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Crohn's disease

Crohn's disease: why the disparity in mortality?

E V Loftus Jr

There has been no significant decrease in mortality in patients with Crohn's disease over the last several decades

It is well accepted that Crohn's disease is associated with a small but real risk of death. Population based reports from Sweden,[1 2] Denmark,[3] and Italy[4] indicate that Crohn's disease patients have a higher mortality rate than expected, although at least one notable exception from the UK demonstrated survival similar to the general population (table 1).[5] A preliminary report from Olmsted County, Minnesota, indicated a mortality rate that was about 20% higher (but not significantly different statistically) than that expected,[6] standing in contrast with the results of a previous report from the same location.[7] The largest study of mortality in Crohn's disease was from a cohort of approximately 6000 patients identified through the General Practice Research Database (GPRD), which contains the computerised medical records of 6% of the British population.[8] The annual mortality rate in Crohn's disease was 1.6% compared with 1.0% in age, sex, and practice matched controls. After adjusting for age, sex, and cigarette smoking, it appeared that the risk of death was 73% higher in Crohn's disease patients than in controls.[8] Although the large cohort size makes this study important, its generalisability is limited by the fact that the cohort was a mixture of incidence and prevalence cases, the average age at entry into the cohort was 42 years (higher than the average age at diagnosis of Crohn's disease of late 20s/early 30s in most studies), and the average follow up was only three years. A recent systematic review of ''hard end points'' in population based cohorts of Crohn's disease concluded that there was no evidence for a significant change in disease outcome over the past 40 years.[9] To summarise, these studies suggest that the mortality rate in Crohn's disease ranges from 30% lower than expected to 70% higher than expected. All of these studies are limited by the fact that most of the patients in these cohorts were not only identified retrospectively, but also diagnosed before the ''modern era'' of medical therapy for Crohn's disease.

The European Collaborative Study Group of Inflammatory Bowel Disease (EC-IBD) prospectively developed a cohort of patients newly diagnosed with Crohn's disease and ulcerative colitis at 20 European and Israeli centres between October 1991 and September 1993. The incidence of Crohn's disease at these centres over this two year period[10] and the clinical course in these patients in the first year after diagnosis[11] have been previously reported. In the present issue of *Gut*, Wolters and colleagues[12] update the follow up of approximately half of the original EC-IBD cohort of Crohn's disease patients (n = 371) to determine absolute, relative, and cause specific mortality ***(see page 510)***. Median age at diagnosis of Crohn's disease was 31 years (range 15–83). Follow up was complete in 92% of the cohort. After an average follow up of approximately 10 years, 37 patients had died (10%). Expected rates of death were calculated using country, age, and sex specific rates from the World Health Organisation (WHO) mortality database. Using actuarial techniques, the 10 year risk of death was 10% versus 7% expected. One would have expected 21 patients to have died based on the WHO mortality rates. The standardised mortality ratio (SMR, which can be thought of as a relative mortality rate) was 1.85, or 85% higher than expected.

The authors examined their cohort for risk factors. For both sexes, SMR was significantly higher than expected.[12] The relative risk of death was numerically higher in the northern European centres (SMR 2.0 (95% confidence interval (CI) 1.3–3.0)) than in southern ones (SMR 1.6 (95% CI 0.8–2.7)) but this difference was not statistically significant. When the SMR analysis was stratified by various aspects of the phenotypic Vienna classification,[13] age ⩾40 years at diagnosis (SMR 1.99 (95% CI, 1.4–2.8)), colonic involvement at diagnosis (SMR 2.1 (95% CI 1.3–3.1)), and inflammatory disease behaviour at diagnosis (SMR 2.2 (95% CI, 1.5–3.2)) all appeared to be associated with increased mortality risk. However, in a multivariate

Table 1 Crohn's disease related mortality from selected population-based cohorts published since 1992

Author (ref)	Location	Cohort type	Study period	No	Median or mean follow up (y)	Overall SMR (95% CI)
Ekbom[1]	Uppsala, Sweden	Incidence (89%) and prevalence (11%)	1965–83	1655	NA	1.6 (1.4–1.9)
Probert[5]	Leicestershire, UK	Incidence	1972–89	610	NA	0.7 (0.5–1.0)
Persson[2]	Stockholm County, Sweden	Incidence	1955–84	1251	NA	1.5 (1.3–1.7)
Jess[3]	Copenhagen County, Denmark	Incidence	1962–87	374	17	1.3 (1.0–1.6)
Card[8]	GPRD, UK	Incidence (31%) and prevalence (69%)	1987–??	5960	3.6	1.7 (1.5–2.0)
Masala[4]	Florence, Italy	Incidence	1978–92	231	15.4	1.5 (1.1–2.1)
Jess[6]	Olmsted County, USA	Incidence	1940–2001	314	13	1.2 (0.9–1.6)
Wolters[12]	EC-IBD, Europe and Israel	Incidence	1991–93	371	10	1.9 (1.3–2.5)

SMR, standardised morbidity ratio (observed/expected); 95% CI, 95% confidence interval; NA, not available; EC-IBD, European Collaborative Study Group of Inflammatory Bowel Disease.

Cox proportional hazards regression analysis, the only independent predictor of mortality was age at diagnosis (hazards ratio per year 1.1 (95% CI 1.08–1.12)).

Cause specific mortality was also examined. Fourteen deaths (38% of all deaths) were thought by the investigators to be definitely or possibly related to Crohn's disease, including eight deaths due to various gastrointestinal causes (for example, postoperative sepsis, toxic megacolon, bowel infarction), two cases of sepsis in patients on corticosteroids, and three deaths due to cardiovascular causes in patients with active Crohn's disease or in the immediate postoperative setting. Among the 23 deaths that were not attributed to Crohn's disease, there were three deaths due to bronchogenic carcinoma, eight due to various cardiovascular conditions such as myocardial infarction or cerebrovascular accident, and three deaths due to pneumonia or chronic obstructive pulmonary disease. These results are somewhat in keeping with other studies that have examined cause specific mortality in Crohn's disease. The percentage of deaths attributed to Crohn's disease ranges from 25% to 40%. Crohn's disease patients are significantly more likely to die from non-malignant gastrointestinal diseases.[1–4 6] In some studies, they were also more likely to die from intestinal cancer[3 6] and bronchogenic carcinoma.[4]

The EC-IBD mortality study[12] has a number of strengths. All cases were from defined geographic regions, newly diagnosed, and prospectively identified. Follow up was complete in greater than 90%. Such studies of population based inception cohorts are the ''purest'' form of natural history and prognosis studies. Secondly, the subgroup analysis, stratified phenotypically by the Vienna classification, is somewhat novel, even though ultimately disease extent and behaviour were not found to be independent predictors of mortality. Increasing age at diagnosis was significantly associated with mortality, but this is often found in mortality studies of any condition.

Several potential weaknesses of this study deserve comment. Firstly, only 10 of the original 20 EC-IBD centres participated (seven refused outright and the other three could not follow up more than 60% of their cohort), leaving only 371 of the original 706 Crohn's patients.[12] It is not known whether mortality among the patients who were not followed is similar to, lower than, or higher than what was observed in this cohort. Did these participating centres have more of an interest in IBD, and thus was the care of patients in these centres somehow different? It is also not clear if similar methods of determining vital status at last follow up were employed—some centres were located in countries with an accessible national death registry while others were not.

While the EC-IBD study provides important information, it raises additional questions. Despite the fact that these patients were diagnosed in the 1990s, an era of more aggressive medical therapy, and despite the fact that follow up in this cohort was only 10 years on average, the authors demonstrated a mortality rate nearly double what had been expected.[12] Comparing this study to others, there has been no significant decrease in mortality (and perhaps an increase?) in Crohn's disease patients over the last several decades. Why is there a disparity in relative mortality across regions, even in recent studies? In other words, why are the mortality rates only 20–30% higher than expected in Olmsted or Copenhagen Counties but 70–90% higher than expected in the GPRD and EC-IBD studies? This disparity is all the more puzzling as 58 members of the EC-IBD cohort were from Copenhagen County, but diagnosed 4–6 years after the latest entry date in the original Copenhagen County study. In the Copenhagen subset of EC-IBD patients, SMR was 2.3 (see table 2 of the Wolters and colleagues study[12]), considerably higher than the 1.3 seen in the earlier Copenhagen cohort.[3] Some differences in SMRs across cohorts can be attributed to differences in expected mortality rates, which are dependent on the overall age and gender makeup of the cohort. Another potential explanation for disparity is variation in disease severity. In the EC-IBD study, patients from northern centres were more likely (31%) than patients from southern centres (17%) to have required azathioprine.[12] Is this a marker for disease severity or is there a causal relationship between azathioprine use and increased mortality? Most of us would suspect the former, but the observational nature of this study does not permit us to answer the question.

The study by Wolters and colleagues reminds us that Crohn's disease is, in fact, still associated with increased mortality at most centres. Crohn's disease is a chronic progressive illness and should be treated as such. While death due to Crohn's disease occurs too infrequently for it to be incorporated as an end point in clinical trials, we should strive to perform studies with novel designs and ''hard end points'' (for example, ''step up versus top down''[14] or SONIC) to determine if earlier or more aggressive medical therapy can alter the natural history of the illness.

Gut 2006;**55**:447–449.
doi: 10.1136/gut.2005.080283

Conflict of interest: declared (the declaration can be viewed on the *Gut* website at http://www.gutjnl.com/supplemental).

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EDITOR'S QUIZ: GI SNAPSHOT

doi: 10.1136/gut.2005.067363

Answer

From question on page 441

Abdominal computed tomography scan demonstrated a voluminous right common iliac aneurysm adjacent to the lumen of the sigmoid. Angiography (fig 3) confirmed this, and laparotomy showed a large aneurysm from the right common iliac artery fistulised in the sigmoid which was embedded in the pelvis. A femoral-femoral bypass grafting procedure for revascularising the right limb was completed, the thrombosed aneurysm removed, and a left colectomy without primary anastomosis was performed. Histological examination of the colectomy specimen confirmed the fistula. The patient was discharged to her local hospital on day 30.

Vascular-enteric fistula is a rare but life threatening disease with a very high mortality. The most frequent is aorto-duodenal fistula in patients with a history of aortic graft surgery. Aorto-colonic fistula accounts for only approximately 5% of all reported cases. Most published cases are secondary fistulas after surgical repair of abdominal aortic aneurysm. Only two cases of primary iliac-enteric fistulas involving the ileum or rectum and arising from common iliac aneurysms have been published. Endoscopic findings included the presence of luminal pulsatile mass, puncture ulceration, visualisation of graft materiel, or pulsatile fresh blood. In our case, colonoscopy was very suggestive because the punctate ulceration was associated with a very pulsate appearance. Angiography may not be diagnostic because of the intermittent nature of the bleed but it can show the aneurysm. In the case of undiagnosed lower gastrointestinal bleeding, vascular-enteric fistula must be considered, especially among old people, whether or not there is a background of previous vascular surgery. Early diagnosis and urgent surgery are necessary to improve the prognosis of this very serious disease, with a mortality rate of approximately 30%.

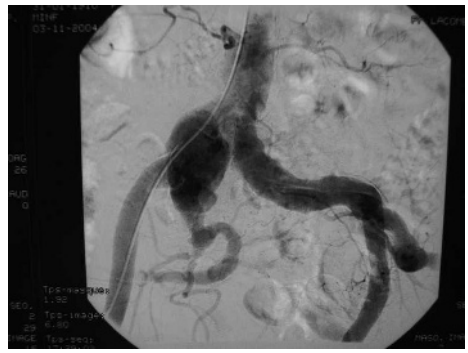

Figure 3 Angiogram showing a large right iliac primary artery aneurysm.