the late-onset patients, with no deaths or emergent surgeries for fulminant colitis in either group, and no differences in the overall colectomy rate during the first year. The presence of severe symptoms or colectomy was more common numerically, although not significantly, at 1 year in the early onset cohort. Although colitis-related hospitalizations were more frequent in the late-onset group, the difference compared with the early onset group was significant only in the cohort diagnosed at an age older than 60 years, a finding reflective of a recent report examining patients older than 65 years.[32] Our findings are more consistent with studies published in the past decade that have included data for late-onset UC patients.[14,15,17,19,20] Contemporary data thus indicate that disease severity, extent, and clinical course over the first year are at least no worse in patients newly diagnosed with UC at an age older than 50 years.

There has been an expansion of therapies available for UC in the decades since the first publications describing late-onset UC.[33] In the United States, newer mesalamine compounds largely have supplanted sulfasalazine as first-line treatment in mild to moderate UC. Moreover, the availability of infliximab and the increased use of weight-based immunomodulator therapy have enhanced the ability to induce and maintain long-term response in UC.[34,35] However, there has been a paucity of literature investigating clinical response and remission when used in an older patient population. Earlier studies reporting medication use in late-onset UC patients reported only on steroids ± sulfasalazine/mesalamine.[18,20] In this study, medication use during the first year was similar between early onset and late-onset UC cohorts with the exception of higher mesalamine use among the late-onset cohort. However, similar numbers of patients in both groups were maintained in clinical remission with mesalamine monotherapy at 1 year. The increased prescribing of mesalamines for the older patient population may be owing to the favorable adverse effect profile, especially when considering a group of patients who are more likely to have comorbid conditions and polypharmacy.

Published studies reporting on the efficacy and safety of immunomodulators in IBD have included older patients,[36,37] although a study specifically examining clinical outcomes with immunomodulators or biologics for this group does not exist. In our study, nearly 30% of each cohort had received infliximab or immunomodulator therapy. Although the number of patients who received immunomodulators was similar in both groups (41 late vs 40 early), a greater percentage of late-onset patients achieved steroid-free clinical remission after 1 year with immunomodulators (43.9% late vs 17.5% early; $P = .016$). A study designed to address this difference as a primary end point would be required to confirm this intriguing finding and authenticate the safety of immunomodulator use in this older group. However, we believe the findings from this study provide some insight into overall use and therapeutic response rates of late-onset UC patients following current treatment paradigms.

A population-based study of the corticosteroid response in UC patients found that approximately one third of UC patients required steroids during their first year of disease with 49% achieving complete or partial remission at 1 year.[38] Notable characteristics of this study compared with our study were a smaller number of patients but in a population-based study, 1-year outcomes that included both complete and partial remission, and fewer available effective maintenance medications during their study period (1970–1993). In the current study, more patients in both groups received steroids during their first year of disease. However, more than half of the late-onset group were in complete steroid-free remission compared with only a third of the younger cohort ($P = .019$), with a trend toward more early onset patients experiencing clinically severe disease activity or colectomy at 1 year. Possible explanations for the superior outcome in late-onset patients include earlier diagnosis, better adherence to therapy, and perhaps a more effective response to medications afforded by age-related differences in the immune system.[39,40]

Some investigators have suggested that late-onset UC may represent a different disease process than early onset UC.[21] In support of this notion, we found that a family history of IBD was more common in the early versus late-onset cohort ($P = .008$), suggesting that genetic factors may predominate with regard to development of early onset UC. As additional genetic markers are identified,[41] examination of polymorphism presence by age at diagnosis may confirm this finding, providing novel insight into disease pathogenesis. In contrast, late-onset UC may manifest as a result of an accumulation of environmental exposures over time, in addition to the effects of age-related changes in the immune system and intestinal barrier function. In this study, we found tobacco exposure to be an important risk factor for the development of UC in the late-adult-onset but not in the early adult-onset UC ($P < .001$), confirming findings reported in earlier studies.[42,43]

Aging is associated with relative systemic immunodeficiency; however, little research has focused on immune system changes that accompany aging.[16] As we age, the production of new lymphocytes decreases owing to thymic atrophy. In addition, there are decreased CD4- and CD8-mediated responses, incomplete T-cell differentiation, and overall decreased cell-mediated immunity in the aging immune system.[44–46] The combination of age-related immune compromise and a higher susceptibility to infections may predispose older patients to dysregulation of the T-cell response, leading to UC. However, this relative state of immunodeficiency in the older population may attenuate the immune response that would typify unremitting disease flares, and perhaps facilitate improved response to medical therapy resulting in an improved disease course.

There were certain limitations to this study. This was a retrospective cohort study analyzing patients who were seen at a large tertiary-care center. Although referral centers tend to see sicker patients, our group of gastrointestinal specialists serve as the primary referral for many area primary care physicians and both of the study cohorts compared here were drawn from the same institutional database. Variability among the treating physicians at the study site also may have affected patient outcomes at 1 year; however, a majority of the patients in this study were under the care of only 2 IBD specialists. The criteria to determine disease severity and extent rely heavily on the accuracy of the medical record and the description of the colonoscopic findings at the time of diagnosis. However, the classification systems used in this study have been validated in published clinical trials, retrospective cohort studies, and population-based studies. To maximize the accuracy of our data, patient

demographics, endoscopic findings, and pathology results were confirmed across multiple clinical data systems and by direct data review whenever possible. Finally, the study was limited by the lack of endoscopic criteria to corroborate clinical remission at 1 year. Strengths of our study, however, included the use of a large, well-characterized UC population, specifically examining the clinical outcomes of late-onset UC and directly comparing these patients with a defined early onset population.

The number of patients diagnosed with late-onset UC likely will continue to increase with the aging of the population. In our study, 30% of adult-onset UC patients seen in a 7-year period were diagnosed at age 50 or older. Despite comparable disease characteristics at initial diagnosis and similar medical therapy, patients diagnosed with UC after age 50 showed better outcomes and improved steroid-free remission rates at 1 year after diagnosis. Treatment of the older UC patient often is challenged by concomitant medication use and comorbid conditions that may affect gastroenterologists' choice of initial induction and maintenance therapies. Given that older patients are at increased risk for steroid-related complications, this work underscores the importance of early initiation of maintenance therapy with mesalamines and consideration of immunomodulator therapy. Additional research focusing on the therapeutic response to these medications in the late-onset UC population is needed to improve our understanding of management of these complex patients. Consideration of the age of disease onset also may be of value in the design and/or analysis of future clinical trials. Finally, further investigation into the environmental and genetic factors that differentiate late-onset versus early onset UC may explain the underlying causes for the observed differences between these 2 populations.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at doi:10.1016/j.cgh.2010.03.022.

References

1. Loftus CG, Loftus EV, Harmsen WS, et al. Update on the incidence and prevalence of Crohn's disease and ulcerative colitis in Olmsted County, Minnesota, 1940-2000. Inflamm Bowel Dis 2007;13:254–261.
2. Zimmerman J, Gavish D, Rachmilewitz D. Early and late onset ulcerative colitis: distinct clinical features. J Clin Gastroenterol 1985;7:492–498.
3. Carr N, Schofield PF. Inflammatory bowel disease in the older patient. Br J Surg 1982;69:223–225.
4. Brandt LJ, Boley SJ, Mitsudo S. Clinical characteristics and natural history of colitis in the elderly. Am J Gastroenterol 1982;77: 382–386.
5. Jones HW, Hoare AM. Does ulcerative colitis behave differently in the elderly? Age Ageing 1988;17:410–414.
6. Gupta S, Saverymuttu SH, Hodgson HJF. Is the pattern of inflammatory bowel disease different in the elderly? Age Ageing 1985; 14:366–370.
7. Myren J, Bouchier IA, Watkinson G, et al. The OMGE multinational inflammatory bowel disease survey 1976-1986. A further report on 3175 cases. Scand J Gastroenterol 1988;144:11–19.
8. Stonnington CM, Phillips SF, Melton LJ, et al. Chronic ulcerative colitis: incidence and prevalence in a community. Gut 1987; 1987:4.
9. Watts JM, De Dombal FT, Watkinson G, et al. Early course of ulcerative colitis. Gut 1966;7:16–31.
10. Sinclair TS, Brunt PW, Mowat NA. Nonspecific proctocolitis in northeastern Scotland: a community study. Gastroenterology 1983;85:1–11.
11. Winther KV, Jess T, Langholz E, et al. Survival and cause-specific mortality in ulcerative colitis: follow-up of a population-based cohort in Copenhagen County. Gastroenterology 2003;125:1576–1582.
12. Toghill PJ, Benton P. Ulcerative colitis in elderly patients. Gerontol Clin 1973;15:65–73.
13. Edwards FC, Truelove SC. The course and prognosis of ulcerative colitis. Gut 1963;4:299–315.
14. Triantafillidis JK, Emmanouilidis A, Pomonis E, et al. Ulcerative colitis in the elderly: clinical patterns and outcome in 51 Greek patients. J Gastroenterol 2001;36:312–316.
15. Piront P, Louis E, Latour P, et al. Epidemiology of inflammatory bowel diseases in the elderly in the province of Liege. Gastroenterol Clin Biol 2001;25:157–161.
16. Robertson DJ, Grimm IS. Inflammatory bowel disease in the elderly. Gastrointest Clin North Am 2001;30:409–426.
17. Tremaine WJ, Timmons LJ, Loftus EV, et al. Age at onset of inflammatory bowel disease and the risk of surgery for nonneoplastic bowel disease. Aliment Pharmacol Ther 2007;25: 1435–1441.
18. Moum B, Ekbom A, Vatn MH, et al. Clinical course during the 1st year after diagnosis in ulcerative colitis and Crohn's disease. Scand J Gastroenterol 1997;32:1005–1012.
19. Hadithi M, Cazemier M, Gerrit AM, et al. Retrospective analysis of old-age colitis in the Dutch inflammatory bowel disease population. World J Gastroenterol 2008;14:3183–3187.
20. Riegler G, Tartaglione MT, Carratu R, et al. Gruppo Italiano Studio Colon-Retto (GISC). Age-related clinical severity at diagnosis in 1705 patients with ulcerative colitis. Dig Dis Sci 2000;45:462–465.
21. Grimm IS, Friedman LS. Inflammatory bowel disease in the elderly. Gastroenterol Clin North Am 1990;19:361–389.
22. Castle SC. Clinical relevance of age-related immune dysfunction. Clin Infect Dis 2000;31:578–585.
23. Pawelec G. Immunosenescence: impact in the young as well as the old? Mech Ageing Dev 1999;108:1–7.
24. Castle SC. Clinical relevance of age-related immune dysfunction. Clin Infect Dis 2000;31:578–585.
25. Hakim FT, Gress RE. Immunosenescence: deficits in adaptive immunity in the elderly. Tissue Antigens 2007;70:179–189.
26. Johnson SA, Cambier JC. Ageing, autoimmunity and arthritis: senescence of the B cell compartment—implications for humoral immunity. Arthritis Res Ther 2004;6:131–139.
27. Zhang HG, Grizzle WE. Aging, immunity, and tumor susceptibility. Immunol Allergy Clin North Am 2003;23:83–102, vi.
28. Silverberg MS, Satsangi J, Ahmad T, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. Can J Gastroenterol 2005; 19:9A–13A.
29. Lichtiger S, Present DH. Preliminary report: cyclosporin in treatment of severe active ulcerative colitis. Lancet 1990;336:16–19.
30. Truelove SC, Witts LT. Cortisone in ulcerative colitis: final report on a therapeutic trial. Br Med J 1955;2:1041–1048.
31. Jang ES, Lee DH, Kim J, et al. Age as a clinical predictor of relapse after induction therapy in ulcerative colitis. Hepatogastroenterology 2009;56:1304–1309.
32. Ananthakrishnan AN, McGinley EL, Binion DG. Inflammatory bowel disease in the elderly is associated with worse outcomes: a national study of hospitalizations. Inflamm Bowel Dis 2009;15: 182–189.
33. Ng SC, Kamm MA. Therapeutic strategies for the management of ulcerative colitis. Inflamm Bowel Dis 2009;15:935–950.

34. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med 2005;353:2462–2476.
35. Gisbert JP, Nino P, Cara C, et al. Comparative effectiveness of azathioprine in Crohn's disease and ulcerative colitis: prospective, long-term, follow-up study of 394 patients. Aliment Pharmacol Ther 2008;28:228–238.
36. Present DH, Meltzer SJ, Krumholz MP, et al. 6-Mercaptopurine in the management of inflammatory bowel disease: short- and long-term toxicity. Ann Intern Med 1989;111:641–649.
37. Bouhnik Y, Lemann M, Mary JY, et al. Long-term follow-up of patients with Crohn's disease treated with azathioprine or 6-mercaptopurine. Lancet 1996;347:215–219.
38. Faubion WA, Loftus EV, Harmsen WS, et al. The natural history of corticosteroid therapy for inflammatory bowel disease: a population-based study. Gastroenterology 2001;121:255–260.
39. Cerveny P, Bortlik M, Kubena A, et al. Nonadherence in inflammatory bowel disease: results of factor analysis. Inflamm Bowel Dis 2007;13:1244–1249.
40. Higgins PD, Rubin DT, Kaulback K, et al. Systematic review: impact of non-adherence to 5-aminosalicylic acid products on the frequency and cost of ulcerative colitis flares. Aliment Pharmacol Ther 2009;29:247–257.
41. Barrett JC, Lee JC, Lees CW, et al. Genome-wide association study of ulcerative colitis identifies three new susceptibility loci, including the HNF4A region. Nat Genet 2009;41:1330–1334.
42. Regueiro M, Kip KE, Cheung O, et al. Cigarette smoking and age at diagnosis of inflammatory bowel disease. Inflamm Bowel Dis 2005;11:42–47.
43. Aldhous MC, Drummond HE, Anderson N, et al. Smoking habit and load influence age at diagnosis and disease extent in ulcerative colitis. Am J Gastroenterol 2007;102:589–597.
44. Dorshkind K, Montecino-Rodriguez E, Signer RAJ. The ageing immune system: is it ever too old to become young again? Nat Rev Immunol 2009;9:57–62.
45. Gruver AL, Hudson LL, Sempowski GD. Immunosenescence of aging. J Pathol 2007;211:144–156.
46. Linton PJ, Dorshkind K. Age-related changes in lymphocyte development and function. Nat Immunol 2004;5:133–139.

Reprint requests

Address requests for reprints to: Matthew A. Ciorba, MD, Division of Gastroenterology, Washington University in St. Louis School of Medicine, 660 South Euclid, Campus Box 8124, St. Louis, Missouri 63110. e-mail: mciorba@dom.wustl.edu; fax: (314) 362-8959.

Conflicts of interest

The authors disclose no conflicts.

Funding

Matthew Ciorba is the recipient of a career development award from the Crohn's and Colitis Foundation of America and NIH grant L30 RR030244-01. Rodney Newberry is supported by the National Institutes of Health (grant 5R21AG028309-02). The Washington University School of Medicine Digestive Diseases Research Core Center provided clinical database management and is supported by NIH grant P30-DK52574.

Supplementary Table 1. Montreal Classification System for UC Disease Extent and Symptom Severity

Extent	Distribution
Ulcerative proctitis	Involvement limited to rectum
Left-sided	Involvement limited distal to splenic flexure
Extensive	Involvement extends proximal to splenic flexure
Severity	**Definition**
Clinical remission	No symptoms of UC
Mild	≤4 stools/d (with or without blood), no systemic toxicity, normal inflammatory markers
Moderate	>4 stools/d with minimal systemic toxicity
Severe	At least 6 bloody stools per day, systemic toxicities including tachycardia, fever, anemia, and increased inflammatory markers

Adapted from Silverberg et al.[28]