of Chest Physicians (ACCP) consensus guidelines for the prevention of VTE in nonorthopaedic surgical patients, recommendations for VTE prophylaxis are made based on this risk stratification scheme.[8] From the ACS NSQIP dataset, the observed 3.3% postoperative VTE risk in ulcerative colitis, which corresponds with a >6% estimated baseline risk in the absence of VTE prophylaxis, would lead to a high-risk designation. For Crohn's disease, the 1.4% observed VTE rate would be considered moderate risk.[5] These risk categories reflect the average aggregate VTE risk for patients with ulcerative colitis and Crohn's disease, but might not be as accurate at predicting individual risk as risk assessment models. For example, the Caprini score enables assessment of individual risk of VTE on the basis of clinical factors including age, type of surgery, presence of coexisting conditions (including IBD), and other known predisposing factors to VTE.[8]

> "Patients with IBD have a well-established ... increased risk of venous thromboembolism..."

The other important consideration in recommending pharmacological VTE prophylaxis is the risk of major postoperative bleeding among patients with IBD, as there might be residual disease among those with Crohn's disease or patients with ulcerative colitis who have undergone subtotal colectomy. A meta-analysis has shown that patients with ulcerative colitis receiving therapeutic doses of heparin as primary treatment for their active disease did not have higher rates of bleeding compared to those not receiving any anticoagulation.[9] In 266 patients with IBD who underwent major abdominal surgery and received pharmacological VTE prophylaxis at our institution, no major bleeding events were reported (95% CI 0–1.1%) (G. C. Nguyen, unpublished data). Thus, the risk of major postoperative bleeding in patients with IBD does not seem to be higher than that reported for general surgical patients undergoing colorectal surgery, and thus, postoperative pharmacological VTE prophylaxis is not contraindicated in the former group.[10]

If we extrapolate from the ACCP guidelines, patients with Crohn's disease who have undergone intestinal surgery are at moderate risk of VTE and should receive pharmacological VTE prophylaxis. Given that patients with ulcerative colitis are in the high-risk category, consideration should be given to both pharmacological and mechanical VTE prophylaxis. This approach is supported by data from Scarpa *et al.*,[7] in which the observed rate of VTE in ulcerative colitis was 2.6% despite all patients receiving pharmacological VTE prophylaxis. This finding raises the issue of whether standard prophylactic dosing of low-molecular-weight heparin is sufficient to prevent VTE. Whether patients with ulcerative colitis would benefit from the extended duration pharmacological prophylaxis (4 weeks) recommended for other high risk groups (such as patients with cancer) remains unclear. Future studies are needed to quantify the risk of postoperative VTE following hospital discharge in those who have undergone major abdominal surgery for IBD.

In conclusion, Wallaert *et al.*[5] present data from a large retrospective cohort quantifying the risk of postoperative VTE in patients with IBD and stratifying the risk between Crohn's disease and ulcerative colitis. These data aid in the interpretation of current ACCP guidelines in the specific contexts of ulcerative colitis and Crohn's disease, and help promote optimal strategies for VTE prophylaxis and improvement in postoperative outcomes.

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HELICOBACTER PYLORI

Tailored therapy with novel sequential quadruple therapies

David Y. Graham and Javier P. Gisbert

Treatment success for *Helicobacter pylori*, a major human pathogen, with popular drug regimens has generally declined to unacceptably low levels. As part of the worldwide effort to identify novel drug regimens that will reliably achieve high levels of success, Tay, Marshall and colleagues report their results with novel multidrug-tailored therapies.

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The effectiveness of traditional *Helicobacter pylori* therapies has declined over the past 10 years coincident with an increase in antimicrobial resistance. Indeed, clarithromycin-containing triple therapy is now not generally recommended for

empirical use unless clarithromycin resistance is rare locally or pretreatment clarithromycin susceptibility has been confirmed (that is, only as a tailored therapy). Tay, Marshall and colleagues have now reported the results of tailored multidrug therapies in patients who have previously failed traditional 7-day triple clarithromycin-containing therapy.[1] Susceptibility testing and penicillin allergies were used to select the treatment regimen for each patient. The preferred regimen was a four-drug hybrid sequential therapy for 10 days consisting of the PPI rabeprazole and high-dose amoxicillin for 10 days with the addition of rifabutin and ciprofloxacin during treatment days 6–10 (referred to as PARC therapy; see Box 1 for dosage information). Those patients with a penicillin allergy received the PPI plus bismuth subsalicylate for 10 days and rifabutin with ciprofloxacin during days 6–10 (referred to as PBRC therapy; Box 1). Finally, those patients with pretreatment ciprofloxacin and/or rifabutin resistance received individualized tailored therapy (Box 1) based on antibiotic susceptibility testing: typically a 10-day nonsequential course of a PPI, bismuth subsalicylate, furazolidone and one additional antibiotic (namely, tetracycline or metronidazole).

PARC therapy was successful in 95.2% (95% CI 91–97%) of the 210 patients who received it and PRBC therapy in 94.2% (95% CI 85–98%) of 69 patients.[1] Success with individualized tailored therapies for those with rifabutin and/or ciprofloxacin resistance (specifically, PBRF, PBFT, PBAC and PRB; Box 1) was 100%; however, there were only 1–4 patients per group. Therapy with PBAF ($n = 15$), PMA ($n = 3$), and PBAT ($n = 2$) was less than 75% effective. The researchers suggested that the two sequential regimens PARC and PBRC could be confidently given to those with known susceptible infections.[1]

Here, we address three questions: are their results applicable to current clinical practice? As susceptibility testing is not widely available, can the results be used as empiric regimens? Finally, are any of the regimes ready for 'prime time' or is further development needed?

In our opinion, neither four-drug sequential therapy is ready for prime time, especially when in the same region one would expect to cure nearly 100% with a 14-day course of bismuth, tetracycline, PPI and either metronidazole or furazolidone quadruple therapies without risking increasing fluoroquinolone or rifabutin resistance in the non-*H. pylori* bacterial populations.[2,3]

Ideally, the rational use of any regimen requires knowledge regarding its effectiveness with susceptible strains as well as the effects of resistance to each of its antimicrobial components. With these data, one can generally assume that knowledge gained from any population with a similar pattern of resistance will be directly transferable to a similar population in any location. Ideal regimens will have also been optimized for each component in relation to: formulation, doses, dosing intervals and relation to meals, and duration of therapy; the modifications to these components needed for resistant infections will have also been identified (for example, 7 days of bismuth-containing quadruple therapy is adequate for susceptible strains whereas 14 days might be optimal when resistance exceeds 40%[4]).

The suggested sequential regimens contain both ciprofloxacin and rifabutin. However, it is not clear if both drugs are necessary and, moreover, the data presented suggest that only one of the drugs was sufficient. For example, in the study by Tay *et al.*[1] 10-day courses using only either ciprofloxacin or rifabutin (such as, PBAC or PBR) provided 100% cure rates with the caveat that with each regimen only one individual was tested. However, Borody *et al.*[5] had previously reported eradication rates of >90% using a rifabutin triple therapy with high-dose amoxicillin (that is, high-dose PPI, 1 g or 1.5 g amoxicillin three times daily, and 150 mg rifabutin daily for 12 days) among Australian patients, also suggesting that ciprofloxacin is redundant.

Besides confirmation that rifabutin and ciprofloxacin both contributed considerably to the outcome, the results presented in the Tay *et al.*[1] study suggest that the efficacy of other combinations, including PBAC, PBR and PBAR, should be examined further. In addition, after deciding on the preferred regimen or regimens among the various therapies tested, optimization would still be needed, especially in terms of doses and durations (for example, would 14 days be better than 7 or 10 days?) and to determine the effect of resistance on outcome (that is, what proportion of resistance will drop the treatment success below 90%?).

The specific drugs used also requires consideration as, for example, rifabutin use is limited in many countries with the goal of 'saving' it for use with tuberculosis, and fluoroquinolone use has tended to focus on second-generation drugs. The prevalence of fluoroquinolone resistance has also increased rapidly worldwide, which has generally undermined the use of this class of drugs for empiric anti-*H. pylori* therapy. As with other infectious diseases, one would prefer to base therapeutic decisions on knowledge of local or patient-specific resistance patterns. Generally, neither fluoroquinolone nor rifabutin resistance can be overcome by increasing the dosage or duration of therapy, suggesting that the two new sequential therapies have limited usefulness except as tailored therapies. Whether second-generation quinolones would provide equivalent or better results also needs to be explored.

A number of other new, highly successful and promising regimens have been introduced by other investigators, including

Box 1 | Quadruple multidrug regimens

First-line therapy

PARC therapy (for patients not allergic to penicillin)

- 10 days of the PPI rabeprazole (20 mg, 3 times daily) and amoxicillin (1,000 mg, 3 times daily); 5 days of rifabutin (150 mg, 2 times daily) and ciprofloxacin (500 mg, 2 times daily) from days 6 to 10

PBRC therapy (for patients allergic to penicillin)

- 10 days of the PPI rabeprazole (20 mg, 3 times daily), bismuth subsalicylate (120 mg, 4 times daily), rifabutin (150 mg, 2 times daily) and ciprofloxacin (500 mg, 2 times daily)

Personalized-based therapy

PBAT (patients who failed PARC)

- 10 days of the PPI rabeprazole (20 mg, 3 times daily), bismuth subsalicylate (120 mg, 4 times daily), amoxicillin (1,000 mg, 3 times daily) and tetracycline (250 mg, 4 times daily)

PBAF (patients who failed PARC)

- 10 days of the PPI rabeprazole (20 mg, 3 times daily), bismuth subsalicylate (120 mg, 4 times daily), amoxicillin (1,000 mg, 3 times daily) and furazolidone (100 mg, 3 times daily)

PBTF (patients who failed PBRC)

- 10 days of the PPI rabeprazole (20 mg, 3 times daily), bismuth subsalicylate (120 mg, 4 times daily), tetracycline (250 mg, 4 times daily) and furazolidone (100 mg, 3 times daily)

Abbreviations: PARC, PPI, amoxicillin, rifabutin, ciprofloxacin; PBAF, PPI, bismuth subsalicylate, amoxicillin, furazolidone; PBAT, PPI, bismuth subsalicylate, amoxicillin, tetracycline; PBRC, PPI, bismuth subsalicylate, rifabutin, ciprofloxacin; PBTF, PPI, bismuth subsalicylate, tetracycline, furazolidone.

a 5-day sequential therapy (comprising high-dose PPI, esomeprazole 40 mg twice daily, amoxicillin 1 g twice daily, levofloxacin 500 mg twice daily, and tinidazole 500 mg twice daily),[6] a 14-day sequential-concomitant hybrid therapy,[7] and a bismuth-containing 14-day sequential therapy programme consisting of pantoprazole (40 mg twice daily for 14 days), colloidal bismuth subcitrate (600 mg twice daily for 14 days) with amoxicillin (1 g twice daily for the first 7 days) and tetracycline (500 mg four times daily) and metronidazole (500 mg three times daily for days 8–14).[8] The results reported by Federico *et al.*[6] of the sequential fluoroquinolone-containing regimen contrast with the majority of studies using a PPI, amoxicillin and a fluoroquinolone for 7 or 10 days as they have rarely achieved eradications of 90% or greater.[9,10] Whether a ciprofloxacin-containing sequential triple therapy based on the Tay *et al.*[1] study protocol would also be effective other than as a tailored regimen remains to be proven.

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ULCERATIVE COLITIS

Steroid-refractory ulcerative colitis—ciclosporin or infliximab?

Manreet Kaur and Stephen R. Targan

Ciclosporin and infliximab are used as rescue therapies for the treatment of severe steroid-refractory ulcerative colitis. Now, an open-label, head-to-head randomized controlled trial has demonstrated that these drugs are well-tolerated and have equivalent efficacy in inducing short-term clinical response, mucosal healing and decreasing colectomy rates at 3 months.

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Severe ulcerative colitis is a life-threatening medical condition with a high risk of colectomy. Corticosteroids were the sole medical treatment option for severe colitis[1] until ciclosporin and infliximab became available as viable rescue therapies for steroid-refractory ulcerative colitis in the 1990s and 2000s, respectively. Now, Laharie *et al.*[2] have published the results of their much-anticipated randomized controlled trial comparing ciclosporin with infliximab in patients with severe ulcerative colitis who are refractory to intravenous steroids.

Evidence for ciclosporin as an effective medication for severe ulcerative colitis was established by a placebo-controlled trial that was terminated early owing to higher than expected differences in response rates between ciclosporin and placebo groups (82% response rate in the ciclosporin group versus 0% in the placebo group, $P<0.001$).[3] Subsequent studies produced similar response rates, establishing ciclosporin as an effective agent for inducing short-term remission of severe ulcerative colitis.[4,5] The long-term data regarding colectomy-free survival are less compelling and might reflect the efficacy of the maintenance regimen rather than ciclosporin activity itself. However, after discontinuation, ciclosporin undergoes rapid systemic clearance and reversal of calcineurin inhibition *in vivo*, lending itself well to scenarios in which iatrogenic immunosuppression needs to be minimized (such as in the event of an emergency surgery or septic complication). This effect could be of considerable benefit to patients who are facing imminent colectomy. Despite convincing data, however, ciclosporin utilization remains restricted to large referral centers owing to concerns regarding its safety and the somewhat laborious nature of administration by continuous intravenous infusion, as well as the need for frequent monitoring of laboratory parameters (such as renal function, serum electrolytes and cholesterol levels) and drug levels.

Although infliximab is used as an alternative to ciclosporin in the treatment of severe ulcerative colitis, there is a relative paucity of data regarding its efficacy in this scenario. In the earliest placebo controlled trial of infliximab for severe ulcerative colitis, four of the eight patients who received infliximab (at 5, 10 or 20 mg/kg) were considered to have