

Saccharomyces boulardii in the prevention of antibiotic-associated diarrhoea in children: a randomized double-blind placebo-controlled trial

M. KOTOWSKA, P. ALBRECHT & H. SZAJEWSKA

Department of Pediatric Gastroenterology and Nutrition, The Medical University of Warsaw, Warsaw, Poland

Accepted for publication 24 November 2004

SUMMARY

Background: Co-treatment with *Saccharomyces boulardii* appears to lower the risk of antibiotic-associated diarrhoea in adults receiving broad-spectrum antibiotics.

Aim: To determine whether *S. boulardii* prevents antibiotic-associated diarrhoea in children.

Methods: A total of 269 children (aged 6 months to 14 years) with otitis media and/or respiratory tract infections were enrolled in a double-blind, randomized placebo-controlled trial in which they received standard antibiotic treatment plus 250 mg of *S. boulardii* (experimental group, $n = 132$) or a placebo (control group, $n = 137$) orally twice daily for the duration of antibiotic treatment. Analyses were based on allocated treatment and included data from 246 children.

Results: Patients receiving *S. boulardii* had a lower prevalence of diarrhoea (≥ 3 loose or watery stools/day for ≥ 48 h occurring during or up to 2 weeks after the antibiotic therapy) than those receiving placebo [nine of 119 (8%) vs. 29 of 127 (23%), relative risk: 0.3, 95% confidence interval: 0.2–0.7]. *S. boulardii* also reduced the risk of antibiotic-associated diarrhoea (diarrhoea caused by *Clostridium difficile* or otherwise unexplained diarrhoea) compared with placebo [four of 119 (3.4%) vs. 22 of 127 (17.3%), relative risk: 0.2; 95% confidence interval: 0.07–0.5]. No adverse events were observed.

Conclusion: This is the first randomized-controlled trial evidence that *S. boulardii* effectively reduces the risk of antibiotic-associated diarrhoea in children.

INTRODUCTION

Antibiotic-associated diarrhoea (AAD) is defined as an acute inflammation of the intestinal mucosa caused by the administration of broad-spectrum antibiotics. The bacterial agent most commonly associated with AAD is *Clostridium difficile*.¹ However, when the normal faecal Gram-negative organisms are absent, overgrowth by staphylococci, yeasts and fungi has been implicated.²

The frequency of AAD depends on the definition of diarrhoea, the inciting antimicrobial agents and host

factors. Almost all antibiotics, particularly those that act on anaerobes, can cause diarrhoea, but the risk is higher with aminopenicillins, a combination of aminopenicillins and clavulanate, cephalosporins and clindamycin.^{3, 4} AAD occurs in approximately 5–30% of patients between the initiation of therapy and up to 2 months after the end of treatment.^{1, 5, 6} The incidence of diarrhoea in children receiving broad-spectrum antibiotics ranges from 11 to 40%.^{7, 8}

Measures to prevent AAD include the use of probiotics, which are live microbial food ingredients that are beneficial to health.⁹ Well-known probiotics include lactobacilli, bifidobacteria and the yeast *Saccharomyces boulardii*. The rationale for the use of probiotics in AAD is based on the assumption that the key factor in the

Correspondence to: Dr H. Szajewska, Department of Paediatric Gastroenterology and Nutrition, The Medical University of Warsaw, 01-184 Warsaw, Dzialdowska 1, Poland.
E-mail: hania@ipgate.pl

pathogenesis of AAD is a disturbance in normal intestinal microflora.¹⁰

Studies have established the effectiveness of *S. boulardii* in the prevention of AAD in adults. A recent meta-analysis of four randomized-controlled trials (RCTs)^{11–14} involving 688 adults showed that compared with placebo, *S. boulardii* was associated with a statistically significant decrease in the incidence of AAD (odds ratio 0.39; 95% CI: 0.25–0.62).¹⁵ However, it is unclear whether similar benefits occur in children, as the only published trial involving children was neither randomized nor blinded.¹⁶ Furthermore, conflicting data about the effects of another probiotic, *Lactobacillus rhamnosus* GG, suggest a different response in adult¹⁷ and paediatric populations^{18, 19} and that results observed in one population cannot be simply extrapolated to the other. Therefore, our study was designed to assess the effectiveness of *S. boulardii* in preventing AAD in children requiring antibiotic treatment for otitis media and/or respiratory tract infection.

PATIENTS AND METHODS

Study design

This was a double-blind, randomized, placebo-controlled clinical trial intended to evaluate the efficacy, safety and tolerability of *S. boulardii* in the prevention of AAD in children.

Randomization

Investigators at the Medical University of Warsaw used computers to generate independent allocation sequences and randomization lists for each study site. To avoid a disproportionate number of patients in the experimental or placebo group, randomization at each site was performed in blocks of six (three received placebo and three, active treatment). To ensure allocation concealment, an independent subject prepared the randomization schedule and oversaw the packaging and labelling of trial treatments. All investigators, participants, outcome assessors and data analysts were blinded to the assigned treatment throughout the study.

Participants

The study was conducted between November 2002 and May 2004. Recruitment took place in Poland, at three

paediatric hospitals (Warsaw, Nowa Deba and Kielce) and two out-patient clinics (Warsaw). Eligible patients were those aged 6 months to 14 years with acute otitis media and/or respiratory tract infection who started short-term treatment with oral or intravenous antibiotics within 24 h of enrolment. Exclusion criteria included the presence of a severe or generalized bacterial infection, antibiotic treatment within the previous 2 months, prophylactic antibiotic treatment, use of a probiotic product for medicinal purposes within the previous 7 days, immunodeficiency, chronic gastrointestinal disease and acute or chronic diarrhoea.

Study procedure

Eligible children were randomly assigned to receive antibiotic therapy (the choice of antibiotic was in line with the Polish recommendations for the treatment of acute otitis media and respiratory tract infections)²⁰ plus either 250 mg of *S. boulardii* or a comparable placebo. Both the active treatment and placebo were taken orally twice daily for the duration of the antibiotic treatment.

The active treatment and placebo used in this study were prepared centrally by the hospital pharmacy at the Medical University of Warsaw as identically appearing wafers. The placebo contained *Saccharum lactis* (250 mg). Each wafer was either swallowed whole or opened with the contents dissolved in a small amount of fluid, according to the child's preferences. Patients received study drugs for the whole duration of antibiotic treatment.

Each patient (or a parent, in the case of very young patients) received a diary to record the frequency of daily bowel movements, as well as any symptoms they considered important. Stool number and consistency were recorded daily. In the event of loose or watery stools, patients were advised to contact their doctors and bring stool samples for analysis. The presence of rotavirus-antigen was investigated in all diarrhoeal stool samples using a commercial latex agglutination test with a rotavirus-specific monoclonal antibody (Slidex Rota-Kit 2; BioMerieux, Lyon, France). Standard stool cultures were used to screen for bacteria (*Salmonella*, *Shigella*), and *C. difficile* toxins A and B were identified by enzyme immunoassay (*C. difficile* TOX A/B Test, TechLab Inc., Blacksburg, VA, USA).

Treatment compliance was assessed by direct interview of the patient (or parent) and review of the diary cards (which documented the number of daily wafers taken).

Treatment responses also were assessed by evaluation of the daily diaries.

Outcome measures

The 'primary' outcome measures were the frequencies of diarrhoea and AAD. Diarrhoea was defined as ≥ 3 loose or watery stools per day for a minimum of 48 h, occurring during and/or up to 2 weeks after the end of the antibiotic therapy. AAD was diagnosed in cases of diarrhoea, defined clinically as above, caused by *C. difficile* (the major enteropathogen in AAD)¹ or for otherwise unexplained diarrhoea (i.e. negative laboratory stool test for rotavirus and negative stool culture). The 'secondary' outcome measures were the frequencies of rotaviral diarrhoea, *Salmonella* diarrhoea, *Shigella* diarrhoea and *C. difficile* diarrhoea; the need for discontinuation of the antibiotic treatment, hospitalization to manage the diarrhoea (in out-patients), or intravenous rehydration in any of the study groups; and adverse events.

Sample size

We assumed that the study withdrawal rate would be at least 20% and that the probability of an episode of AAD occurring in the control group would be equal to 0.25 (25%). Based on this, we estimated that a minimum sample size of 135 children in each treatment group would show, with a 5% level of significance and a power of 80%, a 10% reduction in the proportion of children with AAD in the intervention groups (Fisher exact test).

Statistical analysis

The Student's *t*-test was used to compare mean values of continuous variables approximating a normal distribution. For non-normally distributed variables, the Mann-Whitney *U*-test was used. The chi-square test or Fisher exact test was used, as appropriate, to compare percentages. The relative risk (RR), 95% confidence interval (CI), and number needed to treat (NNT) were calculated using the same computer software. The difference between study groups was considered significant when the *P*-value was <0.05 or when the 95% CI for RR did not exceed 1.0 (equivalent to $P < 0.05$). Statistical analysis was performed using the computer software STATDIRECT^{1,9,12} [(2002-05011); Iain E. Buchan]. All statistical tests were two tailed and performed at the 5% level of significance.

We report the analysis based on allocated treatment, i.e. all of the participants in a trial for which outcome data were available were analysed according to the intervention to which they were assigned, whether or not they received it. A potential problem with this type of analysis is that, unless the absence of an observation is independent of outcome, missing responses can lead to bias. Therefore, for both primary outcome measures, we also investigated the effect of various methods of handling missing responses in a trial.²¹ That is, we compared outcomes in both treatment groups (*S. boulardii* vs. placebo) assuming: (i) all patients in both groups with an unknown outcome to have had either a good or a poor outcome, (ii) extreme case favouring of *S. boulardii* and (iii) extreme case favouring of placebo.

Ethical considerations

Parents were fully informed about the aims of the study, and informed consent was obtained from at least one parent. The study protocol was reviewed and approved by the ethical review committee.

RESULTS

Characteristics and outcome measures

Figure 1 is a flow diagram showing the subjects' progression through the study. Of the 269 children

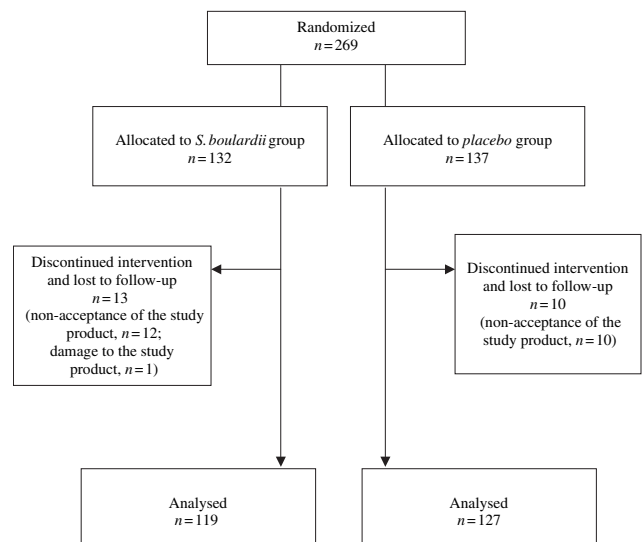


Figure 1. Flow diagram of the subjects' progression through the study.

enrolled in the study, 132 received *S. boulardii* and 137 received placebo. Overall, 23 (8.6%) of the randomized children [13 (9.8%) in the *S. boulardii* group and 10 (7.2%) in the placebo group] withdrew before completing the trial and were lost to follow-up. The reasons for not completing the trial were non-acceptance of the allocated intervention ($n = 22$) or damage of the study product ($n = 1$) (Figure 1). Thus, of the 269 children enrolled, 246 (91.4%) were available for the analyses (experimental group, $n = 119$; placebo group, $n = 127$). Baseline demographic and clinical characteristics did not significantly differ between the two groups (Table 1).

The outcome measures are summarized in Table 2. Overall, diarrhoea was diagnosed in 38 of 246 (15.4%) children and AAD, in 26 of 246 (10.6%) children. The addition of *S. boulardii* vs. placebo to antibiotic therapy reduced the risk of diarrhoea [nine of 119 (7.5%) vs. 29 of 127 (23%), RR 0.3, 95% CI: 0.2–0.7; NNT 7, 95% CI: 5–16]. *Saccharomyces*

boulardii also reduced the risk of AAD when compared with placebo [four of 119 (3.4%) vs. 22 of 127 (17.3%), RR 0.2, 95% CI: 0.07–0.5]. Eight (95% CI: 5–15) children would need to be treated with *S. boulardii* to prevent a single episode of AAD. The risk of documented *C. difficile* diarrhoea was also lower in the *S. boulardii* group compared with the placebo group, but the difference was of borderline significance (RR 0.3, 95% CI: 0.1–1.04). There was no need for discontinuation of antibiotic treatment, hospital treatment because of diarrhoea in the out-patients, or intravenous rehydration in any of the study groups. The *S. boulardii* was well-tolerated, and no adverse events associated with this therapy (or with the use of placebo) were reported.

Table 3 summarizes characteristics of the patients who experienced AAD. Compared with the placebo, *S. boulardii* significantly reduced the risk of diarrhoea caused by oral amoxicillin in combination with clavulanate, and intravenous cefuroxime.

	<i>Saccharomyces boulardii</i>	Placebo	P-value‡
Number of patients	132	137	
Sex (girls/boys)	66/66	82/55	0.2
Age (months, minimum–maximum)*	58.8 ± 44 (6.2–178)	55.8 ± 43.5 (5.2–182)	0.5†
Diagnosis			
Bronchitis	35 (54.7)	29 (45.3)	0.4
Otitis media	36 (45.6)	43 (54.4)	0.4
Pneumonia	35 (56.5)	27 (43.5)	0.3
Tonsillitis	24 (41.4)	34 (58.6)	0.2
Others	2 (33.3)	4 (66.7)	0.4
Antibiotic used			
Cefuroxime axetil	38 (52.8)	34 (47.2)	0.6
Amoxicillin + clavulanate	27 (58.7)	19 (41.3)	0.2
Amoxicillin	13 (39.4)	20 (60.6)	0.2
Cefuroxime (intravenously)	18 (46.2)	21 (53.8)	0.6
Penicillin	13 (39.4)	20 (60.6)	
Clarithromycin	11 (55.0)	9 (45.0)	0.6
Roxithromycin	5 (38.5)	8 (61.5)	0.4
Other	7 (53.8)	6 (46.2)	
Route of administration			
Orally	99 (49.0)	103 (51.0)	0.8
Intravenously	33 (49.3)	34 (50.7)	0.9
Setting			
Out-patient	95 (48.2)	102 (51.8)	0.6
Hospital	37 (51.4)	35 (48.6)	0.8

Values in parentheses expressed as percentage.

* Mean ± s.d.

† Mann–Whitney *U*-test.

‡ Chi-square test or Fisher exact test (as appropriate).

Table 1. Baseline characteristics of the study groups

Table 2. Outcomes measures

Outcome measure	<i>Saccharomyces boulardii</i> (n = 119)	Placebo (n = 127)	RR (95% CI)	NNT (95% CI)
Diarrhoea	9 (7.5%)	29 (23%)	0.3 (0.2–0.7)	7 (5–16)
Cause of diarrhoea				
Rotavirus	5 (4.2%)	7 (5.5%)	0.8 (0.3–2.2)	N.S.
<i>Clostridium difficile</i>	3 (2.5%)	10 (7.9%)	0.3 (0.1–1.04)	N.S.
Unexplained diarrhoea*	1 (0.8%)	12 (3%)	0.2 (0.03–1.4)	N.S.
Antibiotic-associated diarrhoea (<i>C. difficile</i> + unexplained*)	4 (3.4%)	22 (17.3%)	0.2 (0.07–0.5)	8 (5–15)
Need for discontinuation of antibiotic treatment	–	–		
Need for hospitalization of out-patients to manage diarrhoea	–	–		
Need for intravenous rehydration	–	–		
Adverse effects during intervention	–	–		

RR, relative risk; CI, confidence interval; NNT, number needed to treat.

* Negative laboratory stool test for rotavirus and negative stool culture for *Salmonella* and *Shigella*.

Table 3. Characteristics of patients with antibiotic-associated diarrhoea

	<i>Saccharomyces boulardii</i> (n = 4)	Placebo (n = 22)	P-value‡	RR (95% CI)	NNT (95% CI)
Age (months, minimum–maximum)*	39.3 ± 29 (11–70)	39.3 ± 41 (5–168)	<0.7†		
Time to onset diarrhoea (days, minimum–maximum)*	4.8 ± 2.5 (2–8)	4.9 ± 3 (1–11)	<0.9†		
Antibiotic used					
Cefuroxime axetil	2/36 (5.6%)	1/30 (3.3%)	<0.9	1.7 (0.2–12)	N.S.
Amoxicillin + clavulanate	1/23 (4.3%)	5/17 (29.4%)	<0.007	0.15 (0.02–0.9)	4 (3–38)
Amoxicillin	1/11 (9.1%)	7/20 (35%)	<0.2	0.26 (0.04–1.3)	N.S.
Cefuroxime intravenous	0/15 (0%)	6/19 (31.6%)	<0.02	0 (0.7 to ??)	4 (2–13)
Penicillin	0/11 (0%)	1/18 (5.6%)	<0.6	0 (5.9 to ??)	N.S.
Clarithromycin	0/11 (0%)	0/9 (0%)	<1.0	?? to ??	N.S.
Roxithromycin	0/5 (0%)	0/8 (0%)	<1.0	?? to ??	N.S.
Other	0/7 (0%)	2/6 (33.3%)	<1.0	0 (1.4 to ??)	N.S.
Route of administration					
Orally	4/89 (4.6%)	15/97 (15.5%)	<0.01	0.3 (0.1–0.8)	10 (5–41)
Intravenously	0/30 (0%)	7/30 (23.3%)	<0.02	0 (0.5 to ??)	5 (3–10)
Setting					
Out-patient	4/89 (4.5%)	15/96 (15.6%)	<0.01	0.3 (0.1–0.8)	9 (5–39)
Hospital	0/30	7/31 (22.6%)	<0.02	0 (0.5 to ??)	5 (3–11)
Duration of antibiotic treatment (minimum–maximum)	7.8 ± 1 (7–9)	8.1 ± 1.9 (5–13)	<0.9†		

RR, relative risk; CI, confidence interval; NNT, number needed to treat; N.S., not significant.

* Mean ± s.d.

† Mann–Whitney *U*-test.

‡ Chi-square test or Fisher exact test (as appropriate).

?? Infinity.

Investigation of the potential effects of missing responses

Assuming all patients in both groups with an unknown outcome to have had either a good or a poor outcome, our results demonstrate a significant difference in outcomes between the two treatments. Assuming extreme case favouring of *S. boulardii* (i.e. all of the

patients with an unknown outcome in the placebo group and none of the patients in the *S. boulardii* group had diarrhoea or AAD) gave similar results. The only exception was upon assuming (the unlikely) extreme case favouring of placebo (i.e. all of the patients with an unknown outcome in the *S. boulardii* group and none of the patients in the placebo group had diarrhoea or

AAD), which showed no significant difference between the groups.

DISCUSSION

To our knowledge, this is the first RCT to assess the effectiveness of *S. boulardii* in preventing AAD in children. Consistent with previous findings in adults,¹⁵ we found that *S. boulardii* (250 mg twice daily) is effective in preventing AAD in children treated with antibiotics for otitis media and/or respiratory tract infections. For every eight patients receiving daily *S. boulardii* with antibiotics, one fewer will develop AAD. The risk of *C. difficile* diarrhoea was lower in our group of children receiving *S. boulardii* compared with placebo, however, the difference was of borderline significance.

This is also one of the few trials to evaluate potential important consequences of AAD (e.g. need for discontinuation of antibiotic treatment, hospitalization or intravenous rehydration). Despite rather conservative definition of diarrhoea used in this trial (≥ 3 loose or watery stools per day for a minimum of 48 h), no diarrhoeal episodes required hospitalization of outpatients or additional treatment.

The mechanism by which *S. boulardii* exerts its action in preventing AAD is unclear. Possible mechanisms, which have been demonstrated in animals, include the production of a protease that inactivates the toxin A receptor, the production of increased levels of secretory IgA and IgA antitoxin A and competition for attachment sites.^{22–24} *Saccharomyces boulardii* has also been shown to block *C. difficile* adherence to cells *in vitro*.²⁵

The consistency of the results obtained with *S. boulardii* in the paediatric (this study) and adult (prior reports) populations is noteworthy given the conflicting results from RCTs evaluating the efficacy of another probiotic strain, *Lactobacillus* GG. Whereas co-administration of *Lactobacillus* GG (with antimicrobials) reduced both the incidence and duration of associated diarrhoea in two RCTs involving children,^{18, 19} it failed to prevent diarrhoea in a large study of hospitalized adults.¹⁷ Potential reasons for these conflicting results include the use of lower dosages of probiotics in adults, differences in the administered antibiotics, and/or age-related differences in the pathogenesis of AAD.

The design of this study does not allow conclusions about the efficacy of *S. boulardii* in preventing diarrhoea

attributable to any single antibiotic class. However, our result suggests that *S. boulardii* effectively prevents diarrhoea caused by amoxicillin in combination with clavulanate as well as intravenously administered cefuroxime. Larger trials will be necessary to further address these issues.

Patients were only followed up for 2 weeks after their antibiotic treatment. As diarrhoea may occur up to 2 months after the end of such treatment, some cases of AAD may have been missed. Also, because we only evaluated the presence of major enteropathogens in diarrhoeal stool samples, one cannot exclude the possibility that some of the cases of unexplained diarrhoea were caused by unidentified infectious agents. Thus, AAD as defined in this study should be considered of possible, rather than of obvious, antibiotic origin.

In our study, *Saccharum lactis* was used as a placebo. As data regarding the reliability of routine tests for diagnosing lactose malabsorption in children are scarce,²⁶ no specific tests were performed to exclude lactase deficiency. However, we did obtain a detailed history of acute/chronic diarrhoea, as well as any chronic gastrointestinal diseases, in each patient. Thus, we believe it is unlikely that there were any unrecognized cases of lactose malabsorption contributing to the diarrhoea. Furthermore, the double-blind randomized design and large number of participants represent compensatory strengths of our study.

Although our study shows that *S. boulardii* may be useful in preventing AAD, it provides little support for a role of *S. boulardii* in its treatment. Further, RCTs are needed to explore this issue as well as potential treatment complications. Whereas no adverse effects were observed in our study, the administration of *S. boulardii* is not without risk. Almost 30 case reports of *S. boulardii* fungaemia exist in the literature.^{27–37} Most complications have occurred in immunocompromised subjects or in patients with other life-threatening illnesses.

CONCLUSION

Results from this prospective RCT support the use of *S. boulardii* as adjunctive treatment in children undergoing antibiotic therapy for otitis media and/or respiratory tract infections. The likely advantages of probiotic co-administration with antibiotics include ease of administration and potential cost benefits. Yet some issues need to be resolved before widespread use of probiotics is

advocated, including how to identify populations at high risk for AAD. In addition, future trials should address the efficacy of *S. boulardii* in preventing AAD in children caused specifically by *C. difficile* or those antibiotics that are most likely to cause diarrhoea, as well as the effectiveness of *S. boulardii* in treating AAD in children.

ACKNOWLEDGEMENTS

Authors thank Dr M Armańska (Kielce) and Dr J Józefczuk (Nowa Dęba) for their contribution to data collection. Also thank Dr L. Blakemore for the English review of the paper.

REFERENCES

- Bartlett JG, Chang TW, Gurwith M, Gorbach SL, Onderdonk AB. Antibiotic-associated pseudomembranous colitis due to toxin producing clostridia. *N Engl J Med* 1978; 298: 531–4.
- Högenauer C, Hammer HF, Krejs GJ, Reisinger EC. Mechanisms and management of antibiotic-associated diarrhoea. *Clin Infect Dis* 1998; 27: 702–10.
- Barbut F, Meynard JL, Guiguet M, *et al.* *Clostridium difficile*-associated diarrhoea in HIV infected patients: epidemiology and risk factors. *J Acquir Immune Defic Syndr* 1997; 16: 176–81.
- McFarland LV, Surawicz CM, Stamm WE. Risk factors for *Clostridium difficile* carriage and *C. difficile*-associated diarrhoea in a cohort of hospitalized patients. *J Infect Dis* 1990; 162: 678–84.
- Wiström J, Norrby SR, Myhre EB, *et al.* Frequency of antibiotic-associated diarrhoea in 2462 antibiotic-treated hospitalized patients: a prospective study. *J Antimicrob Chemother* 2001; 47: 43–50.
- McFarland LV. Epidemiology, risk factors and treatments for antibiotic-associated diarrhoea. *Dig Dis* 1998; 16: 292–307.
- Turck D, Bernet JP, Marx J, *et al.* Incidence and risk factors of oral antibiotic-associated diarrhoea in an outpatient pediatric population. *J Pediatr Gastroenterol Nutr* 2003; 37: 22–6.
- Elstner CL, Lindsay AN, Book LS, Matsen JM. Lack of relationship of *Clostridium difficile* to antibiotic-associated diarrhoea in children. *Pediatr Inf Dis* 1983; 2: 364–6.
- Diplock AT, Aggett PJ, Ashwell M, *et al.* Scientific concepts of functional foods in Europe: consensus document. *Br J Nutr* 1999; 81 (Suppl. 1): S1–S27.
- Surawicz CM. Probiotics, antibiotic-associated diarrhoea and *Clostridium difficile* diarrhoea in humans. *Best Pract Res Clin Gastroenterol* 2003; 17: 775–83.
- McFarland LV, Surawicz CM, Greenberg RN, *et al.* Prevention of β -lactam-associated diarrhoea by *Saccharomyces boulardii* compared with placebo. *Am J Gastroenterol* 1995; 90: 439–48.
- Lewis SJ, Potts LF, Barry RE. The lack of therapeutic effect of *S. boulardii* in the prevention of antibiotic related diarrhoea in elderly patients. *J Infect* 1998; 36: 171–4.
- Adam J, Barret A, Barret-Bellet C. Essais cliniques contrôlés en double insu de l'ultra-levure lyophilisée: étude multicentrique par 25 médecins de 388 cas. *Gaz Med Fr* 1977; 84: 2072–8.
- Surawicz CM, Elmer GW, Speelman P, McFarland LV, Chinn J, Van Belle G. Prevention of antibiotic-associated diarrhoea by *Saccharomyces boulardii*. *Gastroenterology* 1989; 96: 981–8.
- D'Souza AL, Rajkumar C, Cooke J, Bulpitt CJ. Probiotics in prevention of antibiotic-associated diarrhoea: meta-analysis. *BMJ* 2002; 324: 1361–4.
- Erdeve O, Tiras U, Dallar Y. The probiotic effect of *Saccharomyces boulardii* in a pediatric age group. *J Trop Pediatr* 2004; 50: 234–6.
- Thomas MR, Litin SC, Osmon DR, Corr AP, Weaver AL, Lohse CM. Lack of effect of *Lactobacillus* GG on antibiotic-associated diarrhoea: a randomized, placebo controlled trial. *Mayo Clin Proc* 2001; 76: 883–9.
- Vanderhoof JA, Whitney DB, Antonson DL, Hanner TL, Lupo JV, Young RJ. *Lactobacillus* GG in the prevention of antibiotic-associated diarrhoea in children. *J Pediatr* 1999; 135: 564–8.
- Arvola T, Laiho K, Torkkeli S, *et al.* Prophylactic *Lactobacillus* GG reduces antibiotic-associated diarrhoea in children with respiratory infections: a randomized study. *Pediatrics* 1999; 104: e64.
- Hryniewicz W, Grzesiowski P. Rekomendacje 2003. Zakażenia układu oddechowego – Etiologia, rozpoznawanie, leczenie. Fundacja Centrum Mikrobiologii Klinicznej, Warszawa, 2002.
- Hollis S, Campbell F. What is meant by intention to treat analysis? Survey of published randomized controlled trials. *Br Med J* 1999; 319: 670–4.
- Pothoulakis C, Kelly CP, Joshi MA, *et al.* *Saccharomyces boulardii* inhibits *Clostridium difficile* toxin A binding and enterotoxicity in rat ileum. *Gastroenterology* 1993; 104: 1108–15.
- Wilson KH, Perini I. Role of competition for nutrients in suppression of *Clostridium difficile* by the colonic microflora. *Infect Immun* 1988; 56: 2610–14.
- Qamar A, Aboudola A, Warny M, *et al.* *Saccharomyces boulardii* stimulates intestinal immunoglobulin A immune response to *Clostridium difficile* toxin A in mice. *Infect Immun* 2001; 69: 2762–5.
- Tasteyre A, Barc MC, Karjalainen T, *et al.* Inhibition of in vitro cell adherence of *Clostridium difficile* by *Saccharomyces boulardii*. *Microb Pathog* 2002; 32: 219–25.
- Rasinpera H, Savilahti E, Enattah NS, *et al.* A genetic test which can be used to diagnose adult-type hypolactasia in children. *Gut* 2004; 53: 1571–6.
- Bassetti S, Frei R, Zimmerli W. Fungemia with *Saccharomyces cerevisiae* after treatment with *S. boulardii*. *Am J Med* 1998; 105: 71–2.
- Cesaro S, Chinello P, Rossi L, Zanesco L. *Saccharomyces cerevisiae* fungemia in a neutropenic patient treated with *S. boulardii*. *Support Care Cancer* 2000; 8: 504–5.
- Fredenucci I, Chomarat M, Boucaud C, Flandrois JP. *S. boulardii* fungemia in a patient receiving ultra-levure therapy. *Clin Infect Dis* 1998; 27: 222–3.

- 30 Lherm T, Monet C, Nougere B, *et al.* Seven cases of fungemia with *S. boulardii* in critically ill patients. *Intensive Care Med* 2002; 28: 797–801.
- 31 Niault M, Thomas F, Prost J, Ansari HF, Kalfon P. Fungemia due to *Saccharomyces* species in a patient treated with enteral *S. boulardii*. *Clin Infect Dis* 1999; 28: 930.
- 32 Perapoch J, Planes AM, Querol A, *et al.* Fungemia with *Saccharomyces cerevisiae* in two newborns, only one of whom had been treated with ultra-levure. *Eur J Clin Microbiol Infect Dis* 2000; 19: 468–70.
- 33 Pletincx M, Legein J, Vandenplas Y. Fungemia with *S. boulardii* in a 1-year-old girl with protracted diarrhoea. *J Pediatr Gastroenterol Nutr* 1995; 21: 113–5.
- 34 Rijnders BJA, Van Wijngaerden E, Verwaest C, Peetermans WE. *Saccharomyces* fungemia complicating *S. boulardii* treatment in a non-immunocompromised host. *Intensive Care Med* 2000; 26: 825.
- 35 Viggiano M, Badetti C, Bernini V, Garabedian M, Manelli JC. *S. boulardii* fungemia in a patient with severe burns. *Ann Fr Anesth Reanim* 1995; 14: 356–8.
- 36 Zunic P, Lacotte J, Pegoix M, *et al.* *S. boulardii* fungemia. Apropos of a case. *Therapie* 1991; 46: 498–9.
- 37 Cassone M, Serra P, Mondello F, *et al.* Outbreak of *Saccharomyces cerevisiae* subtype *boulardii* fungemia in patients neighboring those treated with a probiotic preparation of the organism. *J Clin Microbiol* 2003; 41: 5340–3.