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Tailored therapy with novel rifabutin and ciprofloxacin-containing sequential therapies: Commentary on *Helicobacter pylori* eradication in Western Australia using novel quadruple therapy combinations

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Standfirst

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

Keywords

Helicobacter pylori; therapy; ciprofloxacin; rifabutin; bismuth; proton pump inhibitor; furazolidone

The effectiveness of traditional *H. pylori* therapies has declined coincident with an increase in antimicrobial resistance and it is now generally recommended that clarithromycin-containing triple therapy not be used empirically unless clarithromycin resistance is rare locally or clarithromycin susceptibility had been confirmed (i.e., a tailored therapy). Tay, Marshall, and colleagues report the results of tailored multidrug therapies in patients who had previously failed traditional therapies [1]. Susceptibility testing and penicillin allergies were used to choose the treatment regimen. The preferred regimen was a 4 drug hybrid sequential therapy for 10 days consisting of the proton pump inhibitor (P) rabeprazole, 20 mg t.i.d, and high dose amoxicillin (A) (1 g t.i.d.) for 10 days with the addition of 150 mg of rifabutin (R) once daily and 500 mg of ciprofloxacin (C) b.i.d. during days 6 through 10 (PARC). Those with penicillin allergy received the PPI plus bismuth subsalicylate (B) for 10 days and rifabutin 150 mg and 500 mg of ciprofloxacin (both b.i.d.) during days 6 through 10 (PBRC). Finally, those with pretreatment ciprofloxacin and/or rifabutin resistance received individualized tailored therapy based on antibiotic susceptibility testing: typically a 10 day non-sequential course of a PPI, bismuth, furazolidone (F) and one additional antibiotic (T = tetracycline, M = metronidazole).

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PARC was successful in 95.2% (95% C.I. = 91–97%) and PRBC in 94.2 (95% CI = 85–98%). Success with individualized tailored therapies for those with rifabutin and/or ciprofloxacin resistance (i.e., PBRF, PBFT, PBAC, PRB) was 100%; however, there were only 1 to 4 subjects per groups. Therapy with PBAF (n=15), PMA (n=3), and PBAT (n=2) was 70% effective or less. The authors suggested that the two sequential regimens (PARC and PBRC) could be confidently given to those with known susceptible infections.

We address 3 questions: Are their results applicable to current clinical practice? Since 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 4 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 this 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 anywhere. Ideal regimens have also been optimized for each component in relation to formulation, doses, dosing intervals and relation to meals, and duration of therapy, and the modifications needed for resistant infections have been identified (e.g., 7 days of bismuth quadruple therapy is adequate for susceptible strains whereas 14 days may be optimal when resistance exceeds 40% [4]).

The suggested sequential regimens contain both ciprofloxacin and rifabutin. However, it is not clear that both drugs are necessary and data presented suggest that this may not be the case. For example, they report that 10 day courses using only either ciprofloxacin or rifabutin (e.g., PBAC or PBR) provided 100% cure rates with the caveat that with each only one individual was tested. However, Borody et al. had previously reported eradication rates of >90% using a rifabutin triple therapy with high dose amoxicillin (e.g., high dose PPI, 1 or 1.5 g amoxicillin t.i.d, and 150 mg of rifabutin daily for 12 days) among Australian patients, suggesting that ciprofloxacin might be redundant [5].

Besides confirmation that rifabutin and ciprofloxacin both contributed significantly to the outcome, their results suggest other combinations that possibly should be examined further such as PBAC, PBR, and PBAR [1]. However, after deciding on the preferred regimen or regimens, therapies should be optimized, especially in terms of doses and durations (e.g., would 14 days be better than 7 or 10) and to determine the effect of resistance on outcome (i.e., what proportion of resistance will drop the treatment success below 90%).

There are also considerations regarding the drug used (e.g., 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 and this 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 dosages or duration of therapy, suggesting that the two new sequential therapies might 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 a 5 day sequential therapy (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 program consisting of pantoprazole, 40 mg (b.i.d. for 14 days), colloidal bismuth subcitrate, 300 mg 4 for 14 days with amoxicillin, 1 g (b.i.d.) for the first 7 days and tetracycline, 500 mg q.i.d. and metronidazole (t.i.d. for the second 7 days) [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 rarely have 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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