1. Is IBD incidence increasing in Asia?

The incidence and prevalence of IBD has been steadily increasing in the Western World over the last 5 decades. This is thought to be related to environmental changes, in large part driven by industrialization and the “Western” lifestyle. Whether the same pattern is occurring in developing countries and particularly in Asia is unclear. Investigators from countries in the Asia Pacific region have performed a prospective, multi-center, presumably population-based study aimed to determine the actual incidence of IBD in this part of the world. The ACCESS study was conducted in 21 centers (all hospital-based) from 9 countries, including China, Australia, Indonesia, Malaysia as well as a number of other smaller countries. Because no national registries and no disease coding exist, case definitions were based on clinical, endoscopic and radiological criteria with specific exclusion of infectious pathogens, including tuberculosis. Over a period of 1 year, investigators were able to identify 419 new cases of IBD in an overall catchment area of 30.5 million people (of the total of more than 4 billion people living in the Asia-Pacific region) for an overall incidence rate of 1.4/100,000 people. Consistent with other studies from developing countries, UC was more frequently diagnosed than CD (55% vs. 40%) and indeterminate colitis (5%). There was more than 50 fold variation in incidence between areas with low incidence (parts of mainland China) and high incidence (Australia). There was also a wide variation in the IBD incidence among different parts of China. More new IBD cases were diagnosed among men in Asia but there was no gender effect among new cases in Australia. Disease location based on the Montreal classification was similar throughout the region but disease behavior was more severe in Asia (33% strictureing-penetrating phenotype vs. 12% in Australia). Less than 20% of patients were treated with immunomodulators in the first year after diagnosis and 0-2% received biologics. The authors note that there was a significant increase in the incidence of IBD in this part of the world where only 20 years ago these disease were virtually unknown. Whether this dramatic epidemiological phenomenon is due to environmental factors vs. improved access and quality of healthcare is unclear.

Comments: This study supports the evidence of an increasing incidence of IBD in the developing world. Considering the large population living in this area (2/3 of the World population) it is likely that IBD will become an important public health problem in the next few decades. The reason for this phenomenon is unclear but environmental factors are likely to play a role. Increased disease awareness, improving healthcare access and gradual shift towards traditional “Westernized” medicine instead of other more popular traditional healing methods also probably contribute to the observed effect while genetic factors are probably less important. This dramatic increase in incidence along with an increased frequency of severe cases with aggressive phenotype clearly point towards a real epidemiological phenomenon. Moreover, the
rates seem to be stable (and higher) in Australia, a country which has adopted the Western lifestyle and economy decades ago. Several limitations need to be pointed out. First, given the lack of universal coding, the reliability of case ascertainment is unclear. Also, despite the authors intent to perform a population-based study, index cases were identified primarily through public hospitals under the assumption that new IBD cases are likely to be referred to such institutions; this, however, introduces the potential for under-reporting as well as selection bias particularly regarding disease severity. Nonetheless, this is a very important study that may shed some light on important risk factors for the pathogenesis of IBD. Also, if these trends continue, countries in the Asian-Pacific region are likely to overtake the Western World in term of IBD burden and healthcare utilization. Both aspects represent gold mines for epidemiologists and outcomes researchers with an interest in these disorders.

Source: Ref.: Ng SC, Tang W, Ching JY et al. Incidence and phenotype of inflammatory bowel disease based on results from the Asia-Pacific Crohn’s and Colitis Epidemiology Study (ACCESS). Gastroenterol. ’13;145:158-165)

2. Normalization of Vitamin D levels associated with lower risk of surgery in Crohn’s Disease.

Aside from its effects on bone mineralization, Vitamin D (VD) has been shown to have potentially important immunomodulator effects in both epidemiologic and bench research studies. Both animal models as well as a small randomized study showed that Vitamin D administration may protect against experimental colitis or decrease the risk of a flare in patients with IBD in remission. In this retrospective study, investigators evaluated the association of plasma VD levels with the risk of surgery or hospitalization among patients with established IBD evaluated at two large referral centers in the US. The case ascertainment in this population was refined from local EMRs using proprietary smart algorithms which have been previously validated. A subset of 3,200 patients with IBD was selected based on at least one VD level data point available in the health record. The VD levels were modeled as normal (> 30 ng/mL), insufficient (20-29 ng/mL) and deficient (<20). Patient demographics were consistent with other referral center populations but not typical for community-based studies. More than 20% of patients had history of anti-TNF use and 16% already had at least one surgery. 60% of patients had either insufficient or deficient VD levels. There was a significant association between plasma VD and the risk of surgery in both Crohn’s disease (adjusted OR 1.8 for the lowest stratum) and UC (OR 2.1) with a more linear dose-response in CD than UC. Moreover, patients with CD who normalized their Vitamin D level (based on random subsequent testing) had a significantly lower risk of surgery (OR 0.56) and a trend towards lower hospitalization rates compared to those who did not normalize their VD status. In addition, patients with improved VD levels had significantly lower CRP at follow-up. These effects were not seen in UC patients. Age and supplemental VD use were both predictors of normalization; interestingly, initial low level measured during winter was also borderline significantly predictive of normalization.
**Comments:** this study supports the possibility of a significant immune modulator effect of Vitamin D in IBD as it has been seen in other immune-mediated conditions such as systemic sclerosis and multiple sclerosis. Whether this is a cause and effect mechanism or a common determinant factor is unknown. This retrospective study cannot rule out the possibility that both vitamin D level as well as reductions in surgery and hospitalizations are the result of improved disease control through specific medical interventions. In fact, the lower CRP seen in patients who normalized their VD level seems to support the latter hypothesis. The reason why the same phenomenon is not as significant in UC as CD is also unclear. UC patients also seem to have a seasonal variation in their disease flare which may also be related to variations in natural production of Vitamin D. Also, less than 1/3 of patients in this IBD database had any VD testing and a substantial number had only one data point available both of which represent significant selection biases. Until the intricacies of the effect of VD on disease activity are sorted out, I think testing for and supplementing Vitamin D in all patients with IBD on a regular basis is a relatively inexpensive and possibly effective treatment strategy and should be widely recommended particularly in Northern regions where residents enjoy less sun exposure and therefore less physiologic production of Vitamin D and its metabolites.


3. Stem cell transplantation for Crohn's disease: is the juice worth the bone marrow squeeze?

Autologous bone marrow transplantation have been previously utilized in selected refractory cases of Crohn’s disease (CD) in tertiary centers with somewhat mixed results. In a case series published previously from the Northwestern University in Chicago, a substantial proportion of patients receiving autologous stem cells with partial bone marrow ablation responded to therapy but the vast majority required re-introduction of immunosuppressives at 5 years (Burt et al. – Blood ’10). There was a high incidence of significant side-effects including death. ASTIC is an international multi-center prospective randomized study aimed to determine the efficacy of immune-ablation (bone marrow suppression) followed by autologous hemopoietic stem cell transplantation (HSCT) in patients with severe CD refractory to highly effective medical therapy including biologics. Patients were randomized to receive either immediate or delayed HSCT, with the delayed treatment subjects being the control group. The bone marrow ablation protocol is similar but milder than the one utilized in myeloproliferative disorders such as leukemia. The 1 year preliminary results were presented at this year’s DDW in Orlando, FL. In 22 patients who received immediate HSCT and survived, the CDAI dropped by more than 160 points in more than half the patients compared to only 50 points in the 13 control group patients (of which 9 dropped out due to worsening symptoms). There was also a marked improvement in the endoscopic disease activity (from a mean score of 13 to 4). About 2/3 of patients receiving SCT were able to discontinue all Crohn’s medications and half were in
remission. One patient in the HSCT group died of sepsis two weeks after transplant and there was an average of 3.3 serious side effects per person (usually infectious) in the remainder of the stem cell recipients. The study plans to conclude enrollment this year and longer follow-up is planned. The authors propose that HSCT may be an option for a select group of patients with disabling disease refractory to other available medical therapy.

Comments: this is the first randomized trial of HSCT in patients with refractory Crohn’s disease. While the early results are promising, the assumption here is that resetting the immune system in a massive way would result in remission and potentially a cure in some patients. The major flaw to this theory is that the trigger for the aberrant immune response in patients with IBD is unknown and therefore may persist despite the transplant, not to mention that the immune ablation may not be complete and, therefore, the emerging T cell populations may still be or quickly become over-reactive. Therefore the disease may recur following this aggressive, one-time therapy. In fact, the majority of patients in previous case series have experienced a relapse when followed up for longer than 1 year and a substantial number required re-introduction of immunosuppressive therapy. In fact, even in the current study there was evidence of early recurrence in a minority of patients. There is also the significant risk of side-effects which is several levels higher than with any other medical therapy and with a death rate of 5% at this early stage. However, this extreme approach may look promising for a select group of patients with severe, disabling disease and no other available medical or surgical options. It would also be nice to identify a sub-group of patients who are good candidates for this therapy early on, before the outset of irreversible and substantial structural damage such as penetrating disease or short-gut syndrome. Some of the patients in this trial had 12 abdominal surgery before they were enrolled. No medical or surgical therapy other than bowel transplantation can be expected to restore anything resembling normal quality of life in such patients. Long-term results of this study are eagerly awaited.