

Shining a Light on Barrier Function

Matthias Friedrich Dr.rer.biol.hum. (matthias.friedrich@ndm.ox.ac.uk)

Simon Travis DPhil FRCP (simon.travis@kennedy.ox.ac.uk)

Translational Gastroenterology Unit, Nuffield Department of Medicine, Kennedy Institute of Rheumatology, Nuffield Department of Orthopaedics and Biomedical Research Centre, University of Oxford, United Kingdom

(both authors affiliated to all institutions)

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Corresponding author: Professor Simon Travis simon.travis@kennedy.ox.ac.uk /+447917003352

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Shining a Light on Barrier Function

Endpoints in clinical trials and treatment targets in practice are only as good as the outcomes they predict. The outcome that matters most to patients with ulcerative colitis (UC) or Crohn's disease (CD), short of a cure, is the relapse rate. Major adverse outcomes (MAO) such as steroid, biological or immunosuppressant small molecule therapy, let alone hospitalisation or surgery all stem from a relapse. It has become increasingly apparent that the deeper the depth of remission, the lower the risk of relapse, but some definitions of remission are easier to achieve than others (FIGURE). In the early 2000s the concept of deep remission was introduced, meaning symptomatic remission and endoscopic mucosal healing ¹. Now, in the 2020s, the concepts of HEMI (histo-endoscopic mucosal improvement) and HEMR (histo-endoscopic mucosal remission) are gaining traction ²⁻⁵. A meta-analysis of 17 trials in UC showed that the relapse rate after achieving a Mayo Endoscopic Subscore (MES) of 1 was associated with a 29% relapse rate in the following year, but just 14% when the MES was 0 ⁶. However, when there was histologic remission (absence of epithelial or lamina propria neutrophils on mucosal biopsy) as well as MES=0, the 12 month relapse rate was just 5% ⁶. An iceberg analogy has been popular, with symptoms representing the visible berg above the surface and biochemical, endoscopic, histopathologic activity representing the bulk of disease below the surface, with its proclivity to relapse.

Enter ERICA. The Erlangen Remission in IBD trial [PLACEHOLDER REF] studied 181 patients with either UC (n=81) or CD (n=100) in clinical remission, during follow up for a mean (SD) of 25(+/- 11.9) months for UC and 35(+/-6.9) months for CD. These 2-3 years are a material period in a life-long disease. The composite outcome of interest was the occurrence of major adverse outcomes (MAO), including disease flares, IBD-related hospitalization or surgery, and escalation of advanced therapies or steroids. This is a practical endpoint relevant to clinical practice. The MAO predictive value of endoscopy, histopathology and intestinal barrier integrity measured by confocal laser endomicroscopy (CLE) were compared. It is CLE that provides the novelty and interest, useful though it is to have longitudinal studies in UC or CD to assess the predictive pecking order for MAO, assumed to be histopathologic > endoscopic > symptomatic remission. CLE is a technique that allows semi-quantitative scoring of barrier integrity by detecting the leakage of fluorescein into the intestinal lumen, after systemic injection before the procedure (intact barrier = no leakage, also termed barrier healing; functional or structural barrier defect = fluorescein leakage into the intestinal lumen and shedding of epithelial cells, also termed barrier dysfunction). Widely accepted criteria defined endoscopic and histologic remission ⁷.

Of patients with UC in clinical remission (Mayo clinic subscore ≤ 2), 53% were in endoscopic remission (MES ≤ 1); similarly 54% or 52% were in histological remission as defined by the Robarts or Nancy indices, respectively, but on CLE only 26% of patients demonstrated barrier healing. It was barrier healing that was the most sensitive predictive measure for relapse over the next 2-3 years, followed by histologic, endoscopic and symptomatic assessment. Whilst the overall MAO rate over 2 years was 69% for patients with UC, endoscopic remission (MES ≤ 1) or healing (MES=0) decreased MAO rates to 49% or 35%, respectively. For histologic remission defined either by the Nancy or RHI, MAO rates were 50% and 52%. Strikingly, for patients with barrier healing assessed by CLE, the MAO rate was just 19%. Similar relationships for the MAO rate in CD were observed. The overall MAO event rate was 63%, and 57% or 50% for those with endoscopic remission (defined by absence of erosions/ulcerations, or SES-CD ≤ 3 , respectively). The MAO rate was 55% of those in histologic remission (modified Riley score ≤ 5). Again, when there was barrier healing in the colon, the MAO rate was appreciably lower at 30% and if there was barrier healing in the ileum, it was zero (0%), in contrast to 46% if the ileal endoscopic subscore was 0.

Despite unexpected higher MAO rates for histologic remission in UC over endoscopic healing, this is very much in line with the proposed predictive pecking order for MAO, adding CLE as the top predictor (barrier healing > histopathologic > endoscopic > symptomatic remission).

Barrier function matters. Whilst these findings need validation in additional cohorts, they put the spotlight on the importance of transepithelial trafficking and direct contacts between the luminal microbiota and the lamina propria when barrier integrity is lost. It will be exciting to identify the precise mechanisms and how exactly this determines progression to severe CD or UC. CLE has found a home, more useful than dysplasia detection or polyp characterisation, since it explores a field effect and through-the-scope probes are more practicable than designated scopes. The technique provides the opportunity to quantify labelled cell types (eg neutrophils) or molecular mediators of inflammation (eg TNF-alpha), which the authors have already demonstrated in principle ⁸. The accuracy and positive/negative predictive values for the course of disease over 2-3 years described (all exceeding 80%), could represent an early endpoint in clinical trials. This has huge potential to inform the mode of action, limit numbers, and determine success or failure of drugs under testing in relation to a clinically relevant endpoint (MAO). Even if the nuanced distinction between structural and functional barrier dysfunction in CD – defined as luminal shedding of single vs multiple epithelial cells –lack robustness for practice, CLE provides a tool to score barrier integrity in CD, where histological scores are subject to sampling error. It is the overall functional barrier integrity that matters.

Whether CLE will enter clinical practice faces practical challenges. The cost of probes, additional time (2min per segment) and expertise are likely to limit the procedure to clinical trials in the first instance. There is also competition. Artificial intelligence is likely to transform endoscopic interpretation by more clearly defining levels of remission, including techniques such as the Red Density Score and others ^{9, 10}, which will be more feasible to implement in practice. Furthermore, functional barrier integrity is not the base of the berg. Assessment of disease pathology by gene expression (transcriptomics) is in its infancy, but studies demonstrate proof of concept of signatures strongly associated with therapeutic response and course of disease ¹¹⁻¹⁹. Combining transcriptomics with quantitative histopathology may even allow selection of advanced therapy based on pathotypes in individual patients ¹⁸.

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Figure legend. Symptomatic, biochemical, endoscopic and histopathologic scores are currently used to diagnose and assess the severity of IBD. Whilst they are readily available in clinical practice, their predictive value for outcome and selection of advanced therapy is limited. Emerging techniques, such as confocal laser endomicroscopy (CLE) and molecular phenotyping by transcriptomics or proteomics, offer superior depth of assessment, enabling more robust outcome predictions and precision targeting of advanced medications. Whether these techniques can be implemented in clinical practice remains to be determined.