Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: van Santvoort HC, Besselink MG, Bakker OJ, et al. A step-up approach or open necrosectomy for necrotizing pancreatitis. N Engl J Med 2010;362:1491-502.

Supplementary appendix to manuscript:

A step-up approach or open necrosectomy for necrotizing pancreatitis

METHODS

Minimally invasive step-up approach

Step 1: percutaneous or endoscopic drainage

A percutaneous drain was placed in the peripancreatic collection under guidance of CT or ultrasound (step 1a). Minimal drain size was 12-French and multiple drains were allowed. The preferred route was through the left retroperitoneum, thereby facilitating minimally invasive retroperitoneal necrosectomy at a later stage. Transabdominal drainage was performed if a retroperitoneal access route for drainage was not possible. Details on the percutaneous drainage procedures and irrigation protocol have been described elsewhere.[1] Only if neither retroperitoneal nor transabdominal drainage was possible, was endoscopic transgastric drainage performed. For the endoscopic drainage procedures, the collections were punctured with a 19 Gauge needle (Cook). A standard 0.035 inch guidewire was introduced through the needle into the collection, after which the needle was removed. Over the guidewire the outside sheet of a 7 Fr cystotome (Cook) was introduced into the collection using cutting current. Thereafter the tract was dilated with a 8-mm Maxforce dilation balloon (Boston Scientific). Thereafter, 2 double-pigtail plastic stents (7 French, 4 or 5 cm) and a nasocystic catheter were placed in the infected collection. For irrigation the drains were flushed with a bolus of 250 cc of normal saline four times a day.

The next treatment step depended on whether or not the patient's condition improved. *Clinical improvement* was defined as follows: 1) on ICU: improved function of at least two organ systems (i.e. circulatory, pulmonary, renal) and 2) on the ward: at least 10% improvement of two out of three of the following parameters: temperature, white blood cell

count and C-reactive protein. In absence of clinical improvement after 72 hours, CT was repeated. If the position of the drain(s) was inadequate or other collections could be drained, a drainage procedure was repeated once (step 1b) with reassessment after the next 72 hours, if not; minimally invasive necrosectomy was the next step (step 2).

If at any moment after the first and second 72 hours following percutaneous drainage, a patient who initially stabilized failed to show further clinical improvement or even clinically deterioration (according to the predefined criteria), minimally invasive necrosectomy was also performed.

Step 2: minimally invasive retroperitoneal necrosectomy

Video-assisted retroperitoneal debridement (VARD) was performed via a 5 cm incision according to the previously published technique.[2,3] Using the retroperitoneal drain for guidance, only loosely adherent necrosis was removed from the collection with videoscopic assistance after which two large bore drains were inserted. If VARD was technically not possible, (i.e. no retroperitoneal access route), laparotomy was performed according to the technique used in the open necrosectomy group.

Postoperative management

Continuous postoperative lavage amounting up to at least 10 L per 24 hours on the third postoperative day was performed both after open necrosectomy and VARD. All patients underwent contrast-enhanced CT one week after randomization. Other CT scans were performed on demand. Reinterventions for persisting sepsis or complications were performed on demand and, if possible, in accordance with the strategy the patient was initially assigned to. All patients received intravenous antibiotics (imipenem/ cilastatin, meropenem or

piperacillin/tazobactam depending on treatment center) after randomization, which were switched according to culture results. Nutritional support was also standardized.[1]

Costs

Cost-minimization analysis was used to determine economic differences between the minimally invasive step-up approach and primary open necrosectomy. Costs were estimated from a societal perspective.[4] Direct medical costs and indirect costs related to absence from work were estimated during admission and 6 months follow-up. Primary data were used to assess the use of health care resources. In addition, at 3 and 6 months after discharge, patients filled out the validated Health and Labor questionnaire[5] and a diary to capture additional resource use. Costs were assessed according to the Dutch guidelines for (pharmaco-)economic research.[6] Guideline unit costs were used for ICU stay, hospital stay, medication (i.e. antibiotics during admission and antidiabetic medication and pancreatic enzymes during follow-up), visits to primary and outpatient health care clinicians, home care and admission to rehabilitation centers or nursing homes.[6,7] Unit costs for operations, radiological procedures, endoscopic procedures and microbiology diagnostics were calculated at one of the university hospitals in 2008 and included all personnel costs, costs of materials, costs of equipment, and overhead costs. Productivity losses due to absence from paid work were calculated according to the cost friction method.[8] Costs per patient were calculated by multiplying volumes of resource with unit costs.[4] All costs were set at the year 2008 price level using the price index rate of the Dutch health care sector.

Statistical analysis

The original study protocol[1] stated that, for safety reasons, continuous sequential monitoring would be performed on mortality and major morbidity included in the primary endpoint. An

independent biostatistician who was blinded for treatment allocation performed continuous sequential analysis on mortality and major morbidity reported during the trial. The analysis was performed with PEST (PEST 4: user manual. MPS Research Unit (2000), the University of Reading) according to the restricted procedure as described by Whitehead.[9,10] The boundaries for the sequential analysis plot were based on the assumption that the minimally invasive step-up approach would reduce the occurrence of the primary endpoint from 45% to 16%, with 80% power and a two-sided alpha level of 0.05. A conventional sample size analysis yielded a total study population of 88 patients.

If one of the boundaries of the sequential analysis plot was crossed during the analysis of the cumulative data, meaning that the difference in treatment was of at least the predefined expected magnitude (in either direction), the biostatistician would inform the independent monitoring committee which would advise the steering committee on continuation or termination of the study. If the boundaries would not be crossed during the study, the trial would continue until the total of 88 patients was randomized. The prespecified boundaries guarantee the type I error wherever they are crossed.

The prespecified boundaries were not crossed during the period of patient enrollment and consequently the independent monitoring committee and the steering committee were not informed of results of the sequential analysis. The outcome of the sequential analysis was only known to the independent biostatistician.

Early on in the trial it became apparent that the sequential analysis suffered from significant delay because only data on mortality and evident major morbidity reported by local investigators could be sent to the biostatistician, whereas a patient could only be analyzed as not having an endpoint once the follow-up period of 3 months after discharge was completed and data collection was complete. Moreover, it was anticipated that, once the data were checked by the independent auditor, morbidity endpoints could be found in patients who

were already analyzed by the biostatistician as not having an endpoint. Therefore, it was decided that, instead of the sequential monitoring of the provisionally audited primary outcomes, a conventional analysis would be performed after the last patient completed 3 months follow-up and all data were checked by the auditor. Prior to this analysis, an adjudication committee consisting of eight experienced gastrointestinal surgeons assessed all primary (and secondary) endpoints. Every patient was evaluated by each committee member individually with data presented in a standardized format, including all available data collected during follow-up. Disagreements were resolved during a plenary consensus meeting. The adjudication committee was unaware of the outcome of the sequential analysis and was blinded for treatment allocation at all times.

The conventional analysis was performed only after agreement was reached on all endpoints. The occurrence of the primary endpoint was compared between the two treatment groups and results are presented as risk ratios with corresponding 95% confidence intervals (CI). In line with the protocol, we also performed sequential analysis on the adjudicated primary endpoints. Results were in agreement with those of the conventional analysis.

A P value of 0.05 or less was considered statistically significant. All statistical analyses were done with SPSS software (version 15.0).

RESULTS

Details on percutaneous drainage procedures

In the 41 patients undergoing percutaneous drainage in the step-up approach (2 underwent endoscopic drainage), drains were upsized in 4 patients and drains were replaced in 7 patients. The median drain size was 14 French (range 12-24). The median number of drains placed during the first or second drainage procedure was 1 (range 1-3). Multiple drains were placed during the same procedure in 7 patients.

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Supplementary Table. Total direct medical and indirect costs*					
	Minimally invasive step-up approach (N=43)		**Primary open necrosectomy (N=45)**		**Difference†**
	Total costs	**Mean cost per patient**	**Total costs**	**Mean costs per patient**	**Mean costs per patient (95% CI)**
During admission					
Hospital stay	965,294	22,449	988,503	21,967	-482 (-8,135 – 7,171)
ICU stay	1,247,952	29,022	1,326,387	29,475	453 (-20,850 – 21,756)
Necrosectomies (VARD or laparotomy)	84,258	1,960	173,472	3,855	1,896 (881 – 2910)
Other operations	46,623	1,084	113,628	2,525	1,441 (60 – 2823)
Drainage procedures (endoscopic and percutaneous)	33,348	776	13,592	302	-474 (-698 – -249)
Radiologic procedures (except drainage)	72,027	1,675	95,735	2,127	452 (-368 – 1272)
Endoscopic procedures (except drainage)	11,990	279	28,323	629	351 (-158 – 859)
Microbiology	35,503	826	54,521	1,212	386 (-85 – 857)
Medication	96,557	2,245	138,964	3,088	843 (-441 – 2126)
Absence from work	283,679	6,597	297,417	6,609	12 (-4428 – 4451)

During 6 months follow- up					
Visits to general practitioner	6,039	140	10,255	228	88 (13 – 162)
Visits to outpatient clinic	21,573	502	35,251	783	282 (55 – 508)
Readmissions to hospital	67,528	1,570	91,710	2,038	468 (-993 – 1,928)
Admission to rehabilitation center	145,325	3,380	162,808	3,618	238 (-4,495 – 4,972)
Admission to nursing home	53,066	1,234	133,215	2,960	1,726 (-1,275 – 4,727)
Operations	28,360	660	34,979	777	118 (-716 – 952)
Endoscopic procedures	6,915	161	10,850	241	80 (-271 – 432)
Diagnostic procedures	9,740	227	13,930	310	83 (-51 – 217)
Microbiology	1,155	27	513	11	-16 (-35 – 4)
Medication	4,368	102	12,602	280	179 (59 – 298)
Home care	7,122	166	6,301	140	-26 (-139 – 87)
Physiotherapy	7,939	185	11,080	246	62 (-104 – 228)
Aids	339	8	570	13	5 (-12 – 22)
Absence from work	152,302	3,542	283,038	6,290	2,748 (-1,444 – 6,940)
Total direct medical and indirect costs	3,387,335	78,775	4,032,648	89,614	10,839 (-23,878 – 45,556)

* Amounts are in Euro's, for conversion to US dollars multiply by 1,47.

† This is the difference in costs between primary open necrosectomy and the minimally invasive step-up approach.