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Intraoperative versus extended antimicrobial prophylaxis after gastric cancer surgery: a phase 3, open-label, randomised controlled, non-inferiority trial

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Summary

Background Although evidence for the efficacy of postoperative antimicrobial prophylaxis is scarce, many patients routinely receive such treatment after major surgeries. We aimed to compare the incidence of surgical-site infections with intraoperative antimicrobial prophylaxis alone versus intraoperative plus postoperative administration.

Methods We did a prospective, open-label, phase 3, randomised study at seven hospitals in Japan. Patients with gastric cancer that was potentially curable with a distal gastrectomy were randomly assigned (1:1) to receive either intraoperative antimicrobial prophylaxis alone (cefazolin 1 g before the surgical incision and every 3 h as intraoperative supplements) or extended antimicrobial prophylaxis (intraoperative administration plus cefazolin 1 g once after closure and twice daily for 2 postoperative days). Randomisation was stratified using Pocock and Simon's minimisation method for institution and American Society of Anesthesiologists scores, and Mersenne twister was used for random number generation. The primary endpoint was the incidence of surgical-site infections. We assessed non-inferiority of intraoperative therapy with a margin of 5%. Analysis was by intention-to-treat. During hospital stay, infection-control personnel assessed patients for infection, and the principal surgeons were required to check for surgical-site infections at outpatient clinics until 30 days after surgery. This study is registered with UMIN-CTR, UMIN000000631.

Findings Between June 2, 2005, and Dec 6, 2007, 355 patients were randomly assigned to receive either intraoperative antimicrobial prophylaxis alone (n=176) or extended antimicrobial prophylaxis (n=179). Eight patients (5%, 95% CI 2–9%) had surgical-site infections in the intraoperative group compared with 16 (9%, 5–14) in the extended group. The relative risk of surgical-site infections with intraoperative antimicrobial prophylaxis was 0·51 (0·22–1·16), which revealed statistically significant non-inferiority ($p<0·0001$).

Interpretation Elimination of postoperative antimicrobial prophylaxis did not increase the incidence of surgical-site infections after a gastrectomy. Therefore, this treatment is not recommended after gastric cancer surgery.

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Introduction

The Centers for Disease Control and Prevention in the USA has issued guidelines that recommend administration of a first-generation cephalosporin for intraoperative antimicrobial prophylaxis to prevent surgical site infections in clean or clean-contaminated operations.[1] This treatment is usually given within 30 min of the first surgical incision, with supplementary treatments every 3 h or 4 h throughout the operation.[2] Results of a large-scale national cohort study in the USA showed that only 14·5% of 32 603 patients who had major surgery had discontinued antimicrobial prophylaxis within 12 h after the surgery ended and that 26·7% of patients were still receiving this treatment at 48 h after surgery.[3] Furthermore, a questionnaire administered to 3823 Japanese surgeons showed that 56·4% of them gave antimicrobial prophylaxis in clean-contaminated operations until 3–4 days after surgery, whereas only 2·4% of surgeons gave the treatment for 24 h or less after surgery ended.[4] Because of a high prevalence of drain use in gastrointestinal surgery in Japan and the potential risk of surgical-site infections, the Japanese Association for Infectious Diseases and the Japanese Society of Chemotherapy developed guidelines that recommend postoperative antimicrobial prophylaxis for 1–3 days after gastrointestinal surgery.[5] However, postoperative antimicrobial prophylaxis is controversial because evidence for its efficacy is scarce.

Gastric cancer is the third leading cause of cancer deaths worldwide and the most common in eastern Asia. Surgery for gastric cancer is usually accompanied by extended lymph node dissection, known as a D2 lymphadenectomy.[6] The Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG) did a preliminary multicentre phase 2 trial (OGSG0202)[7] to examine the clinical outcomes when postoperative antimicrobial prophylaxis is not given to patients with gastric cancer. 56 patients who were scheduled to have a distal gastrectomy were registered in this study. Cefazolin was given 30 min before the skin incision and every 3 h during the operation without postoperative antimicrobial prophylaxis. Surgical-site infections were recorded in three patients (5·4%), which was similar to the prevalence in historical controls who had received postoperative antimicrobial prophylaxis (6·7%).[7] After the

phase 2 trial, we designed this multicentre, randomised, phase 3 trial (OGSG0501) to assess non-inferiority of the omission of postoperative antimicrobial prophylaxis in patients with gastric cancer.

Methods

Patients

We enrolled patients who had histologically proven gastric adenocarcinoma that was deemed curable with a distal gastrectomy. Patients were also required to have an American Society of Anesthesiologists (ASA) score of 1 or 2. Patients were excluded from the study if they had an active or uncontrolled infection, received neoadjuvant chemotherapy, or had been given steroids. Seven institutions of the OGSG in Japan participated in the trial. The study protocol was approved by the OGSG Steering Committee and the institutional review boards of all of the participating hospitals. All patients provided written informed consent before randomisation. This study was registered with UMIN-CTR,UMIN000000631.

For the **UMIN-CTR database** see http://www.umin.ac.jp/ctr/

***Panel 1:* Definitions of surgical-site infections[1]**

Superficial incisional

Infection occurs within 30 days after the operation and involves only skin or subcutaneous tissue of the incision and at least one of the following:

- purulent drainage, with or without laboratory confirmation, from the superficial incision;
- organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision;
- at least one of the following signs or symptoms of infection: pain or tenderness, localised swelling, redness or heat, and superficial incision is deliberately opened by surgeon, unless incision is culture-negative.

Deep incisional

Infection occurs within 30 days after the operation if no implant is left in place or within 1 year if implant is in place and the infection seems to be related to the operation. The infection involves deep soft tissues (eg, fascial and muscle layers) of the incision and at least one of the following:

- purulent drainage from the deep incision but not from the organ or space component of the surgical site;
- a deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38°C), localised pain, or tenderness, unless site is culture-negative;
- an abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathological or radiological examination.

Organ or space

Infection occurs within 30 days after the operation if no implant is left in place or within 1 year if implant is in place and the infection seems to be related to the operation. The infection involves any part of the anatomy (eg, organs or spaces), other than the incision, which was opened or manipulated during an operation and at least one of the following:

- purulent drainage from a drain that is placed through a stab wound into the organ or space;
- organisms isolated from an aseptically obtained culture of fluid or tissue in the organ or space;
- an abscess or other evidence of infection involving the organ or space that is found on direct examination, during reoperation, or by histopathological or radiological examination.

Randomisation and masking

After confirming the eligibility of patients during surgery, surgeons contacted the OGSG data centre by telephone to receive a randomly generated assignment (1:1) placing the patients in one of the treatment groups. We used Pocock and Simon's minimisation method to stratify treatment groups according to institution and ASA scores, and Mersenne twister for random number generation.[8] The surgeon gave the assigned treatment. Interventions were not masked. The OGSG data centre was responsible for assigning the intervention, data management, central monitoring, and statistical analyses.

Procedures

For both groups, the surgeon did distal gastrectomies and lymphadenectomies according to Japanese Gastric Cancer Treatment Guidelines.[9] In short, D1 lymphadenectomy plus suprapancreatic node dissection (D1+β dissection) was done for patients with cT1 tumours, whereas D2 lymphadenectomy was done for patients with cT2–4 tumours. The reconstruction method and the surgical approach (open or laparoscopic) were not prespecified.

1 g of cefazolin was given 30 min after anaesthesia, and an additional dose was given every 3 h during surgery. For the extended antimicrobial prophylaxis group, 1 g of cefazolin was given on postoperative day 0 (at night) and every 12 h until postoperative day 2 (2 g per day for 2 postoperative days). Care before and after surgery and wound management were done according to respective institutional standards.

Operative methods and pathology results were recorded according to the 13th edition of the Japanese Classification of Gastric Carcinoma.[10] The prognostic nutritional index was calculated as: $0{\cdot}005 \times$ lymphocyte count (cells per μL) $+ 10 \times$ serum albumin (g/dL).[11] Infection control personnel monitored and detected surgical-site infections during the patient's hospital stay. Principal surgeons were required to check for the presence or absence of surgical-site infections at outpatient clinics until 30 days after surgery. The Centers for Disease Control and Prevention's National Nosocomial Infection Surveillance system was used to diagnose surgical-site infections (panel 1),[1] which were classified as superficial incisional, deep incisional, and organ or space.

Statistical analysis

The primary endpoint was the incidence of surgical-site infections. Secondary endpoints were the incidence of infection at remote sites, the incidence of fever higher than 38°C, body temperature on postoperative day 3, duration of hospital stay after surgery, and severe adverse reactions to antimicrobial prophylaxis.

We intended to recruit 342 patients with a power of 80% for the Dunnet–Gent test at a one-sided α of 0·05 to show non-inferiority of incidence of surgical-site infections. This allowed us to detect a non-inferiority margin of 5% for incidence of surgical-site infections in the intraoperative antimicrobial prophylaxis group with an estimation of a 6·7% incidence of these infections in the extended treatment group. The projected accrual period was 3 years, and no interim analysis was planned.

For secondary endpoints, we compared binary variables with Fisher's exact test, and continuous variables with the Mann-Whitney *U* test. Logistic regression analysis was done to adjust for potential confounding factors, including age, sex, lymphadenectomy, reconstruction method, postoperative cancer stage, body-mass index, prognostic nutritional index, and transfusions. Nine subgroups were also analysed with logistic regression to assess statistical interactions between the treatment and various subgroups. Because of the exploratory nature of subgroup comparisons, test results are reported without multiplicity adjustment of type I error.

Because the study was designed to use a one-sided test, we present one-sided p values for the primary analysis results of the non-inferiority test of surgical-site infections. Two-sided p values were calculated for all other tests. All p values less than 0·05 were judged to be statistically significant. Analysis was by intention-to-treat. Statistical analyses were done with SPSS version 17.0 and R version 2.12.2.

Role of the funding source

This study was funded by OGSG, which is a non-profit organisation established to develop cancer treatment. The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between June 2, 2005, and Dec 6, 2007, 355 patients from seven hospitals were randomly assigned: 176 to receive intraoperative antimicrobial prophylaxis, and 179 to the extended antimicrobial prophylaxis group (figure 1). Two patients underwent a total gastrectomy because they had a positive resection margin, and one had palliative bypass surgery with gastrointestinal anastomosis. All patients received all planned antimicrobial doses and were monitored during their hospital stay and until 30 days after surgery. No severe adverse reactions to antimicrobial prophylaxis occurred in either group.

The patients' characteristics in the two groups were well balanced (table 1). Median body-mass index and median prognostic nutritional index were much the same between the two groups. About 60% of patients in both groups had early (T1) gastric cancer. A D2 or more extended lymphadenectomy was done in 123 patients assigned to the intraoperative antimicrobial prophylaxis group (70%) and in 120 patients assigned to the extended antimicrobial prophylaxis group (67%). The between-group differences in median operation time was 9 min and in median blood loss was 10 mL. 14 patients had laparoscopy-assisted distal gastrectomy.

24 patients had surgical-site infections (table 2), all of whom had undergone distal gastrectomy without protocol violation. The incidence of surgical-site infections was 5% (95% CI 2–9%) in the intraoperative antimicrobial prophylaxis group compared with 9% (5–14%) in the extended antimicrobial prophylaxis group. Intraoperative administration was non-inferior to postoperative treatment (one-sided p<0·0001). On the basis of a multiple logistic regression analysis, the odds ratios (ORs) for surgical-site infections with intraoperative antimicrobial prophylaxis was 0·49 (95% CI 0·20–1·16) before and 0·55 (0·21–1·45) after adjusting for eight variables (age, sex, lymphadenectomy, reconstruction method, postoperative cancer stage, body-mass index, prognostic nutritional index, and transfusions).

Most surgical-site infections involved organ or space, and no deep incisional infections arose (table 2).

We assessed statistical interactions between the treatment effects and patient characteristics, including body-mass index, prognostic nutritional index, and operation time (figure 2). No subgroups showed a decrease in the incidence of surgical-site infections with extended antimicrobial prophylaxis. The OR for surgical site infections with intraoperative antimicrobial prophylaxis was 0·31 (95% CI 0·099–0·998; p=0·050) for patients who were not overweight (body-mass index <25)

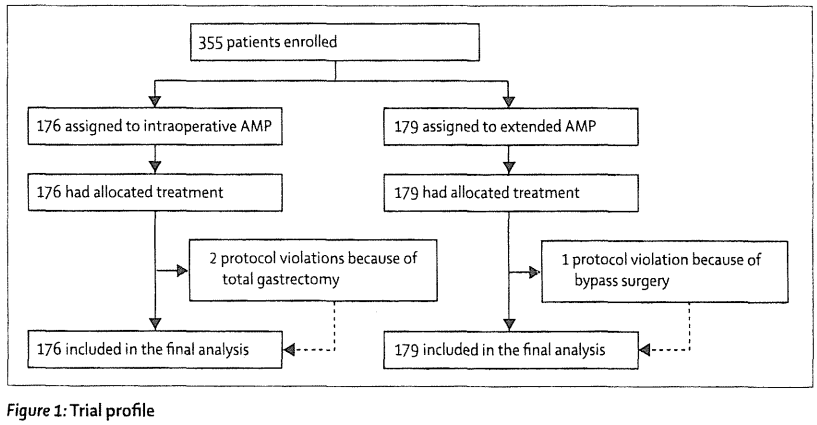

Figure 1: **Trial profile**
AMP=antimicrobial prophylaxis.

	Intraoperative AMP (n=176)	Extended AMP (n=179)
Age (years)	66 (36–84)	65 (35–84)
Sex		
Male	115	125
Female	61	54
Lymphadenectomy		
D1*	53	59
D2–3	123	120
Reconstruction method		
Billroth-I	83	103
Billroth-II	3	1
Roux-Y	90	75
pT stage		
T1	104	111
T2	46	42
T3–4	26	26
pN stage		
N0	114	122
N1	38	36
N2–3	24	21
Body-mass index	22·3 (16·3–33·0)	22·5 (12·4–32·9)
Prognostic nutrition index†	51·1 (25·1–68·9)	51·7 (26·6–66·0)
Approach		
Open	169	172
Laparoscopic	7	7
Anastomotic method		
Hand-sewn	21	34
Autosuture	119	119
Mixed	36	26
Drainage tube		
Yes	157	153
No	19	26
Operation time (min)	209 (58–428)	200 (64–415)
Blood loss (mL)	200 (1–880)	210 (1–1700)
Transfusion		
Yes	0	4
No	176	175

Data are number or median (range). AMP=antimicrobial prophylaxis. pT=primary tumour. pN=lymph node status. *One patient in the extended AMP group who underwent palliative bypass surgery was included in D1. †Data from 28 patients in the intraoperative AMP group and 23 patients in the extended AMP group are missing.

Table 1: **Characteristics of patients**

	Intraoperative AMP (n=176)	Extended AMP (n=179)	Relative risk (95% CI)	p value*
Surgical-site infections	8 (5%)	16 (9%)	0·51 (0·22–1·16)	0·138
Superficial incisional	1 (<1%)	5 (3%)	..	0·215
Deep incisional	0	0	..	..
Organ or space	7 (4%)	11 (6%)	..	0·469
With anastomotic leakage	1	4	..	..
Without anastomotic leakage	6	7	..	..

AMP=antimicrobial prophylaxis. *Two-sided p value for superiority test.

Table 2: **Incidence of surgical-site infections**

and 1·09 (0·25–4·72; 0·91) for patients who were overweight (body-mass index ≥25).

All secondary endpoints were compared between the intraoperative antimicrobial prophylaxis group and extended administration group (table 3). The incidence of remote site infections was 5% (95% CI 2–10) with intraoperative antimicrobial prophylaxis and 3% (1–7) with extended treatment. For remote site infections, two patients had pneumonia or bronchitis and one patient had a urinary tract infection in each group. The incidence of fever higher than 38°C was 34% (27·1–41·6) and 29% (22·5–36·3) in the intraoperative and extended groups, respectively. Median body temperature on postoperative day 3 was about 37°C in both groups and median duration of hospital stay was 12 days with both treatments.

Discussion

Omitting postoperative antimicrobial prophylaxis does not increase the incidence of surgical-site infections in patients with gastric cancer. Extended antimicrobial prophylaxis is associated with greater costs than intraoperative treatment alone because of the use of unnecessary drugs and might increase the risk of adverse drug reactions. Additionally, shortening of the antimicrobial prophylaxis period could help prevent the emergence of resistant strains.[12,13] For these reasons, we do not recommend antimicrobial prophylaxis after gastric cancer surgery.

In a US study, about 60% of patients who had had major surgery were still receiving antimicrobial prophylaxis at 24 h after surgery.[3] Results of a survey of 14 high-volume hospitals in South Korea and Japan showed that at 11 institutions antimicrobial prophylaxis was routinely given for longer than 24 h.[14] Although the national surgical infection prevention guidelines in the USA recommend that this treatment should be discontinued within 24 h of surgery,[15] this approach has not yet been adopted worldwide, because the recommendation is not based on clear evidence. Previously, the standard surgical treatment for gastric cancer was extended D2 lymphadenectomy in eastern Asia,[6,16] but was limited to D0 or D1 lymphadenectomy in the USA and Europe.[17,18] However, in 2010, the European Society for Medical Oncology guidelines for gastric cancer[19] were revised and they now recommend an extended D2 lymphadenectomy as the standard procedure, as in Japanese guidelines. Furthermore, in the latest version (2.2011) of the National Comprehensive Cancer Network Guidelines for gastric cancer, an extended D2 lymphadenectomy was recommended in the USA.[20] Therefore, the question of the appropriate length of antimicrobial prophylaxis after an extended D2 gastrectomy is relevant worldwide.

Mohri and colleagues[21] reported that the incidence of surgical-site infection in gastric cancer surgery was much the same (9·5% *vs* 8·6%) for single-dose and multiple-dose antimicrobial prophylaxis, although their study did not fix the type of surgery and the antibiotics to a single

drug (panel 2). Other retrospective studies have reported incidences of surgical-site infections of 8–12% after a gastrectomy.[23,24] In our phase 3 study, the overall incidence of these infections was 5% in the intraoperative antimicrobial prophylaxis group, which was much the same as the incidence in our previous phase 2 trial (5·4%). The Japanese health system is a suitable setting in which to assess the frequency of surgical-site infections because Japanese institutions allow a long hospital stay after surgery. The median length hospital stay after surgery was 12 days in each group, which enabled infection control personnel to accurately assess the incidence of surgical-site infections for almost half of the follow-up period. Our study required the principal surgeons to check for the presence or absence of surgical-site infections at outpatient clinics until 30 days after surgery. Systematic measurement instruments, which are independent of principal investigators, often result in an underestimation of the incidence of surgical-site infections.[25] Therefore, our results are likely to be an accurate assessment of the frequency of surgical-site infections after a distal gastrectomy.

Several factors such as obesity, malnutrition, transfusions, and operation time increase the incidence of surgical-site infections.[23,26–29] In this study, body-mass index, prognostic nutritional index, and operation time were much the same between the two groups. However, the number of patients who required a transfusion differed between the two groups (none in the intraoperative group and four in the extended group). Of the four patients who received a transfusion, one had an organ or space surgical-site infection after the gastrectomy, which might have led to the unexpected result that the incidence of surgical-site infections was higher in the extended antimicrobial prophylaxis group than in the intraoperative administration group. However, after adjusting for all the potential confounding factors including transfusions by a multivariate analysis, the OR for surgical-site infection with intraoperative antimicrobial prophylaxis was essentially unchanged (0·49 before adjustment *vs* 0·55 after adjustment). An Italian small-scale randomised study[22] that included patients with gastric cancer and colorectal cancer reported that the incidence of surgical-site infections was 16·1% in the intraoperative antimicrobial prophylaxis group and 44·0% in the extended administration group (panel 2). These results and ours suggest that elimination of postoperative antimicrobial prophylaxis might in fact reduce the risk of such infections, although our study was not planned to assess superiority.

The incidence of surgical-site infections in patients who were not overweight (body-mass index <25) was significantly higher in the extended group than in the intraoperative group (p=0·05), whereas the incidence of these infections in patients who were overweight (body-mass index ≥25) was almost same between the two groups (p=0·91). Why postoperative antimicrobial prophylaxis significantly increased the incidence of surgical-site infections in patients who were not overweight is unclear. In the additional analysis in this

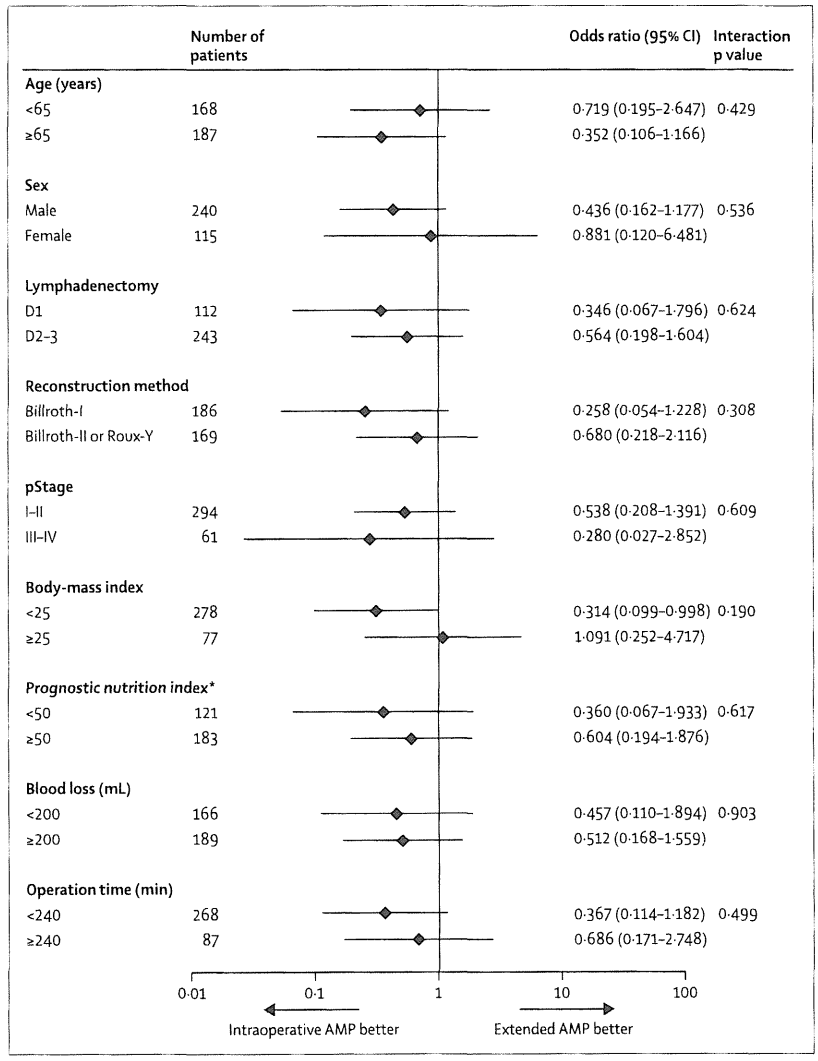

Figure 2: **Forest plot of subgroup analyses**
p values for interactions and odds ratios for surgical-site infections with intraoperative antimicrobial prophylaxis (AMP). *Data for prognostic nutrition index from 51 patients are missing.

	Intraoperative AMP (n=176)	Extended AMP (n=179)	Relative risk (95% CI)	p value
Remote site infections	..	..	1·53 (0·56–4·20)	0·441
Yes	9	6	..	
No	167	173	..	
Fever higher than 38°C	60	52	1·17 (0·86–1·60)	0·361
Body temperature on POD 3 (°C)	37·0 (35·7–40·0)	36·9 (35·3–39·1)	..	0·145
Duration of hospital stay after surgery (days)	12 (7–114)	12 (7–87)	..	0·742

Data are number or median (range) unless otherwise specified. AMP=antimicrobial prophylaxis. POD=postoperative day.

Table 3: **Secondary endpoints**

Panel 2: **Research in context**

Systematic review

We searched PubMed with the terms "gastric cancer", "surgery", and "antibiotics". Two randomised controlled studies[21,22] including patients with gastric cancer have been reported. A small-scale study in Italy[22] included both patients with gastric cancer and those with colorectal cancer and compared 1-day antimicrobial prophylaxis with clindamycin plus gentamicin to 7-day antimicrobial prophylaxis with ampicillin. A Japanese study compared intraoperative antimicrobial prophylaxis to intraoperative plus postoperative (until 3 postoperative days) treatment with cefazolin or ampicillin-sulbactam.[21] Neither study fixed the type of surgery or the antibiotics to a single agent.

Interpretation

Most of the previous studies used as the basis for the US Centers for Disease Control and Prevention guidelines did not include patients with gastric cancer. Because of absence of strong evidence to show that intraoperative administration of antimicrobial prophylaxis is sufficient to prevent surgical-site infections after D2 gastrectomy, antimicrobial prophylaxis is commonly prescribed for more than 24 h to prevent postoperative complications. Our multicentre study group did a phase 2 study to assess the feasibility of intraoperative antimicrobial prophylaxis alone and to confirm the prevalence of surgical-site infections after distal gastrectomy.[7] This is the first phase 3 study to assess the effectiveness of a fixed regimen for postoperative antimicrobial prophylaxis after distal gastrectomy. Our results show that postoperative antimicrobial prophylaxis is not recommended for patients with gastric cancer even after extended lymphadenectomy.

subgroup, patients who were underweight (body-mass index <18·5) and those of normal weight (body-mass index ≥18·5 and <25) had much the same OR for surgical-site infections (underweight 0·36, 95% CI 0·03–4·50; normal weight 0·29, 0·078–1·08). This result could be a false positive resulting from multiple testing. However, this does not affect the most important findings, which are that extended antimicrobial prophylaxis did not decrease the incidence, even in high-risk subgroups, such as patients with a high body-mass index, low prognostic nutritional index, or long operation time.

Our study included only patients with gastric cancer undergoing a distal gastrectomy. A total gastrectomy is usually associated with greater blood loss and a longer operation time than a distal gastrectomy. Because extended antimicrobial prophylaxis was not beneficial in this study, even in subgroups with a long operation time or much blood loss, we believe that our conclusion can be applied to patients with gastric cancer who are undergoing a total gastrectomy and therefore have a similar microflora in the operative field. However, our findings might not apply to patients who require surgery for other organs such as the colon or hepatobiliary tract because of differences in the microflora in the operative field and the baseline incidence of surgical-site infections.[24,30] Further studies are needed to assess postoperative antimicrobial prophylaxis with surgeries that typically have an increased incidence of surgical-site infections.

In three patients who had protocol violations, no surgical-site infections were recorded. Therefore, per-protocol analysis excluding these three patients gave much the same results as the intention-to-treat analysis. One of the limitations of our study was the absence of blinding. We did not use a placebo in this study, and surgeons and care providers were not masked to treatment allocation. The protocol did not specify that patients should be told about their allocation, so that whether they were masked to their treatment group is uncertain. However, during hospital stay, the assessment of surgical-site infections was done by infection control personnel who were not involved in this study. Therefore, we feel the possibility of a bias in assessment of endpoints is negligible.

Contributors

HI and HF conceived and designed the trial. Data collection and statistical analyses were done by TS. YKu and TT drafted the paper. KI, YKi, and SI revised the paper. All authors approved the final version.

Conflicts of interest

We declare that we have no conflicts of interest.

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Randomized clinical trial

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

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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

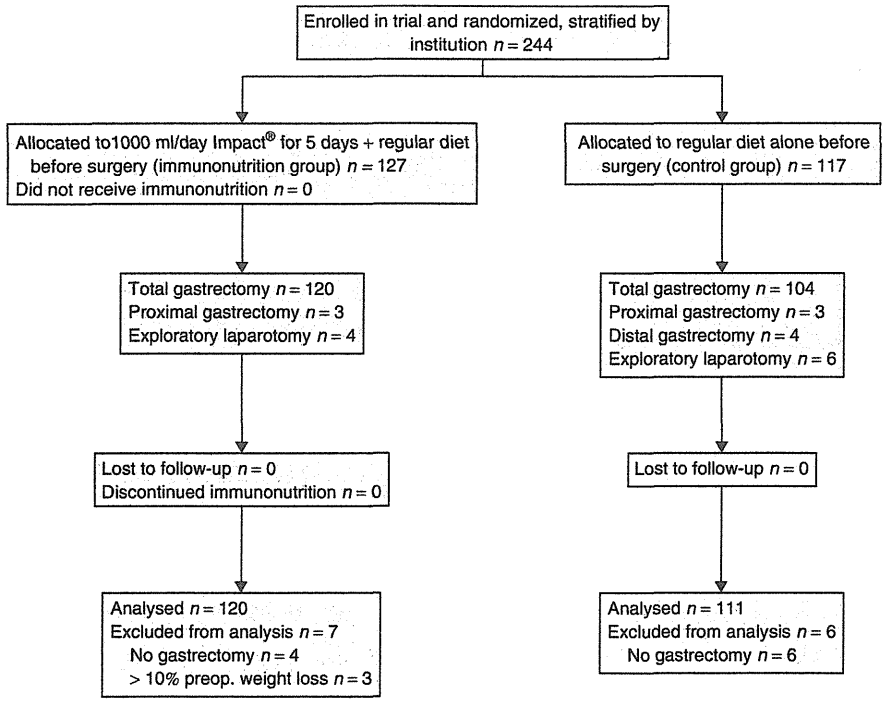

Fig. 1 CONSORT diagram for the trial

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; $P = 0·149$).

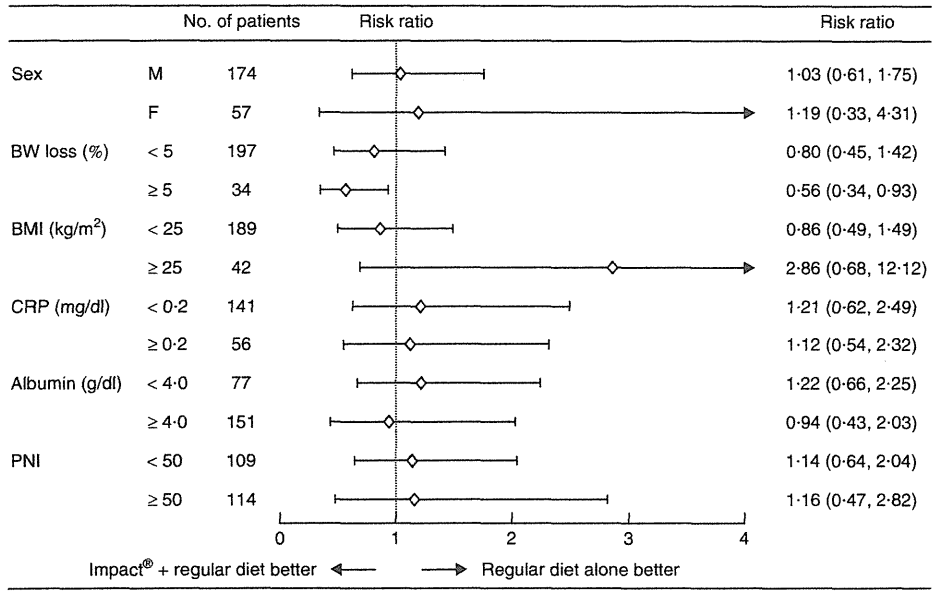

Fig. 2 Effect of enteral nutrition on risk of development of surgical-site infection, in relation to clinical and nutritional characteristics. *BW*, bodyweight; *BMI*, body mass index; *CRP*, C-reactive protein; *PNI*, prognostic nutritional index

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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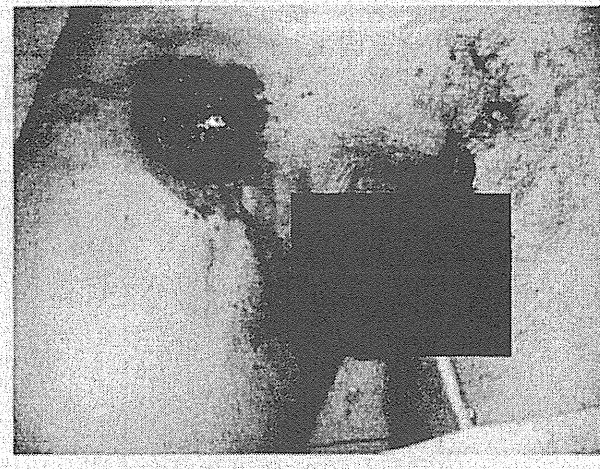
Snapshot Quiz 12/08

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*.

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