Moderate Fluid Resuscitation Is Preferable in Acute Pancreatitis

de-Madaria J, Buxbaum JL, Maisonneuve P, et al. Aggressive or moderate fluid resuscitation in acute pancreatitis. N Engl J Med 2022;387:989–1000.

Almost 1 in 3 patients presenting with acute pancreatitis progress to a moderate or severe form. Aggressive fluid resuscitation has been thought to improve perfusion, and thus outcomes, but the current literature is conflicting regarding the optimal fluid resuscitation strategy.

The WATERFALL (Aggressive Versus Non-aggressive Goal-Directed Fluid Resuscitation in Acute Pancreatitis; NCT04381169) study originally planned to recruit 744 patients with mild acute pancreatitis whose symptoms had started less than 24 hours before and were diagnosed less than 8 hours before and randomize them to either aggressive or moderate fluid resuscitation (AFR or MFR) with lactated Ringer's solution, an intravenous crystalloid with antiinflammatory properties. Those allocated to AFR received a 20-mL/kg fluid bolus followed by a 3-$mL \cdot kg^{-1} \cdot h^{-1}$ infusion, whereas those in the MFR group received a 10-ml/kg bolus (only if hypovolemic) followed by a 1.5-$mL \cdot kg^{-1} \cdot h^{-1}$ infusion. Fluid resuscitation was changed to goal-directed therapy after 12 hours, with patients with ongoing hypovolemia continuing with the strategies outlined above, while normovolemic patients received 1.5 $mL \cdot kg^{-1} \cdot h^{-1}$. Safety checkpoints were regularly undertaken, with fluids decreased or stopped in the event of fluid overload.

The study was halted at the first planned interim safety analysis time point of 249 patients, having found no difference in the primary outcome—the development of moderately severe or severe pancreatitis—between AFR and MFR (22% vs 17%, adjuste relative risk [RR] 1.30, 95% confidence interval [CI] 0.78–2.18), but AFR was associated with higher rates of fluid overload (21% vs 6%, aRR 2.85, 95% CI 1.36–5.94). On average, patients in the AFR group received 7.8 L compared with 5.5 L in the MFR group. There were no differences in secondary outcomes such as organ failure, local complications, respiratory failure, necrotizing pancreatitis, intensive care unit admission, or length of hospitalization. The results were similar in prespecified subgroup analyses for patients with baseline hypovolemia or systemic inflammatory response syndrome.

A study limitation was the exclusion of a large number of subjects who did not meet the relatively strict timelines for symptom duration or diagnosis (276 out of 676 screened patients, 41%). Thus, the results might not be applicable to the almost one-half of patients with acute pancreatitis who present late. In addition, the inability to meet the sample size as a result of the early termination could have affected the detection of differences in the measured outcomes. Nonetheless, the results of this trial support the use of MFR rather than AFR in patients with acute pancreatitis. Some questions regarding the optimal fluid resuscitation strategy in acute pancreatitis remain. For example, is Ringer's the best solution? Should the fluid resuscitation be even more restrictive, especially if oral feeding is commenced early? Or would early aggressive fluid resuscitation for a short period be beneficial?

VILLE SALLINEN
Gastroenterologic Surgery/Transplantation and Liver Surgery
Helsinki University Hospital and University of Helsinki
Helsinki, Finland

Outcomes Associated With Colorectal Cancer After Population-Based Colonoscopy Screening: Results From a European Pragmatic Randomized Trial

Bretthauer M, Løberg M, Wieszczy P, et al. Effect of colonoscopy screening on risks of colorectal cancer and related death. N Engl J Med 2022;387:1547–1556.

Colorectal cancer (CRC) is an ideal target for both opportunistic and population-based screening. Currently recommended screening strategies rely primarily on stool-based modalities such as fecal immunochemical testing (FIT) and endoscopic modalities such as sigmoidoscopy and colonoscopy. Bretthauer et al performed the first randomized trial to assess the effects of population-based screening colonoscopy on CRC and CRC-associated death.

Screening-naïve healthy participants aged 55 to 64 years from 4 European countries were identified from population registries and, in a 1:2 ratio, randomly invited to undergo screening colonoscopy or not invited for screening. Screening colonoscopies were performed from 2009 to 2014. Importantly, no participants received any competing CRC screening modalities outside of the trial during either the screening or follow-up periods.

Follow-up data were available for 84,585 patients. Among the invited group, 42.0% of participants accepted their invitation and underwent colonoscopy. The mean adenoma detection rate (ADR) was 30.7%. In intention-to-treat analyses, the 10-year risk ratio (RR) of CRC was 0.82 (95% confidence interval [CI] 0.70–0.93) in the screening arm, although the risk of CRC-related death was not significantly different (RR 0.90, 95% CI 0.64–1.16). In per-protocol analyses, RRs of CRC and CRC-related death with screening were 0.69 (95% CI 0.55–0.83) and 0.50 (95% CI 0.27–0.77), respectively.

These results have triggered a broad range of reactions. Given the acceptance rate of 42%, one widely repeated stance is that colonoscopy can be effective only if performed, and that the per-protocol analyses may be a better representation of colonoscopy's benefits (Dominitz and Robertson, N Engl J Med 2022;387:1609–1611). While perhaps true at the patient level, the aims of this study were