Secular Trends in Hospitalization for IBD: The Ecological Niche

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One of the most common designs in epidemiology research is the ecological study, in which the units of analysis are populations or groups of people, rather than individuals. In addition to their ease and low-cost, these studies can also provide very valuable information when individual-level data are difficult to obtain or when the primary interest is in the ecologic inference, such as in public policy or program legislation.

The article by Dr. Sonnenberg and colleagues in this month's issue adds to a growing body of ecological studies examining the secular trends (trends that are not cyclical or seasonal but exist over a relatively long period of time) of hospitalizations for inflammatory bowel disease (IBD) in this country [1]. Prior studies have demonstrated stable to increasing hospitalization rates for ulcerative colitis (UC) and increasing hospitalization rates for Crohn's disease (CD) in the US [2, 3]. Dr. Sonnenberg's work extends this analysis to the US military veteran's population, increasing the body of data on age- and race-specific results. The authors found rising hospitalization rates until 1989 when rates of hospitalizations decreased overall. However, when examining these trends by race, they found increasing rates of hospitalization in non-whites, most significantly in the oldest (65+) age group, for both UC and CD throughout the study period. Prior studies have shown race-specific differences in utilization of surgery as well as disease manifestations and complications in IBD patients [4–8]. Age-specific changes in hospitalizations were not found in one prior study [2], but were found to peak during earlier years in CD patients in another [3]. Taken together, these ecological studies suggest that inpatient care for IBD may

represent an increasingly large proportion of our healthcare resources.

There are several reasons why one might observe an increase in IBD hospitalizations over time. The simplest is that there are more people being hospitalized, the same number of people are being hospitalized more often, or a combination of the two. Likewise, if there is an increase in the actual number of patients with IBD, the rate of hospitalization per individual could be less, but the rate of hospitalization could appear to be rising solely because the disease is becoming more common. However, ecological studies are prone to certain biases that can result in an artificial appearance of long-term trends. Like all studies, the data used to examine secular trends needs to be accurately measured to avoid misclassification bias, in which errors occur in classifying populations exposure or disease status. In this article by Sonnenberg, the investigators have measured incidence of hospitalization in each year relative to the total population of the United States. The potential problem with this design is that the total USA population is not eligible to be hospitalized in Veteran Affairs hospitals. Thus, observed trends could reflect disproportionate changes in the demographics and size of the population eligible to use the Veteran Affairs resources rather than a true change in the rates of hospitalizations among eligible Veterans. To address this, Sonnenberg et al. also used the population of patients hospitalized in the Veteran Affairs healthcare system for any reason as an alternative denominator for defining hospitalization rates. This comes closer to defining the truly eligible population, but remains subject to bias from secular trends in hospitalization for other conditions. Reassuringly, results using this alternative denominator were relatively similar to the primary results in their study.

Ecological studies may also suffer from confounding by group, where the apparent association between a group and

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an outcome is influenced by a third variable or confounder. Confounding by group in ecological studies occurs when the groups differ on the distribution of one or more individual-level confounders. This becomes an additional problem when conditions defining confounding are different at the individual and ecologic level. These studies can also suffer from effect modification by group when exposures affect upon rate differences varies across groups in the study.

In addition to projecting needs for healthcare resources, ecological studies are often used to generate hypotheses. If, in fact, there is an increasing rate of hospitalization for IBD within the United States, it would be important to ask why this is the case. In the field of IBD, these issues become more complicated because the inherent mechanism of the disease is unclear. It is increasingly clear that there is a genetic susceptibility underlying IBD, specifically in CD where several combinations of genetic factors have been described. Several of these include genes for intracellular receptors for bacterial cell walls, bacterial clearance and bacterial antigen processing [9], tying this genetic susceptibility to an environmental microbial stimuli. A number of theories have been explored to elucidate the proposed dysbiosis. These include exploration of factors modifying microbial exposure such as the hygiene hypothesis and intestinal pathogen infection; and factors modifying host response to microbes such as defects in host immunoregulation and containment of microbiota [10–12]. Other factors such as differences in diet, industrialization, and climate are also currently being investigated [3, 13, 14]. All of these represent potential confounders or effect modifiers that complicate the interpretation of ecological studies if groups differ on their distribution.

Ecological studies can also possess an additional unique problem of cross-level inference or bias, also referred to as ecological fallacy. This occurs as a result of the assumption that individual members of a group have the average characteristics of the group at large. Relevant to this study, only 40% of enrolled veterans use the VA health care system as their sole source of care, with older veterans comprising the majority of this population [15]. Thirty percent of veterans enroll in the VA health care for prescription medication coverage, in part due to outside private insurance coverage [16]. Most importantly, the use of VA health care varies between veterans of different service eras. Ninety-three percent of World War II veterans reported using VA health care, but the majority of these were also using Medicare coverage to access private providers [15]. This is in contrast to Gulf War veterans of whom only 353,000 of 1,120,000 eligible veterans have actually enrolled for health care benefits through the VA health system [17]. This speaks to a greater overall disparity in the use of the VA health system. Younger veterans

and those with higher education levels and larger incomes are less likely to access the VA for their medical care [15, 16]. A larger number of reservists are serving in active duty, and these veterans are often those who leave and return back to their civilian health care after service [16]. Despite being a medical system with minimal financial barriers, disparities by race in the use and adherence to medical care are also known to exist within the VA medical system similarly to other health care systems [18].

So while ecological studies are easily implemented, they can be difficult to appropriately interpret. Hippocrates is credited with saying that it is more important to know what sort of person has a disease than to know what sort of disease a person has. The strength of ecological studies in IBD stems directly from the uncertainty regarding IBD's pathogenesis; their value stems from understanding their meaning within the context of their limitations. Ecological studies can clarify exposures that are not apparent or subject to a high degree of measurement error or short-term biological variation at an individual-level. They can also expose risk factors for disease that genuinely operate at a population level or that operate as effect modifiers within varying subpopulations. Ultimately, these studies can provide valuable insight into the impact of policies, programs, and legislation. In the next several decades, we can anticipate continued rapid changes in medical therapy of IBD, changes in the structure of health care delivery, and changes in the makeup of our population. What affect these changes will have on healthcare resource utilization will be critically important to address. Ecological studies will continue to be used to answer such questions. The importance of these studies lies in understanding their contextual niche and avoiding over extrapolation of their results.

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