Editorial

More evidence for shortening antibiotic therapy in peritonitis: the DURAPOP trial

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Recently, Montravers *et al.* published the DURAPOP randomised clinical trial of duration of antimicrobial therapy for patients treated in the intensive care unit (ICU) for post-operative peritonitis (1). The investigators should be lauded for a carefully conceived and executed trial in a very challenging and sick patient population.

Patients being treated for post-operative peritonitis were initially enrolled upon admission to the ICU if they had positive surgical samples, had adequate source control, and received adequate empiric therapy within 24 hours of the completion of surgery. On post-operative day 8, patients still undergoing treatment in the ICU were then randomized into either the control group, in which antibiotics were continued for an additional 7 days, or an experimental group, for whom antibiotics were stopped at the time of randomization. The primary outcome was the number of antibiotic-free days from day 8 to 28. Patients dying before day 28 were counted as zero antibiotic-free days. Key secondary endpoints included 28- and 45-day mortality, ICU and hospital length of stay, need for reoperation or drainage, superinfection or recurrent infection, and additional courses of antibiotics for any reason.

On day 8, 249 of the original 410 patients were randomized. Compliance with the protocol was good, with the allocated duration of therapy followed in 79% of the 8-day group and 82% of the 15-day arm. As hypothesized, the median number of antibiotic-free days in the 8-day arm was significantly greater than in the 15-day arm, 15 [interquartile range (IQR), 6–20] versus 12 (IQR 6–13). Overall 45-day mortality was 11% in the 8-day group and 15% in the 15-day group (P=0.43). The number of reoperations were similar between groups, but the percentage of subjects undergoing a percutaneous drainage procedure was higher in the 8-day arm compared to the 15-day arm: 23/120=19% versus 11/116=9%, P=0.041. Interestingly, the number of patients actually diagnosed with a recurrent infection was similar between groups (14 in the 8-day arm, 13 in the 15-day arm), implying that a fair number of the reoperations and percutaneous drainage procedures ended up with sterile cultures and might not be considered treatment failures. Additionally, the rates of the initiation of new antibiotic therapy for either a recurrent intra-abdominal infection or a distant infection were also similar between groups (42% in the 8-day arm, 39% in the 15-day arm). No significant differences were noted in the rates of emergence of multidrug resistant bacteria or fungi.

These data add to the growing number of trials suggesting shorter durations of therapy for the management of serious infections is feasible and safe, starting with the landmark study by Chastre *et al.* comparing 8 versus 15 days of therapy for ventilator-associated pneumonia (2). More recently, the STOP-IT trial sponsored by the Surgical Infection Society randomized patients with intra-abdominal infections to 4 days of antibiotic therapy versus therapy until physiological abnormalities had resolved. They found no differences in outcomes between the two groups (3). Although some patients with healthcare-associated infections and treatment in the ICU were included in

the STOP-IT study, the DURAPOP trial truly focused on critically ill patients. As noted above, those assigned to 8 days of treatment ended up receiving fewer days of antibiotics, and efficacy was similar when 45-day mortality was considered.

The waters are muddied, however, by the finding that significantly more patients in the 8-day group eventually had percutaneous drainage procedures than patients in the 15-day arm. Although this might be considered failure of antibiotic therapy in the 8-day group, the number of patients assessed to have recurrent infection or who had new antibiotic therapy started were almost identical between groups. It is possible, therefore, that in this non-blinded study that clinicians were more aggressive draining fluid collections for diagnostic as well as therapeutic purposes in patients no longer on antibiotics, resulting in more (sterile) procedures. These findings, nonetheless, prevent us from claiming that the outcomes were identical based on duration of antibiotic therapy alone.

Where do these data fit in the algorithm of the management of critically ill patients undergoing treatment for postoperative peritonitis? Although not focused on patients with critical illness, subgroup analysis of the STOP-IT data suggest similar outcomes for 4 and 8 days of antimicrobial therapy among patients with sepsis (4) or predicted to have high failure rates (5). On the other hand, the need for more drainage procedures in patients receiving 8 versus 15 days of therapy in the DURAPOP trial should at least make one thoughtful about the idea of providing fewer than 8 days of therapy in the critically ill. A potential intermediate path would be using the response of a biomarker, such as procalcitonin, to guide the number of days of treatment. However, as already noted by the DURAPOP investigators, the utility of procalcitonin in peritonitis patients with septic shock remains unproven (6). Additionally, the STOP-IT trial data implied that waiting for normalization of the two canonical markers of infection (fever and leukocytosis) did not affect outcomes compared to a fixed duration of treatment. Hence, progress in determining a sensitive and specific biomarker that assesses the presence of live bacteria and not just inflammation is sorely needed.

Absent a study comparing 4 versus 8 days of antimicrobial therapy in the management of ICU patients with postoperative peritonitis, it still seems reasonable that in the presence of adequate source control, 4 days of antimicrobial therapy active against all isolated pathogens should be considered. Realistically, though, in a patient who does not seem to be rapidly responding to therapy, extending the course to 8 days is justifiable after carefully weighing the risks of continued antibiotic exposure. In either case, the physician caring for these patients must be highly vigilant, constantly looking for signs of clinical deterioration that should trigger microbiologic and radiologic evaluation to rule out a recurrent intra-abdominal or distant infection.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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