Randomized clinical trial

Prospective randomized trial of preoperative enteral immunonutrition followed by elective total gastrectomy for gastric cancer

K. Fujitani[1], T. Tsujinaka[1], J. Fujita[4], I. Miyashiro[2], H. Imamura[5], Y. Kimura[3], K. Kobayashi[6], Y. Kurokawa[7], T. Shimokawa[8] and H. Furukawa[5], on behalf of the Osaka Gastrointestinal Cancer Chemotherapy Study Group

Departments of Surgery, [1]Osaka National Hospital, [2]Osaka Medical Centre for Cancer and Cardiovascular Disease and [3]Nippon Telegraph and Telephone Corporation West Osaka Hospital, Osaka, [4]Toyonaka Municipal Hospital, Toyonaka, [5]Sakai Municipal Hospital, Sakai, [6]Kinki Central Hospital of Mutual Aid Association of Public School Teachers, Itami, and [7]Osaka University Medical School, Suita, and [8]Graduate School of Medicine and Engineering, Yamanashi University, Yamanashi, Japan

Correspondence to: Dr T. Tsujinaka, Department of Surgery, Osaka National Hospital, 2-1-14 Hoenzaka, Chuo-ku, Osaka, Japan 540-0006 (e-mail: toshi@onh.go.jp)

Background: **Perioperative enteral immunonutrition is thought to reduce postoperative morbidity in patients undergoing major gastrointestinal surgery. This study assessed the clinical effects of preoperative enteral immunonutrition in well nourished patients with gastric cancer undergoing total gastrectomy.**

Methods: **Well nourished patients with primary gastric cancer, fit for total gastrectomy, were randomized to either a control group with regular diet, or an immunonutrition group that received regular diet supplemented with 1000 ml/day of immunonutrients for 5 consecutive days before surgery. The primary endpoint was the incidence of surgical-site infection (SSI). Secondary endpoints were rates of infectious complications, overall postoperative morbidity and C-reactive protein (CRP) levels on 3–4 days after surgery.**

Results: **Of 244 randomized patients, 117 were allocated to the control group and 127 received immunonutrition. SSIs occurred in 27 patients in the immunonutrition group and 23 patients in the control group (risk ratio (RR) 1·09, 95 per cent confidence interval 0·66 to 1·78). Infectious complications were observed in 30 patients in the immunonutrition group and 27 in the control group (RR 1·11, 0·59 to 2·08). The overall postoperative morbidity rate was 30·8 and 26·1 per cent respectively (RR 1·18, 0·78 to 1·78). The median CRP value was 11·8 mg/dl in the immunonutrition group and 9·2 mg/dl in the control group ($P = 0·113$).**

Conclusion: **Five-day preoperative enteral immunonutrition failed to demonstrate any clear advantage in terms of early clinical outcomes or modification of the systemic acute-phase response in well nourished patients with gastric cancer undergoing elective total gastrectomy. Registration number: ID 000000648 (University Hospital Medical Information Network (UMIN) database).**

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Introduction

Immunonutrition for surgical and critically ill patients, involving nutritional support with arginine, glutamine, ω-3 fatty acids and nucleotides (RNA) either alone or in combination, has been gaining increasing attention[1–4]. Immunonutrition modulates host immune systems and inflammatory responses. The ω-3 fatty acid eicosapentaenoic acid has immunomodulatory and anti-inflammatory properties. It replaces arachidonic acid, an ω-6 fatty acid, in cell membrane phospholipids, and becomes a substrate for the synthesis of the 3-series prostaglandins and the 5-series leukotrienes, which are less proinflammatory than arachidonic acid-derived 2-series and 4-series analogues respectively[5].

Numerous clinical studies on the effects of perioperative immunonutrition following surgery or trauma have shown beneficial effects, reducing postoperative morbidity after major abdominal surgery[6,7]. Before initiating the present

study the authors showed that 5 days of preoperative enteral immunonutrition with 1000 ml/day Impact® (Ajinomoto Pharmaceutical Company, Tokyo, Japan) could alter the cell membrane composition of peripheral blood mononuclear cells and change the ω-3 to ω-6 ratio in membrane phospholipids from 0·24 to 0·32 in patients undergoing elective abdominal major surgery for gastrointestinal cancer[8].

Surgical resection is the mainstay of curative treatment for gastric cancer. Total gastrectomy is associated with postoperative catabolism, and perturbations in the metabolic, endocrine, neuroendocrine and immune systems that contribute to high postoperative morbidity rates in more than 40 per cent of patients[9,10]. Immunonutrition seems a promising treatment option to modify metabolic and immune responses in such patients, reducing the incidence of postoperative complications and shortening hospital stay.

This prospective randomized clinical trial was undertaken to investigate the impact of preoperative enteral immunonutrition on the incidence of postoperative complications and C-reactive protein (CRP) values (as a marker of inflammatory response) in patients undergoing elective total gastrectomy for gastric cancer.

Methods

This study was conducted in accordance with the international ethical recommendations stated in the Declaration of Helsinki. Preoperative staging included chest X-ray, abdominal computed tomography and endoscopy within 4 weeks of entry into the trial, and full blood cell count, liver and renal function tests within 2 weeks before trial entry. Entry criteria were: histologically proven resectable primary gastric adenocarcinoma; fit for elective total gastrectomy with adequate bone marrow function (white blood cell (WBC) count 4000–12 000/mm^3, platelet count at least 100 000/mm^3, haemoglobin 8·0 g/dl or more), hepatic function (total bilirubin no more than 25·65 μmol/l, serum aminotransferases 100 units/l or less) and renal function (serum creatinine no more than the upper institutional limit); performance status 0 or 1 on the Eastern Cooperative Oncology Group scale; age no more than 80 years; bodyweight (BW) loss of 10 per cent or less within 6 months before entry; tolerance of oral feeding; no other severe medical conditions including insulin-dependent diabetes mellitus; no concurrent active infection; no known allergy to any of the ingredients of immunonutrition; no preoperative chemotherapy or radiotherapy; and provision of written informed consent. The study was approved by the institutional review and ethics board of each hospital involved and was registered in the University Hospital Medical Information Network (UMIN) database (ID 000000648).

Study design and enteral regimens

This study was designed to test the hypothesis that preoperative enteral immunonutrition given orally would reduce the incidence of postoperative infectious complications in a population of comparatively well nourished patients after elective total gastrectomy. Patients who met eligibility criteria were randomized into two groups, stratified by institution. Randomization was carried out by data centre staff using the minimization method, with an algorithm that balanced institution. The immunonutrition group received 1000 ml/day of preoperative oral supplementation in the form of an immunonutrient-enriched enteral feed (Impact®) added to normal diet for 5 consecutive days before surgery. The control group had access to a regular diet without any nutritional supplementation. The constituents of Impact® are shown in *Table 1*. Even when patients were unable to take the 1000 ml/day of Impact® orally, it was not administered via an enteral feeding tube. Antibiotic prophylaxis was given routinely at least 30 min before operation and repeated every 3 h during surgery. Postoperative wound management was according to each participating institution's standard.

Outcome measures

Surgical and non-surgical complications from surgery to hospital discharge were documented prospectively. The primary outcome was surgical-site infection (SSI). SSIs were categorized as superficial incisional, deep incisional, and organ or space SSI, as defined in the Centers for Disease Control guidelines[11]. Other complications analysed were abdominal abscess (collection of pus confirmed by percutaneous drainage), pancreatic fistula

Table 1 Composition of Impact®

	Amount (per 100 ml)
Energy (kcal)	101
Protein (g)	5·6
Fat (g)	2·8
Eicosapentaenoic acid (g)	0·20
Docosahexaenoic acid (g)	0·14
n-6 : *n*-3 ratio	4 : 5
Carbohydrate (g)	13·4
Arginine (g)	1·28
RNA (mg)	0·13

(drain output of any measurable volume of fluid on or after the third day after surgery, with an amylase content greater than three times the serum amylase level[12]), anastomotic leakage (positive contrast swallow test), wound infection (purulent exudate in the wound with positive bacterial culture), drain infection (purulent exudate around a percutaneous drainage tube), pneumonia (clinical signs of pneumonia with radiographic evidence and positive sputum culture or bronchoalveolar lavage), venous catheter infection (local signs of inflammation or the isolation of pathogenic organisms in culture), bleeding (need for blood transfusion of at least 2 units), respiratory failure (presence of dyspnoea and respiratory rate over 35 breaths/min or arterial partial pressure of oxygen less than 70 mmHg), pleural effusion, heart failure (unstable blood pressure requiring use of additional intravenous fluids or cardiac stimulants) and ileus.

Systemic inflammatory response syndrome (SIRS) was diagnosed as the clinical manifestation of two or more of the following features in the first week after operation: temperature exceeding 38°C or less than 36°C; heart rate more than 90 beats/min; respiratory rate over 20 breaths/min or arterial partial pressure of carbon dioxide less than 32 mmHg; WBC count over 12 000/mm^3, less than 4000/mm^3 or more than 10 per cent immature (band) forms.

Serum levels of CRP were measured on day 3 or 4 after surgery. The prognostic nutritional index (PNI) was calculated as 10 × albumin (g/dl) + 0·005 × lymphocyte counts (per mm^3), based on albumin levels measured within 2 weeks before trial entry.

Statistical analysis

This study was designed as a multi-institutional prospective randomized clinical trial. The primary endpoint was the incidence of SSI. Secondary objectives were rates of postoperative infectious complications, overall morbidity and highest CRP value on day 3 or 4 after surgery. A *post hoc* subgroup analysis was performed to explore the effects of preoperative nutritional intervention according to the baseline clinical and nutritional status of the patients. Based on an overall rate of SSI following gastrectomy of between 9 and 21 per cent[13–16] and an estimated 10 per cent decrease in the incidence of SSI (5 per cent in the immunonutrition group *versus* 15 per cent in the control group), with a power of 0·80 and a two-sided α of 0·05, it was calculated that the trial required 120 patients in each treatment group.

The χ^2 test or Fisher's exact test was used to compare categorical variables. The Wilcoxon signed-rank test was used for data that were not normally distributed. All statistical tests were two-sided, and $P < 0{\cdot}050$ was

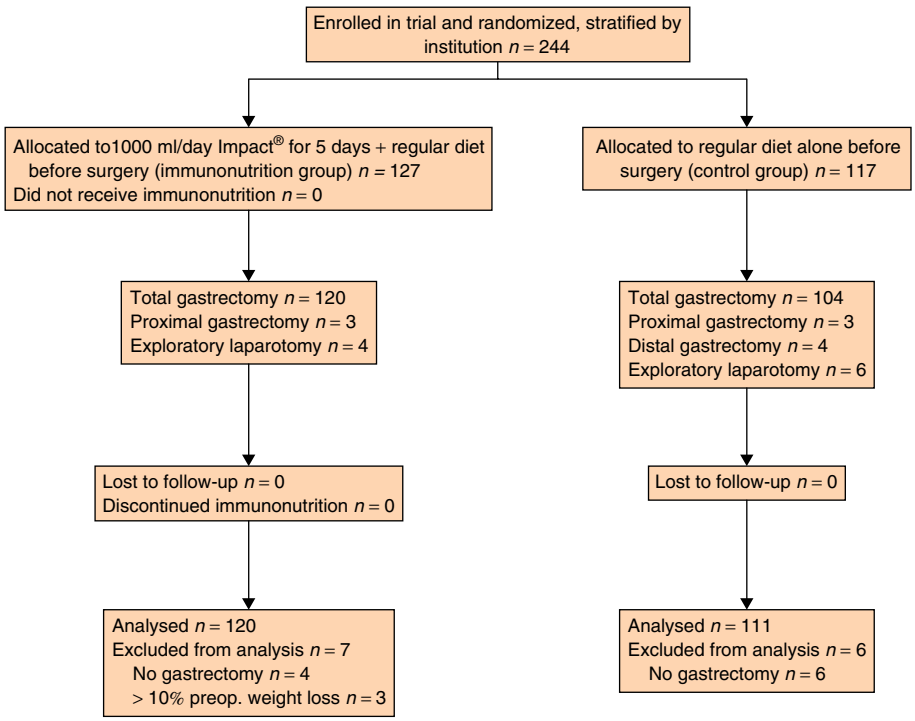

Fig. 1 CONSORT diagram for the trial

Table 2 Clinical and nutritional characteristics

	Immunonutrition ($n = 127$)	Control ($n = 117$)	P†
Age (years)*	64 (26–78)	65 (30–79)	0·323‡
Sex ratio (M : F)	97 : 30	84 : 33	0·465§
Weight (kg)*	60·9 (38·0–97·0)	60·0 (40·1–92·2)	0·182‡
Body mass index (kg/m^2)*	22·8 (15·1–33·8)	22·6 (17·8–33·1)	0·780‡
Weight loss (%)*	0 (0–16·9)	0 (0–10·0)	0·780‡
Nutritional status			0·372§
Well nourished	123 (96·9)	116 (99·1)	
Malnourished	4 (3·1)	1 (0·9)	
Albumin (g/dl)*	4·2 (2·5–4·8)	4·1 (2·4–5·3)	0·447‡
Total lymphocyte count (/mm^3)*	1880 (800–5952)	1765 (700–4446)	0·248‡
CRP (mg/dl)*	0·1 (0–7·2)	0·1 (0–10·3)	0·818‡
Type of surgery			0·155
Total gastrectomy	120 (94·5)	104 (88·9)	
Proximal gastrectomy	3 (2·4)	3 (2·6)	
Distal gastrectomy	0 (0)	4 (3·4)	
Exploratory laparotomy	4 (3·1)	6 (5·1)	
Node dissection			0·223
D0	1 (0·8)	3 (2·7)	
D1	22 (17·9)	20 (18·0)	
D2	100 (81·3)	85 (76·6)	
D3	0 (0)	3 (2·7)	
Combined resection			0·179
Gallbladder	80 (65·0)	77 (69·4)	
Spleen	42 (34·1)	23 (20·7)	
Pancreas	3 (2·4)	5 (4·5)	
Transverse colon	4 (3·3)	2 (1·8)	
Pathological characteristics	$n = 123$	$n = 111$	
Tumour status			0·349
T1	44 (35·8)	42 (37·8)	
T2	36 (29·3)	37 (33·3)	
T3	38 (30·9)	24 (21·6)	
T4	5 (4·1)	8 (7·2)	
Node status			0·382
N0	58 (47·2)	61 (55·0)	
N1	35 (28·5)	24 (21·6)	
N2	29 (23·6)	23 (20·7)	
N3	1 (0·8)	3 (2·7)	
Resection type			0·138§
R0	111 (90·2)	106 (95·5)	
R1–2	12 (9·8)	5 (4·5)	

Values in parentheses are percentages unless indicated otherwise; *values are median (range). General nutritional status at baseline was diagnosed on subjective global assessment. CRP, C-reactive protein. †χ^2 test, except ‡Wilcoxon signed-rank test and §Fisher's exact test.

considered significant. Statistical analysis was performed with SPSS® version 14 (SPSS, Chicago, Illinois, USA).

Results

Between 16 February 2006 and 25 December 2009, 244 patients were recruited and randomized to immunonutrition (127) or control (117) groups (*Fig. 1*). Three patients with more than 10 per cent preoperative BW loss were incorrectly randomized to the immunonutrition group and excluded from the analysis. No patient was withdrawn from the study.

The clinical and nutritional characteristics of the groups are shown in *Table 2*. They were well matched for age, sex, BW, extent of BW loss within the 3 months before surgery, body mass index (BMI), general nutritional status at baseline, preoperative albumin level, total lymphocyte count and CRP level. Most patients in both groups were well nourished. Twenty-one patients in the immunonutrition group and 13 in the control group were mildly malnourished based on 5·1–10·0 per cent preoperative BW loss.

Two hundred and twenty-four patients underwent total gastrectomy, six proximal gastrectomy, four distal gastrectomy and ten had exploratory laparotomy alone

Table 3 Endpoints according to treatment

	Immunonutrition ($n = 120$)	Control ($n = 111$)	Risk ratio*
Surgical-site infection	27 (22·5)	23 (20·7)	1·09 (0·66,1·78)
Superficial incisional	8 (6·7)	7 (6·3)	
Deep incisional	5 (4·2)	1 (0·9)	
Organ or space	17 (14·2)	15 (13·5)	
Infectious complication	30 (25·0)	27 (24·3)	1·11 (0·59, 2·08)
Any complication	37 (30·8)	29 (26·1)	1·18 (0·78, 1·78)
CRP value on day 3 or 4 (mg/dl)†	11·8 (2·3–38·1)§	9·2 (1·1–38·9)	

Values in parentheses are percentages unless indicated otherwise; *values in parentheses are 95 per cent confidence intervals; †values are median (range). Infectious complications include abdominal abscess, infectious pancreatic fistula, anastomotic leakage, wound infection, drain infection, pneumonia and venous catheter infection. CRP, C-reactive protein. §$P = 0·113$ *versus* control (Wilcoxon signed-rank test).

owing to unresectable disease. There were no significant differences between the groups in terms of the surgical procedure, including extent of lymph node dissection, degree of combined resection, or pathological tumour or node status according to the classification of the Japanese Gastric Cancer Association[17].

Even when patients were unable to take the 1000 ml/day of Impact® orally, it was not administered via an enteral feeding tube. No patient received parenteral nutrition before surgery. Compliance with oral Impact® was 91·7, 95·2, 96·6, 96·6 and 92·3 per cent of planned volume over the 5 days before surgery, with an overall rate of 94·5 per cent.

Outcomes were measured in 231 patients, excluding ten patients who had exploratory laparotomy alone and three with more than 10 per cent preoperative BW loss who did not fulfil the entry criteria. SSI occurred in 27 patients (22·5 per cent) in the immunonutrition group and 23 (20·7 per cent) in the control group (risk ratio (RR) 1·09; 95 per cent confidence interval 0·66 to 1·78) (*Table 3*). Infectious complications occurred in 30 patients (25·0 per cent) in the immunonutrition group and 27 (24·3 per cent) in the control group (RR 1·11, 0·59 to 2·08). The overall postoperative morbidity rate was 30·8 per cent (37 patients) and 26·1 per cent (29 patients) respectively (RR 1·18, 0·78 to 1·78). The median CRP value on day 3 or 4 after surgery was 11·8 mg/dl in the immunonutrition group and 9·2 mg/dl in the control group ($P = 0·113$).

Postoperative complications are detailed in *Table 4*. There were no differences in the incidence of abdominal abscess, pancreatic fistula, anastomotic leakage and wound infection or dehiscence between the groups. No significant differences between the groups were found with respect to other postoperative complications or SIRS. There were no reoperations or in-hospital deaths, and median hospital stays were similar.

Table 4 Operative morbidity and mortality

	Immunonutrition ($n = 120$)	Control ($n = 111$)	P†
Any complication	37 (30·8)	29 (26·1)	0·468
Abdominal abscess	11 (9·2)	7 (6·3)	0·469
Pancreatic fistula	8 (6·7)	7 (6·3)	1·000
Anastomotic leakage	3 (2·5)	3 (2·7)	1·000
Wound infection or dehiscence	13 (10·8)	8 (7·2)	0·369
Drain infection	3 (2·5)	1 (0·9)	0·623
Pneumonia	5 (4·2)	0 (0)	0·061
Venous catheter infection	2 (1·7)	1 (0·9)	1·000
Pleural effusion	1 (0·8)	1 (0·9)	1·000
Postoperative bleeding	3 (2·5)	0 (0)	0·248
Ileus	2 (1·7)	1 (0·9)	1·000
SIRS	46 (38·3)	34 (30·6)	0·268
Reoperation	0 (0)	0 (0)	
Hospital death	0 (0)	0 (0)	
Hospital stay (days)*	18 (9–85)	17 (10–88)	0·395‡

Values in parentheses are percentages unless indicated otherwise; *values are median (range). SIRS, systemic inflammatory response syndrome. †Fisher's exact test, except ‡Wilcoxon signed-rank test.

When patients were divided into subgroups based on BW loss (less than 5 per cent *versus* 5 per cent or more), BMI (less than 25 kg/m^2 *versus* 25 kg/m^2 or more), CRP (under 0·2 mg/dl *versus* at least 0·2 mg/dl), albumin (below 4·0 g/dl *versus* 4·0 g/dl or over) and prognostic nutritional index (less than 50 *versus* 50 or more) as indicators of malnutrition, a significant interaction was found between treatment effect and preoperative BW loss (*Fig. 2*). Among 34 patients with at least 5 per cent BW loss in the 3 months before surgery, SSI occurred in 10 of 21 patients in the immunonutrition group and 11 of 13 in the control group. The RR for SSI in the immunonutrition group was 0·56 (0·34 to 0·93; $P = 0·031$). Contrary to the favourable effect of immunonutrition in patients with BW loss of at least 5 per cent, preoperative nutritional intervention seemed unfavourable in patients with a BMI of 25 kg/m^2 or more (RR 2·86, 0·68 to 12·12; $P = 0·149$).

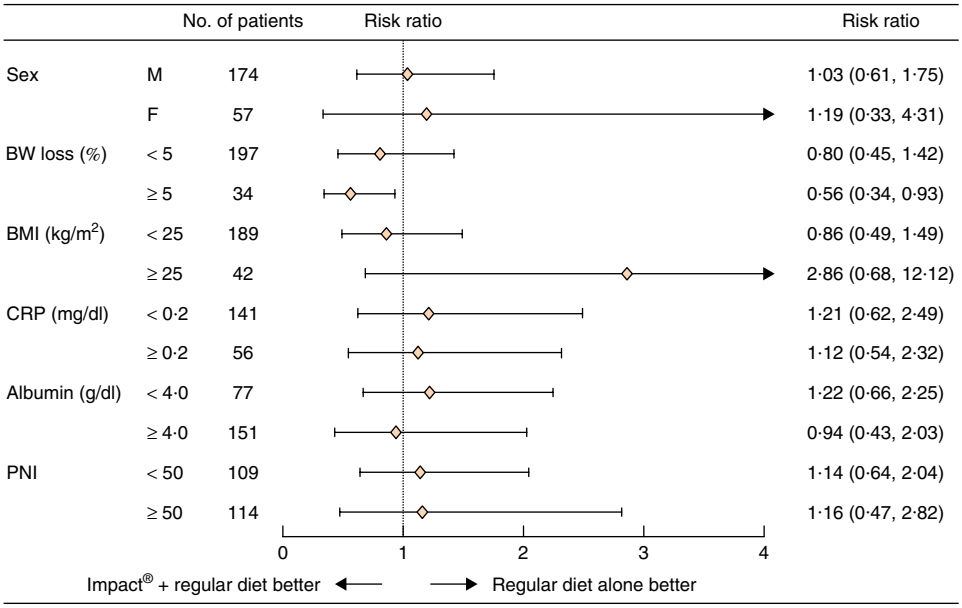

Fig. 2 Effect of enteral nutrition on risk of development of surgical-site infection, in relation to clinical and nutritional characteristics. BW, bodyweight; BMI, body mass index; CRP, C-reactive protein; PNI, prognostic nutritional index

Discussion

The primary goal of nutritional care has changed from the provision of necessary calories to cover a patient's needs to approaches aimed at restoring optimal metabolic and immune responses. Dietary components, such as arginine, glutamine, ω-3 fatty acids and nucleotides, have been shown to provide beneficial effects beyond their nutritional value. Immunomodulatory formulas supplemented with such components have gained increasing attention because of their ability to reduce the rate of postoperative complications compared with standard nutritional formulas[1–4].

Some authors, however, have questioned the importance of immunonutrition[2,18] because perioperative nutritional support reduces the rate of postoperative complications only in selected populations, such as severely malnourished patients and those undergoing major surgical procedures such as oesophagectomy and pancreatectomy[7,19,20]. Although evidence-based guidelines recommend preoperative nutritional intervention for 7–14 days in moderately or severely malnourished patients undergoing major gastrointestinal surgery[21,22], the benefits of nutritional support in well nourished subjects are controversial. This uncertainty regarding the routine use of immunonutrition might be attributed to the heterogeneity of individual studies with regard to definitions of malnutrition and the incidence of malnutrition and other co-morbidities[23,24], as well as inadequate numbers of patients in previous trials. The present study was therefore undertaken to overcome some of these inconsistencies.

Despite adequate patient compliance with Impact®, there were no significant differences in any clinical outcomes between the immunonutrition and control groups. A clear effect of immunonutrition on the systemic acute-phase response to major surgery was absent. Klek and colleagues[25] also failed to demonstrate any clear advantage for routine postoperative immunonutrition, whether enteral or parenteral, in well nourished patients undergoing elective upper gastrointestinal surgery. Heslin and co-workers[26] reported that early postoperative enteral immunonutrition did not reduce rates of postoperative complications or length of hospital stay after upper gastrointestinal surgery for malignancy compared with intravenous crystalloid therapy.

Contrary to these findings, a recent meta-analysis of 13 randomized trials involving 1269 patients demonstrated that perioperative immunonutrition significantly reduced rates of postoperative infection, shortened hospital stay and improved various parameters of immune function in patients undergoing gastrointestinal surgery[4]. Nearly all of these trials, however, involved patients with various degrees of malnutrition, and the proportion of malnourished patients with more 10 per cent weight loss from their preillness BW reached almost 60 per cent in some studies[6,27–32]. It is not clear whether the benefits reported in the meta-analysis by Zheng *et al*.[4] could be generalized

to well nourished patients. In addition, when patients undergoing upper gastrointestinal surgery were stratified by BMI before randomization to minimize the impact of nutritional status on outcomes, patients on immunomodulatory enteral diets had similar rates of postoperative complications to those on standard enteral diets[18]. Taken together with the present findings, well nourished patients undergoing upper gastrointestinal surgery seem unlikely to benefit from immunonutrition, whether administered before or after surgery.

In the present study preoperative immunonutrition significantly decreased the risk of SSI in patients who had at least 5 per cent preoperative BW loss within the 3 months before surgery. This seems to confirm the effectiveness of perioperative immunonutrition in moderate or severely malnourished patients undergoing major gastrointestinal surgery reported elsewhere[4,21,22]. Although immunonutrition appeared to be beneficial in patients with at least 5 per cent BW loss, it seemed unfavourable in those with a BMI of 25 kg/m^2 or more. However, it is acknowledged that BMI has been shown to be an independent risk factor for the development of postoperative surgical complications in patients undergoing gastrectomy[33–35].

Differences in the outcomes of immunonutrition between well nourished and malnourished surgical patients may be attributed to the impact of surgical stress on immune function, which may be much smaller in the former population[24]. Severity of risk associated with surgery or trauma and nutritional status are therefore likely to be key elements affecting the efficacy of immune-enhancing diets.

Uncertainty over the use of enteral immunonutrition can also be attributed to the considerable heterogeneity of individual studies in terms of the timing, duration and composition of nutritional intervention[2,24,27,28,31,32,36,37]. As it is reasonable to assume that immunonutrients should reach suitable tissue and plasma concentrations to exert their maximum effects, preoperative feeding seems logical to achieve this goal in the early postoperative period. Although there is no clear evidence about the exact length of the optimum preoperative feeding period, 5–7 days is commonly used[6,36,38–40].

Regarding the composition of immunomodulatory formulations, a number of studies have been conducted with Impact®[6,26–32]. There are no adequate clinical trials comparing various immune-enhancing formulas. It is not possible to estimate how differences in composition could affect results.

Routine preoperative use of immunonutrition in well nourished patients having gastric cancer resections cannot be recommended.

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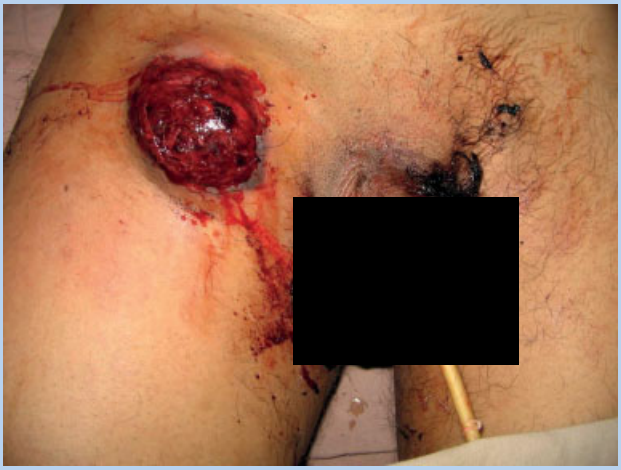
Snapshot Quiz 12/08

Question: A 24-year-old male intravenous drug user presented with this lesion on his right thigh. What is the most likely diagnosis? How this condition is treated?



The answer to the above question is found on p. 636 of this issue of *BJS*.

Qureshi AU: South Surgical Unit, Mayo Hospital, Lahore 54700, Pakistan (e-mail: ahmed_uzairq@hotmail.com)

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