In Reply Dr Qian and colleagues are concerned about the generalizability of the ESCAPE trial and call for a standardized endoscopy strategy for better control of painful chronic pancreatitis.[1]

We acknowledge that international guidelines set the pancreatic stone size for extracorporeal shock-wave lithotripsy at 5 mm or greater instead of 7 mm or greater, as in the trial.[2,3] However, this difference did not lead to another treatment strategy in the trial because the median diameter of stones in the endoscopy-first approach was 10 mm, and only 3 patients had stones between 5 and 7 mm, of whom 2 underwent extracorporeal shock-wave lithotripsy. The 3-session extracorporeal shock-wave lithotripsy technique for stone fragmentation before endoscopic retrograde pancreatography is common practice in many countries and is also the dominant technique in the study of 5000 patients undergoing extracorporeal shock-wave lithotripsy[4] referred to in the letter.

Regarding the stent exchange schedule, international guidelines advise changing stents at regular intervals or when necessary in patients with symptoms of stent dysfunction.[2,3] This is exactly what was done in the trial. The low-quality evidence regarding stent exchange discussed in these guidelines showed no differences in complication rates for both schedule strategies.[2]

The endoscopic duct clearance was somewhat lower in the trial compared with the literature; in the endoscopy-first approach, patients with persistent pain due to failed endoscopy were referred according to protocol for surgery in the short term to achieve complete duct clearance.

Qian and colleagues suggest that in the trial, the majority of the patients may have had end-stage disease with progressive parenchymal destruction and that, according to the burnout theory, they may have been close to pain-free status with surgery accelerating this course. The burnout theory was proposed 20 years ago, after some small studies showed a correlation between pain relief and longer disease duration, but it is unproven and likely outdated. Recent large studies do not show any correlation between duration of disease and pain.[5] Moreover, a correlation between morphologic abnormalities and pain in chronic pancreatitis is variable and contradictory in the literature. This absence of a correlation among duration of disease, morphologic abnormalities, and duration and intensity of pain is also apparent in our trial. Most patients had extensive morphological abnormalities but had only been diagnosed with chronic pancreatitis for 1 year with worsening of pain for which opioid medication was initiated for a maximum of 8 weeks before study inclusion.

The authors propose that the beneficial effect of early surgery could be partly due to the large proportion of patients with an enlarged pancreatic head. Our cohort was a representative sample of all patients with painful ductal obstruction presenting to Dutch hospitals, and we deliberately chose not to exclude patients with an enlarged pancreatic head. We performed an additional post hoc subgroup analysis that showed that in the endoscopy-first approach, patients with an enlarged pancreatic head had less pain during follow-up (mean area-under-the-curve Izbicki score, 45 [SD, 25]) compared with patients with a nonenlarged pancreatic head (mean area-under-the-curve Izbicki score, 54 [SD, 25]), indicating the variable correlation between morphologic abnormalities and clinical response to treatment.

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Vitamin C, Hydrocortisone, and Thiamine for Septic Shock

To the Editor The Vitamin C, Hydrocortisone, and Thiamine in Patients With Septic Shock (VITAMINS) trial found that vitamin C, hydrocortisone, and thiamine, compared with hydrocortisone alone, did not improve outcomes in patients with septic shock.[1]

In randomized trials in sepsis, time spent to select and stabilize patients by initiating early interventions such as antibiotics, fluids, and vasopressors must precede patient enrollment, randomization, and administration of study drug. The VITAMINS trial reflects this—although hydrocortisone use was standardized and presumptively administered quickly, thiamine and vitamin C were delayed.

The idea that early, resuscitative therapy in septic shock is distinct from day-to-day drug selections is supported by the sepsis bundle time limits from the Centers for Medicare & Medicaid Services. It would be expected that interventions targeting prevention of progression of multiorgan dysfunction by treating microvascular dysfunction, mitochondrial injury, and the oxidative burst and stress of sepsis would have time-dependent efficacy. In a before-after study, almost all patients were treated within 6 hours.[2] Another retrospective study found that delays in the administration of hydrocortisone, vitamin C,

and thiamine beyond 12 hours after presentation of sepsis had no influence on patient outcomes, while early therapy was associated with large effects.[3]

In contrast, this trial did not assess early use of vitamin C and thiamine; patients became eligible only after demonstrating an elevated lactate level after the initial fluid resuscitation phase with an additional minimum 2-hour requirement of vasopressors. After this time, the intervention therapy was initiated at a median of 12.1 hours. The time from presentation to the conclusion of fluid resuscitation was not reported, but a conservative estimate would be 18 to 20 hours.[1] This delay to intervention stands in juxtaposition to many critical care intervention trials. It is further puzzling given that the trial included a deferred consent process, an approach intended to minimize delays to therapy.

We have other concerns about the trial. First, more than 20% of patients were surgical patients, a population with many confounders and in which adjuvant therapy is likely to have a lesser effect. Second, excess fluid administration has intense effect on the efficacy of hydrocortisone, vitamin C, and thiamine therapy,[4] yet these data were not reported. Third, more than 15% of patients in the trial had nosocomial infections, differing from the study by Marik et al[2] in which all patients had community-acquired infection; outcomes are generally better for community-acquired vs hospital-acquired septic shock. Fourth, the patients in the trial had fewer comorbidities, a population in which adjuvant therapies are less likely to have an effect.

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In Reply We agree with Dr Long and colleagues that the timing of interventions is important in the management of sepsis. They suggest that early administration of vitamin C is essential for the intervention to have beneficial effects, even though no data on the timing of intervention were reported in the study by Marik et al.[1] In the VITAMINS trial,[2] an elevated lactate level was required to meet the consensus definition of septic shock.[3] During the study period, sepsis resuscitation in Australasian emergency departments for patients with suspected septic shock was administration of 27 mL/kg of intravenous fluids before starting vasopressors, which were commenced a median of 3.5 hours after triage.[4] Moreover, given that patients in the trial were randomized and that vitamin C concentrations in the intervention group increased from low to supraphysiological levels,[5] it is unlikely that the volume and duration of fluid resuscitation affected the results.

In a post hoc subgroup analysis of the trial,[2] we found that early intervention was not associated with an increase in median time alive and free of vasopressors (for intervention vs control [n = 52 in each stratum], respectively: ≤4.8 hours: 120 [95% CI, 57-141] hours vs 123 [95% CI, 61-146] hours; 4.8-11.0 hours: 135 [95% CI, 98-146] hours vs 124 [95% CI, 44-147] hours; 11.0-17.5 hours: 120 [95% CI, 41-145] hours vs 125 [95% CI, 94-150] hours; and >17.5 hours: 116 [95% CI, 76-146] vs 124 [95% CI, 98-142] hours) or with a decrease in 90-day mortality (for intervention vs control, respectively: ≤4.8 hours: 10/21 [47.6%] vs 8/30 [26.7%]; 4.8-11.0 hours: 5/26 [19.2%] vs 9/24 [37.5%]; 11.0-17.5 hours: 6/23 [26.1%] vs 7/29 [24.1%]; and >17.5 hours: 9/34 [26.5%] vs 1/18 [5.6%]).

Given that the trial had a 2-hour window to define shock at enrollment, the first quartile is compatible with the 6-hour time frame suggested. As such, the lack of beneficial effects of the intervention is unlikely to be attributable to the timing of intervention.

Regarding the target population, more than 60% of sepsis-related admissions to Australasian intensive care units are from areas other than the emergency department.[6] In this respect, the trial was designed to reflect real-world practice and to assess the intervention as a widely applicable treatment for all types of septic shock, hospital or community acquired. Because there was no scientific rationale to exclude postsurgical cases, these patients were also enrolled in the trial. Moreover, when assessing the intervention vs control in emergency department patients only, median time alive and free of vasopressors was 135 (95% CI, 96-151) hours vs 119 (95% CI, 61-146) hours (P = .12), and 90-day mortality was 13/48 (27.1%) vs 14/48 (29.2%) (P = .82). Finally, the assertion that comorbidities influence the effect of vitamin C, hydrocortisone, and thiamine on the outcome of septic shock remains speculative as no data exist to support it.

In summary, late timing, excessive fluid therapy, and patient selection do not appear to explain the lack of effect of metabolic resuscitation in the septic shock patients enrolled in the VITAMINS trial.

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