PAPER

# A Phase II Multicenter, Double-blind, Randomized, Placebo-Controlled Study of Three Dosages of an Immunomodulator (PGG-Glucan) in High-Risk Surgical Patients

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**Objective:** To examine the safety and efficacy of multiple doses of PGG-glucan (poly-[1-6]-B-D-glucopyranosyl-[1-3]-B-D-glucopyranose) in high-risk patients undergoing major thoracic or abdominal surgery.

**Design:** An interventional, multicenter, double-blind, randomized, placebo-controlled study.

**Setting:** Four university-affiliated medical centers.

**Patients:** Sixty-seven high-risk patients undergoing major thoracic or abdominal surgery.

**Intervention:** Patients were randomized in a 1:1:1:1 ratio to receive saline placebo or PGG-glucan at a dose of 0.1 mg/kg, 0.5 mg/kg, and 1.0 mg/kg or 2.0 mg/kg. One dose was administered before surgery and three doses were administered after surgery.

**Main Outcome Measures:** To examine the safety and efficacy of PGG-glucan infusion and to identify potentially important factors for a planned phase III study.

**Results:** A dose-response trend with regard to infection incidence among patients who received PGG-glucan was observed. Serious infections occurred in four patients who received placebo and in three patients who received PGG-glucan at a dose of 0.1 mg/kg. However, only one patient who received PGG-glucan at a high dose had a serious infection. The incidence and severity of adverse events was comparable in all groups.

**Conclusions:** PGG-glucan was generally safe and well tolerated, may decrease postoperative infection rates, and warrants further investigation in a planned phase III trial.

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A RECENT STUDY[1] has documented a 25% to 30% infection rate in patients undergoing major gastrointestinal surgery, with accompanying increases in the length of hospitalization. Similar findings have been corroborated (Martin T. Miller Associates, unpublished data, October 1993). These infection rates include surgical site infections and other nosocomial infections such as pneumonia, urinary tract infections, and catheter-related sepsis.[2-4] This high infection rate has occurred despite broad improvements in perioperative care, intensive care technology, and antibiotic therapy. Recently, interest has focused on various immunomodulators as potential agents to reduce the infectious morbidity of high-risk patients who undergo major surgery. We have reported a single-center study[5] that demonstrated the ability of PGG-glucan (poly-[1-6]-B-D-glucopyranosyl-[1-3]-B-D-glucopyranose) to lower the number and severity of postoperative infectious complications and to decrease the length of intensive care stay in high-risk surgical patients. The present study is, to our knowledge, the first multicenter trial to examine the safety and efficacy of a range of doses of PGG-glucan in patients undergoing major thoracic or abdominal surgery.

PGG-glucan (Betafectin) is a glucose polymer that stimulates and enhances specific humoral and cellular responses to challenge by infectious organisms. PGG-glucan belongs to a class of compounds generically known as B-glucans and is a highly purified, soluble, active molecule derived from a proprietary, nonrecombinant yeast strain of *Saccharomyces cerevisiae*.[6] Unlike other B-glucan preparations, PGG-glucan lacks in vivo pyrogenic and inflammatory effects

*See Patients and Methods on next page*

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## PATIENTS AND METHODS

This was a randomized, double-blind, placebo-controlled, phase II study in 67 patients who underwent a major surgical procedure between February 13, 1993, and January 3, 1994, at one of four institutions: Deaconess Hospital or Tufts New England Medical Center in Boston, Mass, or University of Massachusetts Medical Center or The Medical Center of Central Massachusetts in Worcester. Inclusion criteria were the following: age greater than 18 years, scheduled major noncardiac thoracic or abdominal surgery with the patient expected to be hospitalized for at least 5 days after surgery, ability to understand the study requirements, white blood cell count of $4.0\times10^9$/L or greater, and platelet count of $100\times10^9$/L or greater. Patients were excluded from the study if they met any of the following criteria: renal failure requiring hemodialysis or peritoneal dialysis, class III or IV New York Heart Association function cardiac status, scheduled chemotherapy or radiotherapy within 4 weeks before surgery or 2 weeks after surgery, positive findings of human immunodeficiency virus serologic testing, and pregnant females. Patients who had evidence of a preoperative infection and/or who were receiving steroids at the time of surgery were *not* excluded from the study to broaden the population of patients receiving the study drug. However, these infections were not considered in the efficacy analysis. Patients who received placebo and the study drug were distributed evenly amongst the study centers.

Patients were considered evaluable for efficacy analysis if they had received at least two doses of PGG-glucan. On this basis, 67 patients were enrolled in the study and 64 were evaluable. Informed consent, which had been approved by the institutional review board of each hospital, was obtained from each patient before study enrollment. Patients were randomized in a 1:1:1:1 ratio to receive saline placebo or PGG-glucan at a dose of 0.1 mg/kg, 0.5 mg/kg, or 2.0 mg/kg. After six patients were assigned to receive a dose of 2.0 mg/kg, this dose was reduced to 1.0 mg/kg because of the consideration of risk-benefit criteria for this prophylactic indication based on minor adverse experiences in healthy volunteers who received a dose of 2.25 mg/kg. Patients received multiple, sequential doses by intravenous infusion of PGG-glucan or saline placebo at 1 to 6 hours before surgery, within 4 hours after surgery, and at 48 and 96 hours after surgery (**Figure**). Patients returned for follow-up at 4 and 8 weeks after surgery.

PGG-glucan was provided by Alpha-Beta Technology Inc (Worcester, Mass) in sterile 30-mL vials, each containing 20 mL of PGG-glucan at a concentration of 1 mg/mL in a solution of sodium chloride for injection. Physiological saline placebo was provided by the pharmacy at each institution. Up to five vials of PGG-glucan were provided for each patient randomized to active treatment. Sodium chloride injection was used to make up the remaining infusion volume of 50 to 200 mL. Dosing occurred as a continuous intravenous infusion (by pump) over 1 hour.

All adverse experiences observed or reported during the clinical trial were recorded except for routine postoperative incisional pain and atelectasis. Laboratory values that became significantly out of a normal range were considered adverse experiences. Patients who exhibited unacceptable intolerance to any given dose of PGG-glucan did not receive further doses but continued in the study for scheduled assessments.

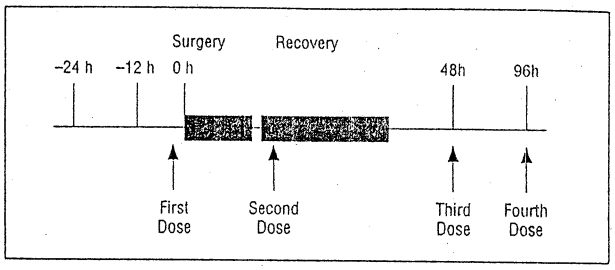
Infectious adverse experiences were defined before the study as follows: bacteremia or fungemia (one or more blood culture specimens positive for any pathogenic organism); septicemia (bacteremia or fungemia in conjunction with clinical signs and symptoms, such as fever, hypotension, confusion, or disseminated intravascular coagulation); pneumonia (sputum, bronchial washing, or lung tissue positive for an organism that was not considered normal flora or a new pulmonary roentgenographic infiltrate without a known noninfectious cause); cellulitis (clinical evidence of erythema, warmth and/or swelling, with or without a positive aspirate or culture); local infection (positive culture specimen from normally sterile fluid or positive culture specimen or physical findings suggesting infection at a local site); abscess (the formation of a single nidus collection of necrotic tissue, bacteria, and leukocytes contained within a single or multiple space within tissue, with or without positive culture specimens); catheter-related infection (positive blood and/or catheter-tip culture specimen from an indwelling venous catheter); and urinary tract infection (urine culture specimen with greater than 100 000 colonies per milliliter of a single organism in an asymptomatic patient or urine culture specimen with greater than 1000 colonies per milliliter in a patient with neutropenia in conjunction with symptoms).

Serious infectious adverse experiences were those that caused or prolonged hospitalization, were fatal, or were life-threatening. Infections were considered as separate incidences when they represented distinct anatomic sites and/or consisted of dramatically different organisms when separated in time by a change in organisms, by eradicative treatment, or by demonstration of eradication during the intervening period. All infections present at the time of study initiation or discovered intraoperatively were not considered in the analysis of infections after surgery. However, stents placed at such surgical sites that subsequently showed evidence of a new infection were considered in the analysis of infections. Infections documented by culture specimens that yielded minimal pathogens or normal flora were not considered as infections unless treatment decisions were made based on the results of the culture specimens. Positive culture specimens without a specific diagnosis or action taken were not considered as an infection.

Statistical analyses were performed using the $\chi^2$ test with Yates' correction. Differences were considered statistically significant at $P<.05$. Data are expressed as mean±SD.

resulting from cytokine induction but retains potent immunostimulatory properties.

Initial in vitro characterizations of PGG-glucan have demonstrated a high affinity for B-glucan receptors of human monocytes and neutrophils and competitively binds to the receptor in a dose-dependent manner at concentrations significantly below those required for other natural B-glucan preparations derived from bakers' yeast.[7] Studies[8-15] have shown that PGG-glucan significantly increases in vitro microbicidal activity of human neutrophils and macrophages against a variety of pathogens without directly stimulating synthesis of the cytokines,




*Schematic depicting time course of administration of PGG-glucan. One dose was given preoperatively and three doses were given postoperatively as shown.*

**Table 1. Summary of Adverse Events (AEs)***

| | | PGG-Glucan, mg/kg | | |
|---|---|---|---|---|
| | Placebo (n=16) | 0.1 (n=18) | 0.5 (n=17) | 1.0+2.0 (n=16) |
| Total No. of AEs | 165 (16) | 194 (18) | 229 (17) | 149 (16) |
| No. of serious AEs† | 7 (5) | 16 (5) | 9 (5) | 18 (4) |

*Numbers in parentheses indicate number of patients.
†No serious AEs were related to PGG-glucan administration.

interleukin-1, or tumor necrosis factor. Finally, PGG-glucan is essentially free from the pyrogenic and proinflammatory effects characteristic of many biological-response modifiers.[16-20]

The first clinical trial examining the safety and efficacy of PGG-glucan in a surgical population was a single-center phase I/II, double-blind, randomized, placebo-controlled study in 34 high-risk patients undergoing major surgery.[5] Patients who received PGG-glucan infusion had significantly fewer infections per infected patient, required fewer number of anti-infective medications, and had a shorter stay in the intensive care unit compared with control patients. In addition, there were no adverse experiences related to PGG-glucan infusion.

## RESULTS

Sixty-seven patients were enrolled in the study and 64 were evaluable; 16 patients received saline placebo and 51 patients received PGG-glucan (18 at a dose of 0.1 mg/kg, 17 at a dose of 0.5 mg/kg, 10 at a dose of 1.0 mg/kg, and six at a dose of 2.0 mg/kg). All patients receiving at least two doses of PGG-glucan were evaluable for efficacy analysis. Three patients received only one dose and were not evaluable. Four patients received three doses of PGG-glucan. Two patients voluntarily withdrew from the study before completion (but after receiving at least two doses of PGG-glucan) owing to adverse experiences: a 72-year-old woman (who received a dose of 0.1 mg/kg) with gastric carcinoma withdrew following the third dose owing to an episode of hypertension, diaphoresis, and nausea, and a 32-year-old woman (who received a dose of 2.0 mg/kg) underwent gastric bypass for morbid obesity and withdrew following the second dose owing to a maculopapular rash on the abdomen and trunk.

Adverse experiences were documented for each patient in the study; most were typical of the postoperative period for patients undergoing major surgery and were generally comparable between groups. Slight dose-related increases in flatulence, anemia, hypovolemia, and hemoptysis were not believed to be related to the study drug. Not more than 13% of adverse experiences reported in any one treatment group were considered to be severe; most adverse experiences were mild in severity. **Table 1** summarizes the incidence and severity of adverse events. Adverse experiences considered by one of us (T.J.B.) to be at least possibly related to PGG-glucan therapy were fever, headache, hypotension, vasodilation, nausea, leukocytosis, and maculopapular rash. Two patients permanently discontinued PGG-glucan therapy owing to a maculopapular rash. However, because of the multiple drugs these patients were receiving, it was not possible to clearly implicate PGG-glucan in the cause of the rash. One patient temporarily discontinued PGG-glucan therapy because of nausea; the relationship to the study drug was unclear.

There were two deaths in the study; both were unrelated to PGG-glucan administration: a 76-year-old man (who received a dose of 0.1 mg/kg) died of sepsis 22 days after resection of gastric adenocarcinoma, and a 72-year-old woman (who received a dose of 2.0 mg/kg) died of a myocardial infarction 5 days after surgery for metastatic adenocarcinoma of the colon.

**Table 2** is a summary of pertinent patient demographics. The study enrolled 46% men and 54% women, ranging in age from 24 to 87 years (mean, 54.4 years). The percentage of diabetics enrolled in the study was 21% and was not significantly different among the groups. Karnofsky scale scores and the data for computing Acute Physiology and Chronic Health Evaluation (APACHE) II scores were comparable across sites and dose groups at baseline.

**Table 3** lists the classification of surgical procedures in the study. The majority of patients (78% [50/64]) underwent gastrointestinal surgical procedures and 22% (14/64) underwent thoracic, vascular, or other surgical procedures. **Table 4** is a summary of possible risk factors for postoperative wound infections. There was no significant difference in the wound classification, duration of surgery, presence of a central venous catheter, amount of blood loss, or amount of blood products given among the various groups. All patients received prophylactic antibiotic therapy as dictated by the discretion of the surgeon. There was no significant difference in the type or amount of prophylactic antibiotics between groups. **Table 5** is a representative sampling of the types of surgical procedures performed in the study.

Infections present at study initiation or discovered intraoperatively were excluded from the efficacy analyses. Four patients had antecedent bacterial or fungal infections and three patients were discovered to have infections at the time of surgery. Eight patients received perioperative steroid therapy for either inflammatory bowel disease or idiopathic thrombocytopenia purpura.

**Table 6** summarizes the incidence and type of confirmed infections among the various groups. Although there was a trend toward a reduced incidence of abdominal abscess in patients treated with PGG-glucan, the number of infections were too small to draw definitive con-

**Table 2. Summary of Patient Demographics***

| | Placebo (n=15) | PGG-Glucan, mg/kg 0.1 (n=17) | 0.5 (n=17) | 1.0+2.0 (n=15) |
|---|---|---|---|---|
| Sex | | | | |
| M | 6 | 9 | 6 | 8 |
| F | 9 | 8 | 11 | 7 |
| Mean (±SD) age, y | 52±19 | 52±20 | 60±12 | 55±17 |
| % Ideal body weight | | | | |
| Mean (±SD) | 130±42 | 122±53 | 125±39 | 132±60 |
| Range | 84-236 | 59-246 | 83-210 | 83-236 |
| Diabetes | | | | |
| Yes | 3 | 2 | 6 | 2 |
| No | 12 | 15 | 11 | 13 |
| Karnofsky status | | | | |
| Median (range) | 80 (60-90) | 80 (50-90) | 80 (70-90) | 80 (70-90) |
| Mean (±SD) APACHE II score† | 4.3±3.3 | 5.1±3.5 | 5.4±3.0 | 4.6±2.5 |

*Data are reported as number of patients except where noted.
†APACHE indicates Acute Physiology and Chronic Health Evaluation.

**Table 3. Types of Surgical Procedures***

| | Placebo (n=15) | PGG-Glucan, mg/kg 0.1 (n=17) | 0.5 (n=17) | 1.0+2.0 (n=15) |
|---|---|---|---|---|
| Gastrointestinal | 12 | 14 | 12 | 12 |
| Thoracic | 0 | 2 | 0 | 1 |
| Vascular | 1 | 0 | 4 | 2 |
| Other | 2 | 1 | 1 | 0 |

*Data are reported as number of patients.

**Table 4. Summary of Surgery Demographics***

| | Placebo (n=15) | PGG-Glucan, mg/kg 0.1 (n=17) | 0.5 (n=17) | 1.0+2.0 (n=15) |
|---|---|---|---|---|
| Wound class | | | | |
| Clean | 4 | 4 | 8 | 3 |
| Clean-contaminated | 11 | 12 | 8 | 12 |
| Contaminated | 0 | 1 | 1 | 0 |
| Mean (±SD) duration of surgery, h | 4.7±1.6 | 4.4±2.7 | 5.7±2.6 | 4.6±2.1 |
| Central venous catheter | | | | |
| Yes | 11 | 13 | 14 | 9 |
| No | 4 | 4 | 3 | 6 |
| Blood loss, mL | | | | |
| ≤1800 | 15 | 16 | 14 | 14 |
| >1800 | 0 | 1 | 3 | 1 |
| Infusion of blood products | | | | |
| Yes | 4 | 6 | 11 | 5 |
| No | 11 | 11 | 6 | 10 |

*Data are reported as number of patients except where noted.

clusions concerning the incidence of specific infections. **Table 7** summarizes the primary efficacy parameters, infection incidence, and number of confirmed infections. Infection incidence is defined as the percentage of infected patients. A comparable infection incidence and number of confirmed infections was observed in the patients who received placebo and in those who received PGG-glucan at a dose of 0.1 mg/kg, while a trend toward a lower incidence was observed in patients who received PGG-glucan at a dose of 0.5 mg/kg or higher. **Table 8** is a summary of the infection rates when patients are grouped according to having received PGG-glucan at doses of 0.5 mg/kg or higher. The incidence of infection among patients with preoperative infection or with surgery lasting more than 8 hours was 75% and 83%, respectively, compared with 34% for all patients. Since these patients were not equally distributed among the groups, the incidence of infection was also evaluated after excluding these patients.

Subgroup analysis was performed to determine the distribution of risk factors among the groups and to examine potential patient selection criteria for future large-scale efficacy trials. The subgroup analysis was not a defined end point of the trial but was specifically identified in the analysis plan, before formal analysis of the data. **Table 9** is an analysis of the incidence of infections for patients who received placebo and PGG-glucan at a dose of 0.1 mg/kg compared with patients who received PGG-glucan at a dose of 0.5 mg/kg or higher, with an indication for the number of patients in each group. Patients were subgrouped according to the presence of diabetes, duration of surgery (0 to 8 hours), diagnosis of morbid obesity, and presence of a central venous catheter at any time during the study. There was a reduction in the number of infected diabetic patients among those who received PGG-glucan in a dose of 0.5 mg/kg or higher. Although not significant, a consistent trend of reduction in the incidence of infection was observed for these subgroups.

**Table 10** is a summary of the length of hospitalization for patients who received placebo and PGG-glucan at a dose of 0.1 mg/kg vs patients who received PGG-glucan at a dose of 0.5 mg/kg. In addition, the length of hospitalization was calculated for all patients, excluding those with baseline infections or with surgery lasting more than 8 hours. Comparison of demographic trends at baseline (age, weight, APACHE II, and Karnofsky scale scores) indicated no evidence of differences in patients excluded in these analyses. Finally, serious infections occurred in four patients who received placebo and in three patients who received PGG-glucan at a dose of 0.1 mg/kg. However, only one patient who received PGG-glucan at a dose of 0.5 mg/kg had a serious infection (**Table 11**).

## COMMENT

The incidence of postoperative infectious complications, including surgical site and other distant nosocomial infections, in high-risk patients is now estimated to be between 25% and 30%.[1] Similar findings have been noted in an independent survey (Martin T. Miller Associates, unpublished data, October 1993). Such infections continue to represent a major morbidity for high-

**Table 5. Listing of Typical Surgical Procedures**

| |
|---|
| Esophageal gastrodissection, gastrectomy, jejunostomy placement |
| Gastric bypass with Roux-en-Y gastrojejunostomy and cholecystectomy |
| Ileal colon resection with primary ileal transverse anastomosis |
| Pancreaticoduodenectomy (Whipple procedure) with insertion of feeding jejunostomy needle catheter |
| Pelvic exenteration with removal of rectum and bladder, and with creation of a ureteroileostomy-urinary conduit |
| Total colectomy-proctectomy with creation of Park's pouch and diverting loop ileostomy |
| Aortobifemoral bypass on left and aorta to profunda graft on right |

**Table 6. Incidence and Type of Confirmed Infections**

| | | PGG-Glucan, mg/kg | | |
|---|---|---|---|---|
| | Placebo (n=15) | 0.1 (n=17) | 0.5 (n=17) | 1.0+2.0 (n=15) |
| No. of infected patients | 6 | 7 | 4 | 5 |
| Surgical site infections, No. | | | | |
| Wound | 2 | 1 | 3 | 2 |
| Abdominal abscess | 2 | 4 | 0 | 0 |
| Abdominal drain | 2 | 2 | 2 | 1 |
| Biliary stent | 2 | 0 | 0 | 0 |
| Other infections, No. | | | | |
| Bacteremia | 1 | 1 | 0 | 1 |
| Urinary tract infection | 0 | 3 | 1 | 1 |
| Pneumonia/respiratory | 1 | 1 | 1 | 3 |
| *Clostridium difficile* | 1 | 0 | 0 | 0 |
| Central venous catheter | 0 | 1 | 0 | 0 |
| **Total No. of Infections** | 11 | 13 | 7 | 8 |

risk patients undergoing major surgery and have been estimated to add an additional $12 000 per patient to the cost of hospitalization.[1] Despite broad improvements in perioperative care, intensive care technology, and antibiotic therapy, there has been no evidence to suggest that postoperative infectious complications are diminishing in number or severity.[21,22] Therefore, various types of immunoprophylaxis are now being examined as potential modifiers of the immunosuppressive effects of major surgery or trauma. As such, this study was the second preliminary trial to examine range of doses and potentially important clinical variables for design of a phase III trial as well as to examine (in a limited fashion) the safety and potential efficacy of this novel compound (PGG-glucan), which is believed to upregulate polymorphonuclear leukocyte and monocyte function in high-risk surgical patients. This immunostimulatory property holds merit as a means to reduce the incidence and severity of postoperative infectious complications.

Biologically derived glucan, either in crude form or partially purified, has long been known to improve immune function in a variety of animal models[23] as well as more recently, following trauma or major surgery, in humans.[24,25] This has been attributed to the release of interleukin-1 by stimulation of the glucan receptor on the surface of monocytes and macrophages.[26,27] PGG-glucan, a highly purified compound derived from a bio-

**Table 7. Primary Efficacy Parameters**

| | | PGG-Glucan, mg/kg | | |
|---|---|---|---|---|
| | Placebo (n=15) | 0.1 (n=17) | 0.5 (n=17) | 1.0+2.0 (n=15) |
| No. (%) of infected patients | 6 (40) | 7 (41) | 4 (24) | 5 (33) |
| No. of infections | 11 | 13 | 7 | 8 |

engineered strain of yeast, has been shown to remain immunologically effective, but it neither elicits nor primes interleukin-1 or tumor necrosis factor production.[9] The absence of significant proinflammatory or febrile responses consequent to administration (presumably due to this lack of cytokine response) resulted in investigations of its role as immunoprophylaxis in surgical patients at high risk for postoperative infections. A single-center study[5] recently demonstrated the ability of PGG-glucan (at a dose of 0.5 mg/kg) to decrease the incidence and severity of postoperative infectious complications, the length of stay in the intensive care unit, as well as the amount of anti-infective medications required in 34 surgical patients.

Based on the presumed mechanism of action, PGG-glucan would be expected to raise the nonspecific host response to infection, thereby limiting the initial number of infection sites as well as their subsequent severity. Immunoprophylaxis might also be effective against the development of systemic infections removed from the site of local contamination by surgery. In such instances, although the initial infection may not be preventable by PGG-glucan administration, the subsequent response of the host to that infection may be favorably altered so as to limit wider dissemination or greater severity.

This study was a multicenter phase II, randomized, double-blind, placebo-controlled trial designed to further examine the critical clinical variables, including patient selection, type and duration of surgery, and range of doses. This study represents the second assessment of the safety and potential efficacy of PGG-glucan in a patient population. There were reductions in the incidence of infections and number of confirmed infections among those patients who received at least 0.5 mg/kg of PGG-glucan compared with those who received placebo and 0.1 mg/kg of PGG-glucan, although this did not reach statistical significance. In addition, serious infections occurred in four patients who received placebo and in three patients who received PGG-glucan at a dose of 0.1 mg/kg. However, only one patient who received PGG-glucan at a dose of 0.5 mg/kg had a serious infection.

Part of the goal of this study was to assist in the design of future, large-scale efficacy trials. As such, patients were grouped according to whether they received placebo or low-dose PGG-glucan (0.1 mg/kg) vs those who received "therapeutic" doses of at least 0.5 mg/kg (ie, 0.5 mg/kg, 1.0 mg/kg, and 2.0 mg/kg) to allow for subgroup analysis. The rationale for this grouping stems from the results of our single-center study (as well as preclinical trials) that demonstrated PGG-glucan to be effective at doses of 0.5 mg/kg or greater. When grouped

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**Table 8. Incidence of Infection***

| | Placebo+0.1 mg/kg of PGG-Glucan | PGG-Glucan, mg/kg 0.5+1.0+2.0 | P† |
|---|---|---|---|
| Incidence of infection | | | |
| All patients | 13/32 (41) | 9/32 (28) | .18 |
| Excluding patients with surgery lasting >8 h | 12/31 (39) | 5/27 (19) | .09 |
| Excluding patients with baseline infection‡ | 10/28 (36) | 6/28 (21) | .23 |

*Data are reported as total number (percentage) of infected patients.
†$\chi^2$ Test for incidence of infection.
‡The total number of infected patients who received placebo and those who received a low dose of PGG-glucan was 29 and that of patients who received a dose of 0.5 mg/kg or higher was 27.

**Table 9. Summary of Selected Subgroup Analyses**

| | Placebo+0.1 mg/kg of PGG-Glucan (n=32) | PGG-Glucan, mg/kg 0.5+1.0+2.0 (n=32) | P* |
|---|---|---|---|
| No. (%) of infected patients | | | |
| Diabetes | 4/5 (80) | 2/8 (25) | .05 |
| Surgery lasting 0 to 8 h | 12/31 (39) | 5/27 (19) | .09 |
| Morbid obesity | 4/10 (40) | 2/12 (17) | .22 |
| Central venous catheter | 9/24 (38) | 6/23 (26) | .40 |

*$\chi^2$ Test for incidence of infection.

**Table 10. Summary of Hospital Days***

| | Placebo+0.1 mg/kg of PGG-Glucan | PGG-Glucan, mg/kg 0.5+1.0+2.0 |
|---|---|---|
| All patients | n=32 | n=32 |
| | 10.4±5.8 | 9.5±5.9 |
| Excluding patients with baseline infection | n=29 | n=27 |
| | 10.5±6.2 | 7.6±4.1 |
| Excluding patients with surgery lasting >8 h | n=31 | n=27 |
| | 10.3±5.8 | 7.7±4.0 |

*Data are reported as mean±SD.

**Table 11. Serious and/or Life-threatening Infections**

| | Placebo+0.1 mg/kg of PGG-Glucan (n=32) | PGG-Glucan, mg/kg 0.5+1.0+2.0 (n=32) | P* |
|---|---|---|---|
| No. of infected patients | 7 | 1 | .023 |
| Surgical site infections | 8 | 1 | .01 |
| Other infections | 3 | 0 | .08 |

*$\chi^2$ Test.

in this manner, diabetic patients who received a dose of 0.5 mg/kg, 1.0 mg/kg, and 2.0 mg/kg also exhibited a significant reduction in the incidence of infections compared with patients who received placebo and PGG-glucan at a dose of 0.1 mg/kg. Diabetic patients, particularly in the setting of hyperglycemia, are known to be at increased risk of infection owing to neutrophil dysfunction.[28] It is possible that PGG-glucan administration might be expected to be particularly effective in such a setting by counteracting this neutrophil defect.[29]

When patients with preoperative infection or with surgery lasting more than 8 hours were excluded from the analysis, patients who received at least 0.5 mg/kg of PGG-glucan demonstrated a trend toward a decreased length of hospitalization. Although there was no significant reduction in the number of infected patients between the placebo and study groups, there were clear trends toward a reduction in the number and severity of infections in patients treated with PGG-glucan, which could have resulted in this decreased length of hospitalization.

Since PGG-glucan may only be effective as immunoprophylaxis (before an infection is established), it seems reasonable that patients with evidence of preoperative infection may not benefit as much from perioperative administration of PGG-glucan. In addition, the likelihood of postoperative infection is high in such situations, making it difficult to measure an effect. In future trials, infected patients will be excluded from entry or analysis. These and other considerations will be examined more closely in future clinical trials.

The increased cost associated with infectious complications is due in large part to the increased length of hospitalization that accompanies these infections, as well as the diagnostic evaluation and anti-infective treatment rendered during that increased length of stay.[30,31] Subgroup analysis revealed that PGG-glucan administration resulted in a decreased length of hospitalization when patients with preoperative infection or with surgery lasting more than 8 hours were excluded from the analysis. Since the average cost per infected patient has been estimated at $12 000, the net savings possible with this therapy will be determined by the ultimate cost of PGG-glucan administration,[32] which is not known at this time.

The proposed mechanism for improved immune function with PGG-glucan administration is the stimulation of microbial killing by phagocytic cells. Initial trials in normal human volunteers have indicated that monocytes and neutrophils from patients treated with PGG-glucan show increased microbicidal activity against *Staphylococcus aureus*.

Measurements of leukocyte function in the first clinical trial[5] demonstrated trends of increased killing against *S aureus* and *Candida albicans* in patients treated with PGG-glucan. However, none of these measurements was statistically significant, perhaps owing to insensitivity of the assays used. In vitro results from this study are pending at this time. Since improved phagocytosis or killing function by monocytes, macrophages, and/or polymorphonuclear leukocytes appears to be the most likely mechanism for the improved outcome vis-à-vis the number and severity of infections, it may require the appli-

TO: RICK GOETZ

cation of more sensitive in vitro tests in the clinical setting to evaluate more fully this possibility.

In summary, this is the second report of a randomized trial and the first report in a multicenter setting of the novel compound PGG-glucan that examined potentially important factors in study design (for a planned phase III study) and provided further experience with safety and efficacy in high-risk surgical patients. Although the study size was limited (64 evaluable patients), PGG-glucan, at a dose of 0.5 mg/kg or higher, caused a decrease in serious infections. In addition, subgroup analysis revealed the potential for a decrease in the length of hospitalization. This preliminary multicenter trial demonstrated a favorable safety and efficacy profile for this new compound that justifies broader investigation into its usefulness for infection prophylaxis in surgery.

*This study was sponsored by Alpha-Beta Technology Inc, Worcester, Mass, and was performed as part of the drug development program of PGG-glucan.*

*Presented at the 14th Annual Meeting of the Surgical Infection Society, Toronto, Ontario, April 29, 1994.*

*Reprint requests to Department of Surgery, Deaconess Hospital, 110 Francis St, Suite 3A, Boston, MA 02215 (Dr Babineau).*

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and distal pancreatectomy in all cases. We believe that the increased morbidity rate in our patients resulted from resection of the spleen and pancreas rather than the extended lymphadenectomy. Most of the postoperative morbidity resulted from subphrenic collections, which occurred in 14 of 29 patients. The high incidence of subphrenic collections if pancreatectomy is performed together with gastrectomy has been reported by others.[3] Splenectomy may have adversely affected the long-term survival in our $R_3$ group. Koga et al. found that the 5-year survival was 41% after gastrectomy alone and 20% after gastrectomy combined with splenectomy. This series was, however, not a randomized controlled comparison, nor was the difference statistically significant.[4]

We agree with Dr. Noguchi that radical lymphadenectomy is likely to benefit only those patients who have metastatic deposits in their lymph nodes. The problem is that intraoperative assessment of node status is notoriously inaccurate, and microscopic deposits are often detected by meticulous examination of the radical lymphadenectomy specimen.[5] A prospective, randomized evaluation of extended lymphadenectomy with node-positive patients will require node status to be predicted preoperatively. This procedure is not practiced routinely but may be possible with computer-assisted analysis of risk factors.[6] Depth of invasion of the stomach wall is one of the major determinants of lymph node metastasis. Accurate preoperative assessment of stomach wall invasion would require expert endosonography.

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S.C. SYDNEY CHUNG
ARTHUR K. C. LI
Shatin, Hong Kong

Dear Editor:

The paper by Babineau and associates[1] published in the November 1994 issue of *Annals of Surgery* is a significant step beyond earlier methods of antibiotics administered prophylactically perioperatively for the control of infection in major clean and clean-contaminated cases.

What caught my eye were the data on postoperative wound infections in the control and PGG-Glucan-treated patients. Three of 13 control subjects had postoperative wound infections (23%), and 3 of the 17 patients in the treated group (17.6%) had wound infections. I could not find a breakdown of patients with wound infections in either group of clean (13) and clean-contaminated (17) patients.

Our study, published in the June 1977 issue of *Annals of Surgery*,[2] reported that of 400 clean control patients, there was 1.5% incidence of postoperative wound infection. In 434 clean operations, in which we used lavage of an antibiotic solution of cephalothin sodium and kanamycin sulfate intermittently from the beginning of the operation to closure, there was only 1 infection (0.24%).

Another report[3] of clean-contaminated patients, involving a controlled, double-blind study of 200 patients who underwent procedures on the gastrointestinal tract, resulted in only nine incidents (9%) of postoperative wound infection in the control group (n = 100) and in only three incidents (3%) in the lavage group (n = 100).

Given the outstanding reputation of the Deaconess Hospital and its surgeons, I am amazed at the high rate of postoperative wound infection reported in the control and treatment groups.

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JERE W. LORD, JR., M.D.
Bedford, New York

Dear Editor:

Thank you for the opportunity to comment on the letter by Dr. Lord. The following is our response.

We appreciate Dr. Lord's comments on the incidence of wound infections in our prospective study of PGG-Glucan for the prevention of postoperative infection in thoracoabdominal surgery. Our experience in this study was recently repeated in another multicenter study of PGG-Glucan that demonstrated a similar incidence of wound infection.[1]

The incidence of postoperative wound infections varies greatly in the literature depending on the patient population studied and the type of study. Prospective studies specifically conducted to study the incidence of infectious complications tend to demonstrate a higher incidence of wound infection than do retrospective studies. In such a prospective study, Christou et al. found that 17.3% of patients undergoing clean-contaminated surgery had postoperative wound infections.[2] In

addition, the population that we studied represented a particularly high-risk elderly population (mean age, 61 years) with a high incidence of diabetes (33%) who underwent relatively long procedures (mean length of procedure ~4 hours). With use of the predictive index of Haley et al.,[3] these patients would fall into the high-risk category with a risk of infection of 15.8% for clean procedures and 17.7% for clean-contaminated procedures. In view of the prospective nature of our study, the patient population studied, and the complexity of the operative procedures that the patients underwent, we believe that the observed infection rate in the placebo group of 23% is consistent with the previously published experience.

Again, we appreciate Dr. Lord's interest in our article and hope that this letter helps to clarify some of the issues that he presented.

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TIMOTHY J. BABINEAU, M.D.
Boston, Massachusetts

Dear Editor:

This interesting article by Phillips et al.[1] documenting 51 cases of laparoscopic colectomies from two institutions and six different surgeons is the first such article to be published in your journal. Assuming that cases were divided equally between the two institutions, that would mean that 1.4 of these operations were performed per hospital per month over the 18-month study period. Although it appears that these surgeries were safe, there was one death in this series, and approximately one in five patients had to undergo some type of a laparotomy for completion of the procedure. It is difficult to understand, despite the interesting results reported in this article, why in his editorial, Dr. Pappas stated that we now need to begin teaching "an entire nation of general surgeons a new operation."[2]

This preliminary descriptive article on a potpourri of patients with colonic diseases can only reasonably conclude what the authors stated in their last sentence, "These early clinical results justify continued work in this area."

We are still in the feasibility and efficacy stage of evaluating laparoscopic colectomy in the treatment of colonic diseases. Many questions remain before these procedures can be recommended as the operations of choice.

Incidentally, how many of the 24 cancer operations were curative versus palliative in this series? And what type of informed consent and institutional approval was procured for patients undergoing such curative procedures?

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JEFFREY W. MILSOM, M.D.
Cleveland, Ohio

Dear Editor:

I apologize for the delay in responding to the letter to the editor of January 13, 1993.

Your first question regarding the case distribution[1] between institutions and surgeons is answered as follows: The 51 cases were not equally divided. Two thirds of the cases were Dr. Morris Franklin's, and the rest my own. Dr. Franklin and I were the primary surgeons. Though residents were involved in some of my cases, they did not function as primary surgeons. The other authors are our associates and are involved in all the cases. As you know, assisting in these advanced laparoscopic procedures is often more difficult than being the primary surgeon. The pooling of information between our two institutions was important not only to determine the feasibility and safety of laparoscopic colectomy but also to disseminate the techniques and pitfalls encountered as the operative techniques evolved.

Regarding the reported deaths, they were in Dr. Franklin's series and reflect his willingness to perform laparoscopic surgery in the critically ill and in those with advanced cancer. I restricted my cases to healthy patients who could tolerate longer operating times associated with my learning curve. Even today, with a series of more than 100 cases, I have not had no deaths. Dr. Franklin has experienced three nonprocedure-related deaths among nearly 300 patients.

Regarding your query of Dr. Pappas' editorial comment, I agree with you that his enthusiasm was not based on the results of our study. However, 2 years have passed and I am convinced that the laparoscopic technique does have a place in surgery of the colon. Your comment as to the number of cases that required "some type of laparotomy to complete the procedure" raises the key issue involved in comparing open versus laparoscopic and laparoscopic versus laparoscopic techniques. Certainly, a facilitated resection that results in the same or close to the same incision to perform the operation is of little advantage, thus I have recommended the following nomenclature to help compare apples with apples:

1. Dissection facilitated: laparoscopic-guided division of postfetal adhesions.
2. Resection facilitated: laparoscopically guided mobilization and division of the bowel and blood supply. An incision is used to perform the anastomosis extracorporeally and remove the specimen.
3. Near completely laparoscopic: Dissection, resection, and anastomosis are performed laparoscopically and an incision is performed to remove the specimen and/or to exteriorize the proximal bowel for the insertion of an anvil or a biodegradable anastomotic device.