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Citation	Abstract
<p>Kournikakis B, Mandeville R, Brousseau P, Ostroff G</p> <p>Anthrax-Protective Effects of Yeast Beta 1,3 Glucans</p> <p><i>MedGenMed.</i> 2003 March 24.</p>	<p>Context The recent events increasing the threat of bioterrorism have prompted a widespread search for defenses against this peril.</p> <p>Objective To evaluate the anthrax-protective effect of β1,3-glucan immune modulators (PGG-Glucan and WGP Beta Glucan) in an experimental animal model.</p> <p>Design β1,3-glucan immune modulators were administered by subcutaneous injection to Balb/c mice 2 days prior to anthrax challenge. WGP Beta Glucan was administered by daily oral gavage for 7 days prior to challenge, or in drinking water for 10 days post-challenge with a lethal dose of <i>B. anthracis</i> spores. Survival, survival time and microbial bioburden relative to an infected, untreated control group were assessed.</p> <p>Results A single injected dose of PGG-Glucan or WGP Beta Glucan immune modulators given two days before challenge significantly: a) increased the survival rate of infected mice (2.5-fold), b) diminished the bacterial load in the lungs of infected mice (4-8 fold), and c) increased the proportion of bacteria-free animals 10 days after challenge (2-fold). In mice prophylactically administered oral WGP Beta Glucan for one week prior to infection, survival increased from 50 to 100%; therapeutic administration of oral WGP Beta Glucan for ten days post-infection increased survival from 30% up to 90% in treatment groups.</p> <p>Conclusions These results demonstrate the potential for β1,3-glucan immune modulators to provide a significant degree of protection against anthrax, a potential biological warfare (BW) agent in a mouse model of anthrax infection. Further studies are needed to optimize protection, evaluate activity in combination with other treatment options, demonstrate activity in a validated primate model of infection, and determine if protection is effective against other potential BW agents.</p>
<p>Vetvicka, V, Terayama K, Mandeville R, Brousseau P, Kournikakis B, Ostroff G</p> <p>Orally-administered Yeast β1,3-glucan prophylactically protects against anthrax infection and cancer in mice</p> <p><i>Journal of the American Nutraceutical Association.</i> Vol. 5, No. 2, Spring 2002: 16-20.</p>	<p>β1,3-glucans from various bacterial, mushroom, yeast, and cereal sources have been established as immunomodulators. In the present paper we demonstrate that orally-administered yeast β1,3-glucan had significant effects as a prophylactic treatment to reduce the mortality of anthrax infection in mice. In addition, the same type of treatment also inhibited the growth of metastatic cancer cells <i>in vivo</i>. The mechanism of action involves the stimulation of three important cytokines: IL-2, IFN-γ, and TNF-α. These results provide preclinical evidence for the beneficial effects of orally-administered yeast β1,3-glucan.</p>

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<p>Liang, J., D. Melican, L. Cafro, G. Palace, L. Fiset, R. Armstrong, and M. L. Patchen.</p> <p>Enhanced clearance of a multiple antibiotic-resistant <i>Staphylococcus aureus</i> in rats treated with PGG-glucan is associated with increased leukocyte counts and increased neutrophil oxidative burst activity.</p> <p><i>Int. J. Immunopharmacol.</i> 1998. 20:595-614.</p> <p>PMID: 9848393 [PubMed - indexed for MEDLINE]</p>	<p>PGG-Glucan [Betafectin], a highly purified soluble beta-(1-6)-branched beta-(1 3)-linked glucan isolated from <i>Saccharomyces cerevisiae</i>, has broad in vitro and in vivo anti-infective activities unrelated to cytokine induction. Here we present in vivo results on the anti-infective activity of PGG-Glucan against a multiple antibiotic resistant <i>Staphylococcus aureus</i>. PGG-Glucan (0.25-4 mg/kg) was administered intramuscularly to male Wistar rats 48 h, 24 h, and 4 h before and 4 h after intraperitoneal implantation of a gelatin capsule containing 10(8)<i>S. aureus</i> colony forming units (CFU). Blood samples were collected at various times after challenge to determine CFU levels, leukocyte counts and neutrophil oxidative burst activity; serum TNF-alpha, and IL-1beta levels were also evaluated. The 0.25 mg/kg PGG-Glucan dose had no effect on reducing blood CFU levels; however, PGG-Glucan doses of 0.5 mg/kg, 1 mg/kg, 2 mg/kg or 4 mg/kg significantly reduced blood CFU levels by 48 h after challenge. Reduced CFU levels correlated with significantly elevated absolute monocyte counts, absolute neutrophil counts, and neutrophil oxidative burst activity in the absence of any effect on TNF-alpha or on IL-1beta levels. In additional studies, effects on mortality and blood CFU levels were evaluated in rats treated with ampicillin (an antibiotic to which the <i>S. aureus</i> was resistant), PGG-Glucan, or both agents. Mortality and blood CFU levels were reduced most in combination-treated rats compared to saline control rats or rats treated with either ampicillin alone or PGG-Glucan alone. We conclude that in vivo (1) PGG-Glucan can enhance clearance of an antibiotic resistant <i>S. aureus</i>, (2) that this clearance is accompanied by an increase in monocytes and neutrophils as well as a potentiation of neutrophil oxidative microbicidal activity without alteration of the proinflammatory cytokine response, and (3) PGG-Glucan can enhance the effectiveness of traditional antibiotic treatment.</p>
<p>Dellinger EP, Babineau TJ, Bleicher P, Kaiser AB, Seibert GB, Postier RG, Vogel SB, Norman J, Kaufman D, Galandiuk S, Condon RE.</p> <p>Effect of PGG-glucan on the rate of serious postoperative infection or death observed after high-risk gastrointestinal operations. Betafectin Gastrointestinal Study Group.</p> <p><i>Arch Surg.</i> 1999 Sep;134(9):977-83.</p> <p>PMID: 10487593 [PubMed - indexed for MEDLINE]</p>	<p>Background: Postoperative infections remain common after high-risk gastrointestinal procedures. PGG-glucan (Betafectin; Alpha Beta Technology Inc, Worcester, Mass), derived from yeast cell walls, promotes phagocytosis and intracellular killing of bacterial pathogens by leukocytes, prevents infection in an animal model of wound infection, and acts synergistically with antibiotics to reduce mortality in rat peritonitis.</p> <p>Hypothesis: We hypothesized that infectious complications in these patients might be reduced by the administration of a nonspecific immune-enhancing agent.</p> <p>Design: Multicenter, prospective, randomized, double-blind, placebo-controlled trial of 1249 patients prospectively stratified into colorectal or noncolorectal strata.</p> <p>Setting: Thirty-nine medical centers throughout the United States.</p> <p>Patients: Aged 18 years or older, scheduled for gastrointestinal procedure lasting 2 to 8 hours, with 2 or more defined risk factors.</p> <p>Interventions: PGG-glucan, 0.5 mg/kg or 1.0 mg/kg, or placebo once preoperatively and 3 times postoperatively. All patients received standardized antibiotic prophylaxis.</p> <p>Main Outcome Measures: Serious infection or death within 30 days.</p>

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	<p>Results: All randomized patients revealed no difference in serious infections and deaths in the treated groups compared with placebo groups (15% vs 14%, $P > .90$). In the prospectively defined noncolorectal stratum ($n = 391$), PGG-glucan administration was associated with a statistically significant relative reduction (39%) in serious infections and death (placebo, 46 [36%] of 129 vs either PGG-glucan group, 29 [21%] of 132 and 28 [22%] of 130, $P < .02$). PGG-glucan reduced postoperative infection or death in malnourished patients having noncolorectal procedures (31 [44%] of 70, placebo group; 16 [24%] of 68, 0.5-mg/kg PGG-glucan group; 12 [17%] of 72, 1.0-mg/kg PGG-glucan group; $P < .001$). Study drug was stopped owing to adverse effects more frequently for patients receiving PGG-glucan than placebo (2%, 4%, and 7% for the placebo group, 0.5-mg/kg PGG-glucan group, and 1.0-mg/kg PGG-glucan group, respectively, $P < .003$).</p> <p>Conclusion: Perioperative administration of PGG-glucan reduced serious postoperative infections or death by 39% after high-risk noncolorectal operations.</p>
<p>Kaiser AB, Kernodle DS.</p> <p>Synergism between poly-(1-6)-beta-D-glucofuranosyl-(1-3)-beta-D-glucofuranose glucan and cefazolin in prophylaxis of staphylococcal wound infection in a guinea pig model.</p> <p><i>Antimicrob Agents Chemother.</i> 1998 Sep;42(9):2449-51.</p> <p>PMID: 9736583 [PubMed - indexed for MEDLINE]</p>	<p>To determine whether the infection-preventing capability of the neutrophil-activating agent poly-(1-6)-beta-D-glucofuranosyl-(1-3)-beta-D-glucofuranose glucan (PGG-glucan) can be enhanced with antibiotic prophylaxis, we administered PGG-glucan and cefazolin, alone and in combination, to guinea pigs inoculated with isolates of staphylococci. Guinea pigs receiving both PGG-glucan and cefazolin had 50% infective doses that were 8- to 20-fold higher than those obtained with cefazolin alone and 100- to 200-fold higher than those obtained with PGG-glucan alone. PGG-glucan and cefazolin are synergistic in their ability to prevent staphylococcal wound infection.</p>
<p>Tzianabos AO, Gibson FC 3rd, Cisneros RL, Kasper DL.</p> <p>Protection against experimental intraabdominal sepsis by two polysaccharide immunomodulators.</p> <p><i>J Infect Dis.</i> 1998 Jul;178(1):200-6.</p> <p>PMID: 9652441 [PubMed - indexed for MEDLINE]</p>	<p>Two immunomodulating polysaccharides, poly-(1-6)-beta-glucotriosyl-(1-3)-beta-glucofuranose (PGG)-glucan and <i>Bacteroides fragilis</i> polysaccharide A (PS A), were evaluated for the prevention of mortality and abscess formation associated with experimental intraabdominal sepsis. Prophylactic treatment with a combination of these compounds significantly reduced mortality (8% vs. 44% in the saline-treated control group) and the incidence of abscesses (30% vs. 100% in the saline-treated control group) after challenge with rat cecal contents. These compounds were also effective when administered therapeutically after bacterial contamination of the peritoneal cavity. PS A treatment conferred long-term protection against abscess formation and resulted in significantly fewer total aerobes and anaerobes in the peritoneal fluid of animals challenged with cecal contents. These data demonstrate the usefulness of two immunomodulatory polysaccharides in preventing experimental intraabdominal sepsis in the absence of antimicrobial therapy and may represent a new adjunct to antibiotic regimens currently used to prevent clinical cases of this disease.</p>

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<p>Kernodle DS, Gates H, Kaiser AB.</p> <p>Prophylactic anti-infective activity of poly-[1-6]-beta-D-glucopyranosyl-[1-3]-beta-D-glucopyranose glucan in a guinea pig model of staphylococcal wound infection.</p> <p><i>Antimicrob Agents Chemother.</i> 1998 Mar;42(3):545-9.</p> <p>PMID: 9517930 [PubMed - indexed for MEDLINE]</p>	<p>The judicious use of perioperative antibiotic prophylaxis reduces the infectious complications of surgery. However, increased bacterial resistance within hospitals may make antibiotic prophylaxis less effective in the future and alternative strategies are needed. New immunomodulatory agents might prevent wound infections by stimulation of the host immune system. To test this hypothesis, we administered poly-[1-6]-beta-D-glucopyranosyl- [1-3] -beta-D-glucopyranose glucan (PGG glucan), which enhances neutrophil microbicidal activity, intravenously to guinea pigs in doses ranging from 0.015 to 4 mg/kg of body weight on the day before, on the day of, and on the day after intermuscular inoculation with methicillin-resistant strains of <i>Staphylococcus aureus</i> and <i>Staphylococcus epidermidis</i>. Abscesses were identified at 72 h, and median infective doses (ID50) and statistical significance were determined by logistic regression. Guinea pigs receiving PGG glucan and inoculated with methicillin-resistant <i>S. aureus</i> and <i>S. epidermidis</i> exhibited ID50 of as much as 2.5- and 60-fold higher, respectively, than those of control guinea pigs not receiving PGG glucan. Maximal protection was observed with a dose of 1 mg of PGG glucan per kg, and efficacy was reduced at higher as well as at lower PGG glucan doses. Furthermore, a single dose of PGG glucan given 24 h following bacterial inoculation was found to be effective in preventing infection. We conclude that PGG glucan reduces the risk of staphylococcal abscess formation. Neutrophil-activating agents are a novel means of prophylaxis against surgical infection and may be less likely than antibiotics to be affected adversely by the increasing antibiotic resistance of nosocomial pathogens.</p>
<p>Hetland G, Lovik M, Wiker HG.</p> <p>Protective effect of beta-glucan against <i>mycobacterium bovis</i>, BCG infection in BALB/c mice.</p> <p><i>Scand J Immunol.</i> 1998 Jun;47(6):548-53.</p> <p>PMID: 9652822 [PubMed - indexed for MEDLINE]</p>	<p>Beta-1,3-glucan is a potent stimulator of macrophage functions and has a protective effect against a range of infections in rodent models. We examined whether the agent could also protect against the intracellular <i>Mycobacterium bovis</i>, bacillus <i>Calmette-Guerin</i> (BCG) infection in mice. BCG-susceptible BALB/cmice were injected intravenously (i.v.) with beta-glucan or vehicle 3 days before, or with beta-glucan 7 days after i.v. challenge with live BCG bacilli The animals were killed 4 or 8 weeks later, their organs were homogenized and applied to object slides and stained with auramin for counting of bacilli, or seeded onto agar in Petri dishes. Mice treated with beta-glucan both pre- and postchallenge had significantly lower numbers of BCG bacilli and BCG colony-forming units in spleen homogenates compared with controls 4 weeks after challenge. A similar, but not statistically significant, tendency was observed in spleen homogenates from mice killed 8 weeks after challenge. In homogenates of liver and lungs there were similar findings, but less pronounced. There was a dose-dependent effect of beta-glucan injected before BCG challenge on the number of BCG bacilli found in spleen and liver homogenates. In addition, antibody cross-reactivity was demonstrated between <i>M. tuberculosis</i> cell wall and beta-glucan. The results suggest that beta-glucan has a protective effect against <i>M. bovis</i>, BCG infection in susceptible mice.</p>

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<p>Meira DA, Pereira PC, Marcondes-Machado J, Mendes RP, Barraviera B, Pellegrino Junior J, Rezkallah-Iwasso MT, Peracoli MT, Castilho LM, Thomazini I, Da Silva CL, Foss NT, Curi PR.</p> <p>The use of glucan as immunostimulant in the treatment of paracoccidioidomycosis.</p> <p><i>Am J Trop Med Hyg.</i> 1996 Nov;55(5):496-503.</p> <p>PMID: 8940980 [PubMed - indexed for MEDLINE]</p>	<p>A group of 10 patients, nine of them seriously infected with <i>Paracoccidioides brasiliensis</i> (G1), received glucan (beta-1,3 polyglucose) as an immunostimulant intravenously once a week for one month, followed by monthly doses (10 mg) over an 11-month period, together with a specific anti-fungal agent as an immunostimulant. A second group of eight moderately infected patients (G2) was treated with only the anti-fungal agent. Among the patients in G1, there was only one case of relapse compared with five in G2. Values for the erythrocyte sedimentation rate (ESR) showed a significant difference ($P < 0.001$) post-treatment in G1 patients, when compared with the pretreatment levels. There was also a significant reduction ($P < 0.001$) in the level of serum antibodies to <i>P. brasiliensis</i> in the G1 patients in post-treatment examinations. The phytohemagglutinin (PHA) skin test showed a positive reaction among the patients in G1 ($P < 0.01$) post-treatment and there was a tendency towards an increase in the number of CD4+ T lymphocytes in both groups after treatment. The serum level of tumor necrosis factor (TNF) proved to be significantly higher ($P < 0.02$) in the G1 patients during treatment. In the G1 patients, the correlation between ESR and TNF tended to be negative whereas that between ESR and serum antibodies was positive. The present results indicate that the patients who received glucan, in spite of being more seriously ill, had a stronger and more favorable response to therapy.</p>
<p>Compton R, Williams D, Browder W.</p> <p>The beneficial effect of enhanced macrophage function on the healing of bowel anastomoses.</p> <p><i>Am Surg.</i> 1996 Jan;62(1):14-8.</p> <p>PMID: 8540639 [PubMed - indexed for MEDLINE]</p>	<p>Inadequate healing and subsequent leakage of bowel anastomoses are serious postoperative complications in abdominal surgery. Previous studies have demonstrated the macrophage to be a key cell in the physiology of wound healing. The current study was undertaken to evaluate the effects of enhanced macrophage function on the healing of bowel anastomoses. Sprague-Dawley rats (250 gm) underwent laparotomy and jejunojejunostomy following IV treatment with glucan (100 mg per kg), a potent macrophage stimulant, or 5 per cent dextrose 24 hours before surgery and again on the day of surgery. Animals were killed and the anastomoses underwent wound tensiometry on Day 3 using a computer-assisted constant velocity tensiometer. The glucan-treated animals had a significantly greater anastomotic breaking strength (88.5 gm +/- 10.7 versus 45.45 gm +/- 5.1) ($P < 0.01$). Formalin fixation increased the breaking strength of the untreated anastomosis but not of the treated anastomosis (92.9 gm +/- 11.77 versus 92.3 +/- 12.44). Analysis of macrophage supernatant for the growth factors epidermal growth factor (EGF), platelet derived growth factor (PDGF), and transforming growth factor-beta (TGF-beta) was accomplished by immunoblot assay. Results indicated no difference in the presence of EGF in the stimulated and unstimulated macrophage supernatants. PDGF and TGF-beta were decreased in the stimulated macrophage supernatants. We conclude that 1) Enhanced macrophage function had a beneficial effect on the early tensile strength of bowel anastomoses. 2) Effects of the activated macrophage on bowel anastomoses may not be related to secretion of conventional growth factors. 3) Immunopharmacologic agents that enhance macrophage function may be an important adjunct to surgical therapy requiring bowel anastomosis.</p>

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<p>Babineau TJ, Hackford A, Kenler A, Bistrrian B, Forse RA, Fairchild PG, Heard S, Keroack M, Caushaj P, Benotti P.</p> <p>A phase II multicenter, double-blind, randomized, placebo-controlled study of three dosages of an immunomodulator (PGG-glucan) in high-risk surgical patients.</p> <p><i>Arch Surg.</i> 1994 Nov;129(11):1204-10.</p> <p>PMID: 7979954 [PubMed - indexed for MEDLINE]</p>	<p>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.</p> <p>Design: An interventional, multicenter, double-blind, randomized, placebo-controlled study.</p> <p>Setting: Four university-affiliated medical centers.</p> <p>Patients: Sixty-seven high-risk patients undergoing major thoracic or abdominal surgery.</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>Conclusions: PGG-glucan was generally safe and well tolerated, may decrease postoperative infection rates, and warrants further investigation in a planned phase III trial.</p>
<p>Pedroso M.</p> <p>Application of beta-1,3-glucan to prevent shipping fever in imported heifers.</p> <p><i>Arch Med Res.</i> 1994 Summer;25(2):181.</p> <p>PMID: 7919809 [PubMed - indexed for MEDLINE]</p>	<p>Particulated beta-1,3-glucan from <i>Saccharomyces cerevisiae</i> was evaluated to prevent shipping fever in imported heifers during the 15 days following their arrival to Cuba. Seventy seven animals received a single subcutaneous dose (5 mg/kg body weight) during the first 12 h following their arrival, whereas 44 served as untreated controls. Clinical symptoms were observed in 3 treated and 19 untreated animals ($p < 0.001$). One untreated heifer died. These observations confirm the usefulness of beta-1,3-glucan to prevent shipping fever.</p>
<p>de Felipe Junior J, da Rocha e Silva Junior M, Maciel FM, Soares Ade M, Mendes NF.</p> <p>Infection prevention in patients with severe multiple trauma with the immunomodulator beta 1-3 polyglucose (glucan).</p> <p><i>Surg Gynecol Obstet.</i> 1993 Oct;177(4):383-8.</p> <p>PMID: 8211583 [PubMed - indexed for MEDLINE]</p>	<p>In a effect to prevent nosocomial pneumonia and sepsis, we treated patients with severe multiple trauma with an immunomodulator--beta 1-3 polyglucose (glucan). Forty-one patients with no infection at admission were stratified using Trauma Score and included in a randomized double-blind controlled trial. They were divided into a control group ($n = 20$) and a glucan group ($n = 21$). Pneumonia occurred in 11 of 20 patients in the control group and in two of 21 recipients of glucan ($p < 0.01$). Sepsis occurred in seven of 20 patients in the control group and in two of 21 patients treated with glucan ($p < 0.05$). Considering patients with pneumonia and sepsis, a decrease was observed in nosocomial infection from 65.0 to 14.4 percent ($p < 0.001$). The mortality rate related to infection was 30.0 percent in patients in the control group and 4.8 percent in the group treated with glucan ($p < 0.05$). The general mortality rate, cerebral deaths excluded, was 42.1 percent in the control group and 23.5 percent in the glucan group.</p>

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<p>Browder W, Williams D, Pretus H, Olivero G, Enrichens F, Mao P, Franchello A.</p> <p>Beneficial effect of enhanced macrophage function in the trauma patient.</p> <p><i>Ann Surg.</i> 1990 May;211(5):605-12; discussion 612-3.</p> <p>PMID: 2111126 [PubMed - indexed for MEDLINE]</p>	<p>Host immunosuppression after trauma contributes to septic morbidity. The macrophage is a key element in the host immune response. This study evaluated glucan, a macrophage stimulant, in a prospective, randomized, double-blind study of 38 trauma patients undergoing surgery. Glucan (21 patients), 50 mg/m², or placebo (17 patients) was given intravenously daily for 7 days. Delayed hypersensitivity skin testing was performed on days 1 and 7 after trauma. Serum interleukin-1 (IL-1) and tumor necrosis factor (TNF) were assayed after trauma. While the total mortality rate was significantly less in the glucan group (0% versus 29%) (p less than 0.05), the mortality rate from sepsis was not statistically different (0% versus 17.6%). Glucan therapy significantly decreased septic morbidity (9.5% versus 49%; p less than 0.05). Serum IL-1 had a greater increase in glucan patients on day 3 after trauma (143.4 +/- 19.3% versus 78.6 +/- 11.7%; p less than 0.05), but there was no difference thereafter. Serum TNF did not vary between groups. Early increase in IL-1 correlated with subsequent skin test conversion to positive. Neither serum IL-1 nor TNF was a reliable indicator of future sepsis. Further clinical trials are indicated to evaluate biologic response modifiers that activate macrophages in the trauma patient.</p>
<p>Rasmussen LT, Seljelid R.</p> <p>Dynamics of blood components and peritoneal fluid during treatment of murine <i>E.coli</i> sepsis with beta-1,3-D-polyglucose derivatives. I. Cells.</p> <p><i>Scand J Immunol.</i> 1990 Oct;32(4):321-31.</p> <p>PMID: 2237287 [PubMed - indexed for MEDLINE]</p>	<p>Beta-1,3-D-polyglucose derivatives protect mice against otherwise lethal bacterial infections. This protective effect has previously been considered to be mediated through mononuclear phagocytes. We have now investigated the cellular composition in blood and peritoneal fluid after administration of the beta-1,3-D-polyglucose before and after challenge with <i>Escherichia coli</i>. In animals treated with beta-1,3-D-polyglucose derivatives, the total white cell number was significantly increased in both blood and peritoneal fluid before and after challenge with <i>E. coli</i>. The increased total cell number was mainly the result of raised levels of granulocytes. The effects of beta-1,3-D-polyglucose-derivatized microbeads (GDM) and soluble aminated beta-1,3-D-polyglucose (AG) were similar. Bacterial counts in peripheral blood in GDM- and AG-treated animals increased with 6 h after challenge and approached zero after 24 h. In untreated animals the bacterial counts increased gradually until the animals died after about 12 h. Bacterial counts in peritoneal fluid of GDM- and AG-treated animals declined to zero after 24 h. In untreated animals there was a slight increase in bacterial counts until the animals died after about 12 h. By using radioactive labelling, we localized the bacterial as well as the beta-1,3-D-polyglucose derivatives during the period following injection. Particle-bound beta-1,3-D-polyglucose was recovered mainly in the milky spots of the omentum. A conspicuous number of bacteria were also recovered in the milky spots. The soluble aminated beta-1,3-D-polyglucose was recovered mainly in the liver. However, on a weight basis, the greatest concentration of radioactivity was in the milky spots.</p>

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<p>Rasmussen LT, Fandrem J, Seljelid R.</p> <p>Dynamics of blood components and peritoneal fluid during treatment of murine <i>E.coli</i> sepsis with beta-1,3-D-polyglucose derivatives. II. Interleukin 1, tumour necrosis factor, prostaglandin E2, and leukotriene B4.</p> <p><i>Scand J Immunol.</i> 1990 Oct;32(4):333-40.</p> <p>PMID: 2173131 [PubMed - indexed for MEDLINE]</p>	<p>The influences of pretreatment with beta-1,3-D-polyglucose derivatives on levels of cytokines and arachidonic acid metabolites in body fluids in experimental peritonitis in mice are reported. Peritonitis was induced by an intraperitoneal injection of 10(8) live <i>Escherichia coli</i>. Pretreated animals survived the infection, untreated animals died about 12 h after inoculation with <i>E. coli</i>. Levels of IL-1 in plasma and peritoneal fluid, measured by cytotoxicity assay of the HT-2 cell line, increased significantly during the first 48 h after intraperitoneal treatment with beta-1,3-D-polyglucose-derivatized microbeads (GDM) or soluble, aminated beta-1,3-D-polyglucose (AG). After subsequent challenge with <i>E. coli</i>, the levels of IL-1 were significantly lower than in untreated animals. There was no increase in levels of TNF after treatment with GDM or AG, measured by cytotoxicity assay of the WEHI clone 13 cell line. After challenge with <i>E. coli</i>, TNF in plasma and peritoneal fluid was significantly lower compared with untreated animals. Both PGE2 and LTB4, measured by radioimmunoassay kits, were increased in peritoneal fluid after treatment with GDM and AG. After challenge with <i>E. coli</i>, PGE2 and LTB4 in peritoneal fluid increased to about half the concentration of infected control animals. Intraperitoneal injection of indomethacin to pretreated animals resulted in increased levels of IL-1 and TNF and decreased levels of PGE2 following challenge with <i>E. coli</i>. The levels of IL-1 and TNF remained elevated until the animals died after about 12 h. These studies demonstrate that the raised levels of arachidonic acid metabolites after pretreatment with GDM or AG seem to inhibit the otherwise lethal elevation of IL-1 and TNF in body fluids which is seen in untreated animals.</p>
<p>Maheshwari R, Siddiqui MU.</p> <p>Immunoprotection by beta-1,3 glucan antigen combination in <i>Plasmodium berghei</i> infection in mice.</p> <p><i>Indian J Med Res.</i> 1989 Nov;89:396-403.</p> <p>PMID: 2695459 [PubMed - indexed for MEDLINE]</p>	<p>In an attempt to protect mice against experimental infection with <i>P. berghei</i>, mice were immunized against soluble extract of <i>P. berghei</i> in combination with beta-1,3 glucan or FCA and also independently. Mice immunized against <i>P. berghei</i> antigen-glucan developed well defined cell mediated and humoral immune responses, while mice injected with antigen FCA or antigen alone developed only an antibody response. Antigen-glucan immunization afforded a high degree of immune protection to the host against the challenge with live parasites.</p>

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<p>Williams DL, Yaeger RG, Pretus HA, Browder IW, McNamee RB, Jones EL.</p> <p>Immunization against Trypanosoma cruzi: adjuvant effect of glucan.</p> <p><i>Int J Immunopharmacol.</i> 1989;11(4):403-10.</p> <p>PMID: 2506140 [PubMed - indexed for MEDLINE]</p>	<p>Trypanosoma cruzi, the causative agent of Chagas' disease, infects humans and animals in tropical, subtropical and some temperate regions of the western hemisphere. At present, there is no effective vaccine for T. cruzi infection. Glucan, a beta-1,3 polyglucose biological response modifier, possesses significant adjuvant activity. The present study investigated the adjuvant activity of particulate glucan when combined with a vaccine of glutaraldehyde-killed T. cruzi culture forms. ICR/HSD mice (20 g) were injected s.c. with glutaraldehyde-killed T. cruzi on days 21, 14 and 7 prior to challenge with 50 T. cruzi blood forms. Particulate glucan (1 mg/mouse) was administered s.c. either alone or in conjunction with T. cruzi vaccine. Isovolumetric dextrose served as control. Dextrose, glucan or T. cruzi vaccine as single treatment regimens showed 100% mortality with 20.5, 21.4 and 21.6 day median survival times, respectively. In contrast, glucan administered with T. cruzi vaccine showed an 85% (P less than 0.01) survival at 275 days post-challenge. In addition, the number of T. cruzi observed in the blood of glucan--T. cruzi immunized mice was lower than the appropriate controls. However, immunized mice which survived at 275 days were positive for the presence of T. cruzi by xenodiagnosis. Histopathologic evaluation of glucan--T. cruzi mice revealed no parasites or cardiac pathology, but a mild splenic hyperplasia and inflammation of skeletal muscle were noted. In subsequent studies, mice were immunized with the same regimen of glucan--T. cruzi and challenged with 500 or 5000 T. cruzi. Glucan significantly (P less than 0.05) increased survival as denoted by 60% and 50% survival in the glucan-T. cruzi group vs 0% in controls.(ABSTRACT TRUNCATED AT 250 WORDS)</p>
<p>Bowers GJ, Patchen ML, MacVittie TJ, Hirsch EF, Fink MP.</p> <p>Glucan enhances survival in an intraabdominal infection model.</p> <p><i>J Surg Res.</i> 1989 Aug;47(2):183-8.</p> <p>PMID: 2755122 [PubMed - indexed for MEDLINE]</p>	<p>The immunomodulator glucan exists in two forms, particulate (glucan-P) and soluble (glucan-F). Both preparations of glucan, either alone or in combination with antibiotic therapy, were evaluated for their ability to augment survival in rats following cecal ligation and puncture (CL/P). Adult male rats were infused once daily for 5 consecutive days with either glucan-P (10 mg/kg), glucan-F (10 mg/kg), or 5% (w/v) dextrose in water. Three days later all rats underwent CL/P. Postoperatively, the rats received (a) no therapy, (b) saline (1 ml subcutaneously every 12 hr) or (c) ampicillin (33 mg/kg subcutaneously every 12 hr) for 7 days. Without any associated pre-or postoperative treatment, CL/P was associated with an 85% 7-day mortality. Neither glucan preparation alone significantly altered this mortality. Administering ampicillin postoperatively decreased the mortality to 53% (P less than 0.001 vs</p>

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	<p>untreated controls). When postoperative ampicillin therapy was combined with preoperative glucan treatment, the mortality was reduced even further (26% for glucan-P, 21% for glucan-F; P less than 0.02 vs ampicillin-treated controls). We conclude from these results that (i) neither glucan preparation alone effectively enhances survival following CL/P when using the doses and administration schedule employed herein, (ii) both glucan-P and glucan-F do act synergistically with antibiotics to enhance survival in this rat model of polymicrobial sepsis, and (iii) in this particular model, nontoxic glucan-F is as efficacious as glucan-P.</p>
<p>Williams DL, Sherwood ER, Browder IW, McNamee RB, Jones EL, Di Luzio NR.</p> <p>The role of complement in glucan-induced protection against septic shock.</p> <p><i>Circ Shock</i>. 1988 May;25(1):53-60.</p> <p>PMID: 3042187 [PubMed - indexed for MEDLINE]</p>	<p>Previous studies from our laboratory have shown that glucan will significantly enhance survival, decrease bacteremia, maintain reticuloendothelial function, and reduce histopathology in a murine model of gram-negative septic shock [1]. The present study was undertaken to evaluate the role of complement in glucan-enhanced protection against septic shock. AKR/J mice, which are congenitally C5-deficient, and ICR/HSD mice that were complement-depleted by treatment with purified cobra venom factor (CVF), were injected IP with glucan (50 mg/kg) on days 5 and 3 prior to IP challenge with 1×10^8 <i>E. coli</i>. Survival data indicated that glucan (p less than 0.05) increased survival in both C5-deficient and complement-depleted mice. Glucan prophylaxis resulted in a neutrophilic leukocytosis 8 h following <i>E. coli</i> challenge. However, glucan did not alter bone marrow proliferation. We conclude that, 1) glucan's protective effect on survival is not dependent on complement, 2) complement is not required for glucan-induced neutrophilic leukocytosis in this model, and 3) glucan does not enhance bone marrow proliferation in complement-deficient mice.</p>
<p>Williams DL, Sherwood ER, Browder IW, McNamee RB, Jones EL, Rakinic J, Di Luzio NR.</p> <p>Effect of glucan on neutrophil dynamics and immune function in <i>Escherichia coli</i> peritonitis.</p> <p><i>J Surg Res</i>. 1988 Jan;44(1):54-61.</p> <p>PMID: 3275833 [PubMed - indexed for MEDLINE]</p>	<p>Previous studies from our laboratory have demonstrated that glucan, a nonspecific immunomodulator, modifies the course of murine <i>Escherichia coli</i> peritonitis. The protective effect of glucan was mediated, in part, by macrophages. In the present study, leukocyte dynamics in the peritoneal cavity and peripheral blood of glucan-treated mice following <i>E. coli</i> challenge was examined. Additional studies examined in vitro bone marrow proliferation, as well as phagocytosis and intracellular killing of <i>E. coli</i> by neutrophils following glucan administration. ICR/HSD mice were injected ip with glucan (150 mg/kg) or dextrose (5% w/v) on Days 5 and 3 prior to ip challenge with 1×10^8 <i>E. coli</i>. Glucan increased (P less than 0.05) total peritoneal neutrophil numbers prior to and following septic challenge. Examination of peripheral blood revealed that ip glucan treatment in <i>E. coli</i> peritonitis significantly (P less than 0.001) increased the number of circulating neutrophils. Additionally, neutrophils from glucan-treated mice showed increased phagocytosis of <i>E. coli</i> in vitro. Glucan therapy also increased bone marrow proliferation. We conclude that (1) glucan enhances peritoneal neutrophil levels, (2) peripheral blood neutrophils are increased following glucan and <i>E. coli</i>, (3) ip glucan increases bone marrow proliferation, and (4) neutrophils from glucan-treated mice showed enhanced phagocytosis of <i>E. coli</i> in vitro. Thus, the beneficial effect of glucan is mediated not only by activated macrophages, but also by the neutrophilic leukocyte.</p>

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<p>Browder W, Williams D, Sherwood E, McNamee R, Jones E, DiLuzio N.</p> <p>Synergistic effect of nonspecific immunostimulation and antibiotics in experimental peritonitis.</p> <p><i>Surgery.</i> 1987 Aug;102(2):206-14.</p> <p>PMID: 3303398 [PubMed - indexed for MEDLINE]</p>	<p>To assess the role of combined immunomodulator and antibiotic therapy in sepsis, glucan--a beta 1,3 polyglucose--and gentamicin were administered in a model of murine peritonitis. ICR/HSD mice received one of four treatment regimens: 5% dextrose; gentamicin 0.02 mg intramuscularly (sub-MIC) 2 hours before peritonitis; glucan 0.1 mg intraperitoneally 24 hours before peritonitis; combined glucan-gentamicin treatment. All animals were challenged with 1×10^8 <i>Escherichia coli</i> intraperitoneally. Long-term survival was significantly enhanced in the combined therapy group (56%, p less than 0.05) when compared with D5W (0%), gentamicin alone (0%), or glucan alone (9%). Macrophage secretory activity, as assayed by interleukin-1 (IL-1) production, was significantly enhanced by combined therapy when compared with the other three treatment groups. Combined therapy significantly reduced <i>E. coli</i> bacteremia at 8 hours after inoculation, when compared with the other three groups. Availability of host neutrophils was assessed by peripheral counts and bone marrow proliferation assay. Combined glucan-gentamicin significantly enhanced bone marrow proliferation when compared with the other three groups and this enhancement correlated with increased circulating neutrophils. Combined immunomodulator and antibiotic therapy had synergistic effects on survival in <i>E. coli</i> peritonitis. This combined therapy enhanced macrophage secretory activity and bone marrow proliferation. Clinical use of immunomodulators may alter conventional use and dosage of antibiotics.</p>
<p>Almdahl SM, Bogwald J, Hoffman J, Sjunneskog C, Seljelid R.</p> <p>The effect of splenectomy on <i>Escherichia coli</i> sepsis and its treatment with semisoluble aminated glucan.</p> <p><i>Scand J Gastroenterol.</i> 1987 Apr;22(3):261-7.</p> <p>PMID: 3296131 [PubMed - indexed for MEDLINE]</p>	<p>Rats were subjected to sham laparotomy or splenectomy and were challenged with either 0.2×10^9 <i>Escherichia coli</i> intravenously or 1×10^9 <i>E. coli</i> intraperitoneally. By means of quantitative blood culturing asplenic animals were shown to have a significantly impaired ability to clear the bacteria in both forms of challenge. Treatment with intraperitoneally injected semisoluble aminated glucan (SAG), known to have strong macrophage-stimulatory properties, compensated completely for the asplenic state. The substance protected against postsplenectomy sepsis both when given before and when given after removal of the spleen. This protective effect of SAG seemed to last at least 3 weeks.</p>
<p>Seljelid R, Rasmussen LT, Larm O, Hoffman J.</p> <p>The protective effect of beta 1-3D-glucan-derivatized plastic beads against <i>Escherichia coli</i> infection in mice.</p> <p><i>Scand J Immunol.</i> 1987 Jan;25(1):55-60.</p> <p>PMID: 3544199 [PubMed - indexed for MEDLINE]</p>	<p>Pretreatment with beta-1,3-D-glucan-derivatized plastic beads conferred strong protection against <i>Escherichia coli</i> infection in mice. The protective effect showed a dose-response relationship to the amount of beads injected and was dependent on the time point of the injection relative to the infection with <i>E. coli</i>. A similar protection could be obtained in nude mice. Experiments with radioactively labelled bacteria as well as beads indicated a systemic effect of the beads. Macrophages extracted from animals treated with glucan plastic beads appeared highly stimulated. This was also true of cells that did not contain beads and presumably therefore not glucan, which seems to indicate a soluble stimulatory factor.</p>

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<p>Seljelid R, Bogwald J, Rasmussen LT, Larm O, Hoffman J, Berge A, Ugelstad J.</p> <p>In vivo activation of mouse macrophages with beta-1,3-D-glucan-derivatized plastic beads.</p> <p><i>Scand J Immunol.</i> 1985 Jun;21(6):601-5.</p> <p>PMID: 4023630 [PubMed - indexed for MEDLINE]</p>	<p>Macrophages obtained from animals treated with beta-1,3-D-glucan-derivatized plastic beads were greatly stimulated, as judged by morphology, esterase release, and cytostatic effect on L-929 tumour cells in vitro. The pretreatment of mice with such beads conferred an apparent absolute local resistance to an otherwise lethal pneumococcal infection but had no effect on the growth of intraperitoneal AA ascites sarcoma. Moreover, peritoneal cells from animals pretreated with glucan beads did not protect the animals in a Winn assay.</p>
<p>Browder IW, Williams DL, Kitahama A, Di Luzio NR.</p> <p>Modification of post-operative <i>C. albicans</i> sepsis by glucan immunostimulation.</p> <p><i>Int J Immunopharmacol.</i> 1984;6(1):19-26.</p> <p>PMID: 6724765 [PubMed - indexed for MEDLINE]</p>	<p>Glucan, a beta-1,3 polyglucose, was evaluated for its ability to enhance resistance of post-operative mice to experimentally induced <i>C. albicans</i> sepsis. Male C57BL/6J mice were injected i.v. with glucan (0.45 mg/mouse) on days 10,7,4 and 1 prior to midline laparotomy and intravenous challenge with 3 X 10(6) <i>C. albicans</i>. The detrimental effect of surgery on survival following <i>C. albicans</i> infection was manifested by a 47% survival in the non-surgery-infected group in contrast to 20% in the surgery-infected group. Protection against <i>C. albicans</i> was observed in the glucan-treated groups. The glucan-treated non-operated mice manifested 100% survival while the surgery group had a 73% survival. Glucan significantly enhanced macrophage phagocytic function in control and operated mice. Laparotomy alone did not significantly depress macrophage phagocytosis. Histopathological studies revealed that glucan markedly inhibited the renal pathology associated with <i>C. albicans</i> challenge both in the presence and absence of laparotomy. These data indicate that glucan increased survival and reduced renal pathology associated with <i>C. albicans</i> challenge in the post-operative period. These observations suggest that Biologic Response Modifiers such as glucan may be effectively employed in patients who are at risk for post-operative infections.</p>
<p>Browder W, Rakinic J, McNamee R, Jones E, Williams D, Di Luzio N.</p> <p>Protective effect of nonspecific immunostimulation in postsplenectomy sepsis.</p> <p><i>J Surg Res.</i> 1983 Dec;35(6):474-9.</p> <p>PMID: 6656237 [PubMed - indexed for MEDLINE]</p>	<p>The enhanced risk of severe sepsis following splenectomy is now well recognized in both adult and pediatric patients. Prophylactic antibiotics and bacterial vaccines have been utilized with limited success to inhibit the high morbidity and mortality. This study reports the use of glucan, a beta-1,3-polyglucose, as a nonspecific immunostimulant for postsplenectomy pneumococcal sepsis. ICR mice were treated with glucan or glucose (5% w/v) following splenectomy or sham operation. Mice were then challenged with 1 X 10(9) <i>Streptococcus pneumoniae</i> intranasally. Glucan significantly increased survival in the splenectomy group (75%) compared to controls (27%). Phagocytic function, as measured by the clearance of 131I-triolein-labeled reticuloendothelial test lipid emulsion, was increased in the glucan group when compared to control glucose animals, both in the presence and absence of pneumococcal infection. Splenectomy alone did not significantly decrease phagocytic function. An increased leukocytosis in response to pneumococcal infection was observed in splenectomized glucan-treated animals. Nonspecific immunostimulation appears to have significant potential as a treatment strategy against postsplenectomy infection.</p>

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<p>Williams DL, Browder IW, Di Luzio NR.</p> <p>Immunotherapeutic modification of <i>Escherichia coli</i>--induced experimental peritonitis and bacteremia by glucan.</p> <p><i>Surgery</i>. 1983 Mar;93(3):448-54.</p> <p>PMID: 6338616 [PubMed - indexed for MEDLINE]</p>	<p>Previous data from our laboratory have demonstrated that glucan administration significantly alters the course of a variety of experimentally induced infectious diseases. In view of the increasing incidence of gram-negative infections, studies were initiated to evaluate the effect of intraperitoneal glucan therapy on <i>Escherichia coli</i>-induced peritonitis and sepsis. Male ICR/Tex mice were injected intraperitoneally with glucan or dextrose on days 5 and 3 prior to intraperitoneal challenge with 1.0×10^8 <i>E. coli</i>. Glucan administration resulted in a significant enhancement of survival. Evaluation of the mechanism of protective action of glucan revealed that both the glucan and dextrose control groups showed an equivalent level of blood-borne <i>E. coli</i> at early periods. At 6 hours after challenge the glucan group showed a significant decrease in blood-borne <i>E. coli</i>. In contrast, the dextrose control group demonstrated progressive bacteremia. A significant depression of phagocytic activity occurred in <i>E. coli</i>-infected mice as compared with control mice that were not exposed to the bacterial challenge. The enhancement in phagocytic function observed in glucan-treated control mice was unaltered in <i>E. coli</i> challenged, glucan-treated mice. The possible importance of hyperfunctional macrophages in reduction of mortality from <i>E. coli</i> sepsis was denoted by methyl palmitate-induced reversal of the glucan hyperfunctional state. Methyl palmitate-treated glucan injected mice were not protected against <i>E. coli</i> infection. These data denote that the intraperitoneal administration of glucan significantly modifies the course of <i>E. coli</i>-induced peritonitis and bacteremia due, in part, to glucan-induced enhancement of macrophage function.</p>
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