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RISK STRATIFYING IN REAL LIFE

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Risk stratification in inflammatory bowel disease (IBD) is important to help identify patients who need early intensive therapy, and to avoid the risks and costs associated with overtreating patients who may respond adequately to less intensive therapy. Risk stratification in IBD management encompasses: prioritization of drug therapy risks and benefits; use of predictive tools to monitor therapeutic response; and use of appropriate preventive strategies that may favorably alter the disease course.

Prioritizing risk versus benefit involves identification of "red flags" or poor prognostic factors. Poor prognostic factors in Crohn's disease (CD) include: age under forty; steroids at presentation; weight loss; ileal/ ileocolonic disease; extensive small bowel disease; perianal disease; deep ulceration on endoscopy; and smoking.[1, 2] Poor prognostic factors in ulcerative colitis (UC) include: age under forty; male gender; persistent blood in stool; stool frequency of more than 10 bowel actions per day; hospitalization and steroids within six months; intravenous steroids; use of salvage therapies (cyclosporine or infliximab); and the presence of extensive colitis or sclerosing cholangitis.[3, 4]

High risk patients require the most intensive drug therapy to alter the natural history of disease. Recent data from the CALM study suggest that timely escalation with anti-tumor necrosis factor (anti-TNF) therapy based on regular monitoring of clinical symptoms and biomarkers in patients with early CD, results in better clinical and endoscopic outcomes than symptom-driven decisions alone.[5] In clinical practice,

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therapeutic decisions require constant risk reassessment and re-evaluation to tailor the right drug, to the right patient at the right time.

An integral component of risk assessment is the use of predictive indices to monitor therapeutic response. Acute Severe Ulcerative Colitis (ASUC) represents an example of a life-threatening clinical situation in IBD for which timely risk assessment is critical to reduce morbidity and mortality. ASUC occurs in 25% of patients with UC. Forty percent of patients with ASUC fail to respond to corticosteroids, and 50% fail to respond to salvage therapy.[6] The cumulative risk of developing ASUC during the course of disease is increased in UC patients who, at the time of diagnosis, are found to have extensive disease, a C-reactive protein (CRP) >10 mg/L and anemia.[7] Early escalation of medical therapy should therefore be considered in such high risk patients to reduce the risk of development of ASUC.

Among patients who develop ASUC, endoscopic assessment using the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) helps predict the need for salvage therapy and risk of progression to colectomy. It should therefore be used as part of endoscopic risk assessment in patients presenting with ASUC.[8] The Oxford criteria have been used to assess response to first-line therapy with intravenous corticosteroids by day 3-7.[9] The need for salvage therapy is determined by a day 3 assessment of ≥ 8 stools per day or ≥ 3 stools per day with a CRP > 45 mg/L which is associated with an 85% positive predictive value (PPV) for colectomy within same admission, or a day 7 assessment of ≥ 3 stools per day with visible blood which is associated with a 40% PPV for colectomy within three months. Prolonged intravenous steroid therapy without clear improvement is futile and increases the risk of complications and mortality. Risk prediction tools such as the Oxford criteria are therefore imperative to inform timely decision-making regarding the need for salvage therapy.

Despite attempts to predict outcome in ASUC there remain several unanswered questions including: (1) whether steroid response can be predicted earlier; (2) whether more anti-TNF should be given as part of induction; (3) how best to rescue early non-responders, and; (4) what constitutes the ideal maintenance therapy post salvage therapy. Prospective randomized clinical trials comparing dose intensified therapy to standard dose therapy in ASUC are both planned and underway (PREDICT UC; NCT02770040). The trials may help answer these questions, allowing risk profiles to be generated to help predict the outcome for patients who present with this challenging clinical condition.

Risk stratification in clinical practice also allows preventive strategies to be tailored to the risk of disease progression. In Crohn's disease a preventive strategy should be implemented after intestinal resection given the high risk of postoperative recurrence of Crohn's disease.[10] Whilst anti-TNF therapy is effective at preventing disease recurrence there is a risk of over-treating patients if it is applied to all patients indiscriminately.

The POCER (Post-Operative Crohn's Endoscopic Recurrence) study aimed to identify the optimal strategy to prevent post-operative disease recurrence based on risk of recurrence.[11] Patients at risk of earlier recurrence of Crohn's disease are those who: (1) smoke; (2) have had previous bowel surgery, or (3) have internal penetrating disease. The POCER study demonstrated that intensifying treatment based on these risk factors and colonoscopy six months after surgery is more effective than conventional drug therapy alone in preventing the recurrence of Crohn's disease after surgery. Moreover, selective use of stronger intensity medications, such as anti-TNF therapy, adjusted on the basis of colonoscopy, leads to effective disease control in the majority of patients. Intensifying treatment at six months brings about 40% of patients with recurrence into remission a year later. However, remission at six months does not guarantee that remission is maintained one year later. A small group of patients were found to have recurrent disease despite monitoring with

colonoscopy and intense treatment. Fecal calprotectin is also potentially a non-invasive marker for Crohn's disease recurrence, response to treatment and to determine which patients required colonoscopy.[12]

In summary, risk stratification in real life involves prioritizing risk versus benefit, predicting outcome using indices to monitor therapeutic response and adopting appropriate strategies to prevent disease progression. The potential to mitigate the risk associated with progressive disease is only as good as clinicians' ability to recognize and treat patients according to the risks at hand. Risk assessment needs to be a dynamic process that is coupled with timely adjustments to therapy based on ongoing monitoring of clinical symptoms together with biomarkers, endoscopy and/or imaging techniques if there is to be a chance of altering the natural history of disease.

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References

1. Beaugerie L, Seksik P, Nion–Larmurier I, et al. Predictors of Crohn's disease. Gastroenterology 2006;130(3):650-656.
2. Allez M, Lémann M. Role of endoscopy in predicting the disease course in inflammatory bowel disease. World Journal of Gastroenterology 2010;16(21):2626.
3. Colombel JF, Rutgeerts P, Reinisch W, et al. Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. Gastroenterology 2011;141(4):1194-1201.
4. Solberg IC, Lygren I, Jahnsen J, et al. Clinical course during the first 10 years of ulcerative colitis: results from a population-based inception cohort (IBSEN Study). Scandinavian Journal of Gastroenterology 2009;44(4):431-440.
5. Colombel J-F, Panaccione R, Bossuyt P, et al. Effect of tight control management on Crohn's disease (CALM): a multicentre, randomised, controlled phase 3 trial. The Lancet 2017;390(10114):2779-2789.
6. Seah D, De Cruz P. The practical management of acute severe ulcerative colitis. Alimentary Pharmacology & Therapeutics 2016;43(4):482-513.
7. Cesarini M, Collins GS, Rönnblom A, et al. Predicting the individual risk of acute severe colitis at diagnosis. Journal of Crohn's and Colitis 2017;11(3):335-341.
8. Corte C, Fernandopulle N, Catuneanu AM, et al. Association between the ulcerative colitis endoscopic index of severity (UCEIS) and outcomes in acute severe ulcerative colitis. Journal of Crohn's and Colitis 2015;9(5):376-381.
9. Travis S, Farrant J, Ricketts C, et al. Predicting outcome in severe ulcerative colitis. Gut 1996;38(6):905-910.
10. De Cruz P, Kamm MA, Prideaux L, et al. Postoperative recurrent luminal Crohn's disease: a systematic review. Inflammatory Bowel Diseases 2012;18(4):758-777.
11. De Cruz P, Kamm MA, Hamilton AL, et al. Crohn's disease management after intestinal resection: a randomised trial. The Lancet 2015;385(9976):1406-1417.
12. Wright EK, Kamm MA, De Cruz P, et al. Measurement of fecal calprotectin improves monitoring and detection of recurrence of Crohn's disease after surgery. Gastroenterology 2015;148(5):938-947. e1.