

## **S015 Mucosal Healing and Top Down Therapy- Pediatric Perspectives**

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Recent studies regarding the natural history of Crohn's disease (CD) in both adults and children have shown that a significant number of patients will progress from an inflammatory state (B1 by the Montreal classification ) to a more complicated course of the disease characterized by fibrostenotic or penetrating disease ( B2, B3). Progression from B1 to B2 or B3 results in a high rate of surgical interventions ( 30-50% of patients require surgery within 10 years of disease) as well as hospitalizations and need for recurrent steroid therapy. This has been interpreted as a failure of the step up treatment period long in use in Crohn's disease. Furthermore, recent studies have shown that patients who achieve mucosal healing are less likely to require steroids and surgical interventions over time.

While mucosal healing is associated with a better course of the disease, it is not clear if this is due to mucosal healing or better maintenance strategies that also induce mucosal healing. Exclusive enteral feeding, azathioprine and biologics have been found to induce mucosal healing in a significant proportion of patients , while corticosteroids achieve this in a small proportion of patients. However, steroids are not effective for maintenance of remission to start with, and steroid dependence can be viewed as a failure of an effective maintenance strategy in many patients. The recent SONIC trial found better mucosal healing with infliximab , or a combination of infliximab and azathioprine , in comparison to azathioprine alone ( mucosal healing only ). However, the study enrolled patients with moderate to severe disease, 40% of whom were steroid dependent, who had never received a thiopurine or biologic ( effective maintenance therapy. The patients in the azathioprine arm did not have remission induced, while the infliximab arm patients received infliximab induction + maintenance therapy, so that these were not real life scenarios. A recently published study that evaluated steroid dependent patients with active disease, that had remission induced with steroids and received concomitant azathioprine achieved mucosal healing in 60% at one year, possibly indicating that effective induction of remission accompanied by an effective maintenance therapy may induce mucosal healing. Finally, 5 recent pediatric studies evaluating patients who responded to infliximab induction a high rate of infliximab dependence, if patients did not receive q 8 week maintenance therapy they did not maintain remission. Thus, though biologics induce remission and mucosal healing, this does not prevent early relapse, indicating that mucosal healing is not enough to prevent disease progression, and simply may be a proxy for effective maintenance therapy.

Top down therapy at present is hypothetical, the two studies evaluating top down therapy did not compare thiopurines + steroids to infliximab at disease onset. However, multiple studies in pediatric populations have shown lower relapse rates and a decrease in surgical resections for patients receiving early thiopurine use. Early use of biologics (though not at disease onset) in pediatric populations were associated with better remission rates. Thus, in 2009 , we have no data to support top down therapy, but we have a quite a bit of data that would suggest a third strategy, accelerated step up therapy in pediatric patients. We require randomized controlled studies to evaluate top down and accelerated step up therapy, in order to optimize treatment strategies for the future.

### **References**

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