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Saccharomyces boulardii prevents diarrhea in critically ill tube-fed patients*

A multicenter, randomized, double-blind placebo-controlled trial

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Abstract *Objective*: To assess the preventive effect of *Saccharomyces boulardii* on diarrhea in critically ill tube-fed patients and to evaluate risk factors for diarrhea.
Design: Prospective, multicenter, randomized, double-blind placebo-controlled study.
Setting: Eleven intensive care units in teaching and general hospitals.
Patients: Critically ill patients whose need for enteral nutrition was expected to exceed 6 days.
Intervention: *S. boulardii* 500 mg four times a day versus placebo.
Measurements and results: Diarrhea was defined by a semiquantitative score based on the volume and consistency of stools. A total of 128 patients were studied, 64 in each group. Treatment with *S. boulardii* reduced the mean percentage of days with diarrhea per feeding days from 18.9 to 14.2 % [odds ratio (OR) = 0.67, 95 % confidence interval (CI) = 0.50–0.90, $P = 0.0069$]. In the control group, nine risk factors were significantly associated with diarrhea: nonsterile administration of nutrients in open containers, previous suspension of oral feeding, malnutrition, hypoalbuminemia, sepsis syndrome, multiple organ failure, presence of an infection site, fever or hypothermia, and use of antibiotics. Five independent factors were associated with diarrhea in a multivariate analysis: fever or hypothermia, malnutrition, hypoalbuminemia, previous suspension of oral feeding, and presence of an infection site. After adjustment for these factors, the preventive effect of *S. boulardii* on diarrhea was even more significant (OR = 0.61, 95 % CI = 0.44–0.84, $P < 0.0023$).
Conclusion: *S. boulardii* prevents diarrhea in critically ill tube-fed patients, especially in patients with risk factors for diarrhea.

Key words Enteral feeding · Diarrhea · Intensive care

Introduction

Diarrhea is a common complication in critically ill tube-fed patients. Its frequency has been reported to be from 2.3 to 68 % in patients receiving enteral nutrition [1–3]. The consequences of diarrhea may be clinically important: electrolyte losses, increased risk of nosocomial infections and pressure sores, and change to parenteral nutrition at greater risk and cost.

Many factors have been reported to be associated with diarrhea in tube-fed patients. Some can be controlled by state-of-the-art management: sterile, ready-to-use diet; constant flow administration; absence of lactose in the diet or drugs or elixir containing poorly absorbed sugars as sorbitol or mannitol [4, 5]. Others cannot be avoided, since they are associated with the patient's condition: hypoalbuminemia, sepsis or previous shock [6, 7]. Some are due to treatment, especially antibiotics, which have been reported as the factor the most strongly associated with diarrhea during tube feeding [3].

Saccharomyces boulardii has been demonstrated to be effective in the prevention of antibiotic-associated

diarrhea, in the treatment of diarrhea and colitis due to *Clostridium difficile* and in some other conditions [8, 9]. It is a viable, non-pathogenic yeast used as a lyophilized powder in some European countries against diarrhea.

The aim of this study was to assess the preventive effect of *S. boulardii* on diarrhea in critically ill tube-fed patients. In addition, the study was designed to define prospectively potential risk factors for diarrhea in such patients.

Patients and methods

This prospective study was conducted in 11 medical or surgical intensive care units (ICU) in general and teaching hospitals. Adult patients were consecutively included when they were expected to require enteral nutrition for 6 days or more.

Exclusion criteria were: (1) previous gastrointestinal disease, (2) diarrhea occurring on the day before inclusion, (3) severe immunodepression, (4) antifungal treatment, (5) associated treatment modifying intestinal transit, such as fiber, resins, osmotic agents, laxative or antidiarrheical treatment, (6) intestinal or colic stoma.

All patients received a intact protein standard diet without fiber or lactose by mean of a nasogastric tube or jejunostomy tube. The rate of infusion was kept constant by gravity or with the use of a pump; boluses were avoided.

The study was double blind. Patients were randomly assigned to either the treatment group or the placebo group. Patients in the treatment group received *S. boulardii* 500 mg four times a day. The placebo powder was indistinguishable from the *S. boulardii* powder. Each dose of *S. boulardii* or placebo was diluted in 20 ml of tepid water and then injected into the feeding tube. Randomization was stratified by center and balanced by blocks of four patients. Data were collected daily from the medical record, the bedside flow sheet, and a special sheet designed to note the consistency and volume of each stool. The study period for each patient was limited to 21 days or to the withdrawal of enteral nutrition. Before unblinding, an inclusion committee examined all observations to ensure conformity with the protocol. The protocol was designed according to French law on biomedical research on human beings. It was approved by the regional Ethics Committee. Informed consent was obtained from each patient before inclusion in the study.

Fifteen risk factors for diarrhea in tube-fed patients frequently reported in the literature were systematically recorded [10]. Eight factors were noted at inclusion: use of jejunostomy, Simplified Acute Physiology Score [11], mechanical ventilation, antacid or antisecretory treatment, intestinal ischemia, previous suspension of oral nutrition and total parenteral nutrition (TPN), malnutrition and hypoalbuminemia < 26 g/l. Malnutrition was clinically diagnosed by subjective global assessment. Seven factors were noted before admission to the ICU or during the ICU stay: positive blood culture, nonsterile administration of enteral feed from an open container, sepsis syndrome, organ failure, infection site, fever or hypothermia, use of antibiotics. Stool cultures and *C. difficile* cytotoxin assay were performed for patients with diarrhea and, on the 7th feeding day, for patients without diarrhea. No other test was performed on stools.

The frequency of diarrhea was expressed as percentage of days with diarrhea for each patient. Diarrhea was defined according to a diarrhea score based on the volume and consistency of each stool, described by Hart and Dobb (Table 1) [12]. Briefly, a score was given to each stool by a semiquantitative evaluation of volume and a qualitative evaluation of consistency. The daily sum of the scores gave the daily score. Diarrhea was defined as a daily score equal to or greater than 12. Another frequently used definition of diarrhea in the literature (i.e., three or more nonformed stools per day) has also been tested.

Table 1 Diarrhea score[a]

Consistency	Estimated volume (ml)		
	< 200	200–250	> 250
Formed	1	2	3
Semi-solid	3	6	9
Liquid	5	10	15

[a] The daily score was obtained by summing the scores for every stool in a day. Diarrhea was defined as a daily score greater than 12. From Hart and Dobb [12]

Data were expressed as mean ± SD. Data were analysed by analysis of variance or non parametric tests for continuous data, by chi-square or Fisher's test for categorical data, and by the *t*-test for correlations between numerical data. Relative risk was estimated by the odds ratio and 95% confidence intervals were calculated. Univariate and multivariate analyses were used to determine the degree of association of various risk factors with diarrhea. Statistical analyses were performed using SAS 6.08 (SAS Institute, Cary, N.C., USA). A p value ≤ 0.05 was considered significant.

Results

Demographic data

From april 1992 to June 1993, 131 patients (65 placebo, 66 *S. boulardii*) were enrolled. No patient was subsequently excluded because of death or diarrhea severe enough to stop enteral nutrition. Three patients (1 placebo, 2 *S. boulardii*) were excluded by the inclusion committee because of violation of the study protocol (treatment excluded by study criteria). Therefore, 128 patients – 64 placebo and 64 *S. boulardii* – were analysed for 683 and 648 nutrition days, respectively.

No statistically significant difference was found between the two groups with regard to any demographic variable (Table 2). The groups were identical for age, sex, height and weight, length of stay before inclusion, type of illness, and presence or importance of organ failures. The two groups also had similar values for blood urea nitrogen, creatinine, partial pressure of oxygen in arterial blood, bilirubin, bicarbonate, sodium, potassium, aspartate aminotransaminase/alanine aminotransferase and glucose (data not shown). The mean duration of feeding per patient was 10.1 ± 6.1 days. All patients received enteral feeding for at least 6 days, and diarrhea was not severe enough to stop enteral feeding in any patient.

Table 2 Demographic data for 128 critically ill tube-fed patients. Values are mean (SD) unless otherwise indicated

	Placebo ($n = 64$)	*Saccharomyces boulardii* ($n = 64$)	p
Sex			NS
Male (n)	46	45	
Female (n)	18	19	
Age (years)	64.9 ± 14.1	61.6 ± 12.3	NS
Height (cm)	68 ± 11	169 ± 8	NS
Weight (kg)	71.1 ± 18.1	71.5 ± 172	NS
Type of patients			NS
Medical (n)	50	46	
Surgical (n)	13	18	
Lenghth of hospitalization before inclusion (median and range)	9 ± 12.1 4 (0–59)	7.2 ± 7.7 6 (0–44)	NS
Length of ICU stay before inclusion in study (median and range)	4.5 ± 4.9 3 (0–21)	4.8 ± 5.0 3 (0–25)	NS
Type of illness (n)			NS
Trauma	2	3	
Neurologic	9	14	
Pulmonary	41	26	
Cardiac	8	9	
Digestive	1	4	
Renal	1	3	
Miscellaneous	2	5	
Feeding days	10.7 ± 6.4	10.1 ± 6.1	NS

Risk factors for diarrhea

Univariate analysis

The association between clinical and laboratory variables and diarrhea was considered for the placebo group only. Four variables (use of jejunostomy, mechanical ventilation, antisecretory or antacid treatment, intestinal ischemia) were not tested because subgroup sizes were too small.

Among the 11 variables tested, univariate analysis showed that 8 were significantly associated with diarrhea: previous TPN with suspension of oral nutrition, malnutrition, hypoalbuminemia < 26 g/l, presence of sepsis syndrome, presence of organ failure, presence of an infection site, fever or hypothermia and use of antibiotics (Table 3). There was a significant correlation between the frequency of diarrhea and the number of different antibiotics given to each patient ($r = 0.97$; $P < 0.01$). The effect of nonsterile administration of diet with open containers could not be assessed because of an interaction (p = 0.01) between the type of container and the treatment group.

Stool cultures and *C. difficile* cytotoxin assay could not be performed according to the initial protocol for technical reasons. Specimens were obtained only from 21 patients with diarrhea (three positive cultures and two positive toxin assays) and 26 patients without diarrhea (two positive cultures and no positive toxin assay).

Multivariate analysis

All 11 variables tested in the univariate analysis were incorporated in a multivariate analysis of the placebo group. Five risk factors (presence of infection site, hypoalbuminemia < 26 g/l, malnutrition, previous TPN, and fever or hypothermia) were independently associated with the occurrence of diarrhea in the control group (Table 3).

Comparison of the 2 groups concerning risk factors

The placebo and *S. boulardii* groups were compared for each of the independent risk factors as defined by the multivariate analysis. No significant difference was found for any of these variables between the two groups (Table 4).

Efficacy of *S. boulardii*

The mean frequency of diarrhea days was lower in the treatment group (14.2 %) than in the placebo group (18.9 %) (OR = 0.67, 95 % CI: 0.50–0.90, $p = 0.0069$) (Table 5). The total number of diarrhea days was lower in the group of patients treated with *S. boulardii* (Table 5). Diarrhea occurred on 134/683 feeding days (19.6 %) in the placebo group and on 91/648 feeding days (14 %) in the treatment group (OR = 0.71, 95 % CI: 0.54–0.95, $P < 0.01$) (Table 5).

According to the other definition of diarrhea (i. e., three or more nonformed stools per day), the frequency of diarrhea was also significantly lower in the *S. boulardii* group. We observed 87 diarrhea days in the placebo group (12.7 %) and 50 diarrhea days in the *S. boulardii* group (7.7 %) (OR = 0.61, 95 % CI: 0.42–0.87, $P < 0.01$). Twenty-four patients in the placebo group had diarrhea on at least 1 day (daily score > 12) and 18 patients in the treatment group (OR = 0.75, 95 % CI: 0.37–1.51, $P = 0.26$).

The preventive efficacy of *S. boulardii* on diarrhea was investigated in the whole study population after adjustment for risk factors for diarrhea as previously defined. These 5 variables and the treatment were incorporated in a multivariate analysis. After adjustment for risk factors, the percentage of days with diarrhea in the treatment group was still significantly lower than in the placebo group (OR = 0.61, 95 % CI: 0.44–0,84, $P = 0.0023$).

Table 3 Univariate and multivariate analyses of risk factors for diarrhea in critically ill tube-fed patients in the placebo group: comparison of the mean percentage of diarrhea days per feeding days per patient in the placebo group ($n = 64$) according to presence or absence of risk factors

Risk factors	Mean frequency (%)		Univariate analysis			Multivariate analysis		
	Absent	Present	*p*	Odds ratio	95% CI	*p*	Odds ratio	95% CI
Temperature < 36.5 or > 38.5°C	9.1 ± 24.7	23.6 ± 22.7	0.00011	3.59	1.88–6.87	0.039	2.30	1.04–5.09
Infection site	14.3 ± 23.4	24.5 ± 23.5	8.10^{-6}	2.41	1.64–3.55	0.002	2.38	1.38–4.13
Malnutrition	17.4 ± 22.7	30.8 ± 28.2	0.0008	2.20	1.39–3.49	0.013	2.20	1.18–4.08
Albuminemia < 26 g/l	14.8 ± 21.2	28.8 ± 25.1	0.0007	2.16	1.38 ± 3.36	0.003	2.32	1.35–4.01
Sepsis syndrome	17.2 ± 25.2	23.4 ± 19.8	0.0006	1.98	1.34–2.92	0.80	0.92	0.47–1.78
Multiple organ failure	13.7 ± 22.1	22.5 ± 24.5	0.003	1.81	1.22–2.68	0.78	0.92	0.51–1.67
Open feed container	28.1 ± 28.0	15.0 ± 20.9	[a]	1.79	1.21–2.64	[a]	1.47	0.83–2.61
Previous TPN	16.5 ± 22.8	21.8 ± 25.6	0.015	1.65	1.10–2.46	0.004	2.18	1.28–3.72
Simplified Acute Physiology Score > 11.5	19.4 ± 25.3	18.5 ± 22.8	0.18	1.30	0.89–1.90	0.49	1.19	0.73–1.97
Bacteremia	18.0 ± 24.0	23.4 ± 23.6	0.46	1.19	0.76–1.87	0.73	0.89	0.46–1.72
Number of antibiotics			0.025	1.12	1.01–1.23	0.58	1.05	0.89–1.23

[a] Interaction between type of feed container and treatment group

Table 4 Comparison between placebo and *S. boulardii* groups of critically ill tube-fed patients for the presence of independent risk factors. Values represent number of patients with risk factor/total number of patients (%)

Risk factors	Placebo ($n = 64$)	*Saccharomyces boulardii* ($n = 64$)	*p*
Previous TPN	23/62 (37.1)	32/64 (50.0)	0.14
Malnutrition	10/62 (16.1)	8/63 (12.7)	0.59
Hypoalbuminemia < 26 g/l	13/60 (21.7)	15/58 (25.9)	0.59
Infection site	29/64 (45.3)	31/64 (48.4)	0.72
Fever or hypothermia	44/62 (71.0)	50/64 (78.1)	0.36

The tolerance of for *S. boulardii* was good and no adverse effect was noted.

Efficacy of S. boulardii in patients with risk factors

The efficacy of *S. boulardii* was tested in subgroups of patients with each of the 5 independent risk factors previously defined (Table 6). The improvement of diarrhea was more important in these subgroups with a decrease in the percentage of diarrhea days between 28 and 42% versus 25% in the whole study population. Although group sizes were small, the difference fell short off significance for 2 risk factors: infection site ($P = 0.063$) and fever or hypothermia ($P = 0.053$).

Discussion

The main result of this prospective, multicenter, placebo controlled study is the demonstration of the efficacy of *S. boulardii* in the prevention of diarrhea in critically ill tube-fed patients.

There is no generally accepted definition of diarrhea. The most precise definition is based on stool volume. Wyman et al., in a study of the daily stool output of healthy subjects, has defined diarrhea as more than 250 g of stool per day, which represents a daily stool output exceeding 3 SDs from the mean fecal output [13]. In severely ill patients, stool collection is not easy. Different definitions are frequently used, most of them based on the frequency of bowel movements (more than one, more than two, more than three liquid stools per day) or alteration of bowel habit associated with passage of loose or frequent stools, sufficient to be noticed by the patient or by the nursing staff [2, 14, 15]. However, the subjective assessment of diarrhea using the frequency of bowel movements does not correlate with the weight of stools and thus is not reliable when evaluating diarrhea [16]. Hart and Dobb have proposed a semiquantitative score according to the volume and the consistancy of stool [12]. Although partially subjective, this score allows a more accurate assessment of diarrhea and is more easily used in intensive care patients.

Enteral nutrition by itself has been shown to be a risk factor for diarrhea in the ICU [2] but it must be preferred to parenteral nutrition, whenever possible, because the risks which parenteral nutrition outweigh those with enteral nutrition [17]. Some of the risk fac-

Table 5 Efficacy of *S. boulardii* in preventing diarrhea in critically ill tube-fed patients. Diarrhea is defined as a diarrhea score ≥ 12

	Placebo	*Saccharomyces boulardii*	*p*	OR (95% CI)
Mean (SD) percentage of days with diarrhea per feeding days	18.9 ± 23.8	14.2 ± 20.7	0.0069	0.67 (0.50–0.90)
Number of observation days	683	648		
Number (%) of days with diarrhea	134 (19.6)	91 (14.0)	< 0.001	0.71 (0.54–0.95)
Number of patients	64	64		
Number (%) of patients with at least 1 day with diarrhea	24 (37.5)	18 (28.1)	0.26	0.75 (0.37–1.51)

Table 6 Efficacy of *Saccharomyces boulardii* in subgroups of critically ill tube fed-patients with independent risk factors for diarrhea (mean frequency of days with diarrhea per feeding days). Values are mean (SD)

Risk factors	Placebo	*Saccharomyces boulardii*	*p*
Albuminemia < 26 g/l	28.8 ± 25.1 (*n* = 13)	13.9 ± 16.6 (*n* = 15)	0.107
Infection site	24.5 ± 23.5 (*n* = 29)	14.0 ± 21.7 (*n* = 31)	0.063
Previous TPN	21.8 ± 25.6 (*n* = 23)	12.5 ± 15.0 (*n* = 32)	0.258
Fever or hypothermia	23.6 ± 22.7 (*n* = 44)	15.9 ± 22.2 (*n* = 50)	0.053
Malnutrition	30.8 ± 28.2 (*n* = 10)	22.1 ± 12.5 (*n* = 8)	0.688
All patients after adjustment for risk factors	18.9 ± 23.8 (*n* = 64)	14.2 ± 20.7 (*n* = 64)	0.0023

tors may be avoided by proper use of enteral nutrition and were controlled for in our study. Diarrhea due to bolus feeds can be avoided by constant infusion by gravity or a flow-controlled pump. The osmolarity of usual feeds is no longer regarded as a major cause of diarrhea [18]. The presence of lactose and insufficency of micronutrient supplements can be avoided [19].

Several other risk factors for diarrhea have been reported and may depend on the treatment or the severity of the patient's condition. Five independant risk factors have been identified in a multivariate analysis in our study: presence of infection site, hypoalbuminemia < 26 g/l, fever or hypothermia, malnutrition, and previous TPN. Hypoalbuminemia < 26 g/l has been reported by Brinson and Kolts as responsible for diarrhea in critically ill patients receiving enteral feeding [7]. These results were confirmed by some authors [20, 21] but not by all [22]. It is not yet established whether hypoalbuminemia is responsible by itself. In a univariate analysis in our study, the presence of numerous risk factors: fever, sepsis syndrome, infection site, or organ failure may support the argument that hypoalbuminemia demonstrates the relationship between diarrhea and the severity of the patient's underlying disease. However, in a multivariate analysis, hypoalbuminemia was significantly related to diarrhea, suggesting an independent association with diarrhea.

The presence of severe infections has already been identified as a risk factor for diarrhea. Perrotin et al. observed that diarrhea was significantly associated with infection and a positive blood culture [23]. Hart and Dobb found a correlation between diarrhea and the number of infection sites apart from the gastrointestinal tract [12]. It is not clear whether infection by itself is responsible for diarrhea or if the diarrhea is associated with the severity of the disease or use of antibiotics. In our study, frequency of diarrhea was correlated in a univariate analysis with the number of antibiotics used, but in a multivariate analysis antibiotics were not an independent risk factor when infection (fever, infection site) was. The correlation between the number of antibiotics and diarrhea has been found by others and suggests the role of altered intestinal microflora after antibiotic use [12].

In our study, clinical malnutrition and/or suspension of oral alimentation and TPN were shown to be risk factors for diarrhea. To our knowledge, such findings have not been reported until now in critically ill patients. Malnutrition is correctly appreciated on a clinical basis as described by Detsky et al. as "subjective global assessment"[24]. Intestinal dysfunction and diarrhea have been described in malnutrition [25]. TPN and suspension of oral alimentation have been reported as responsible for mucosal atrophy experimentally [26]. In humans, mucosal atrophy has been observed but appears less frequent [27, 28]. These alterations may cause diarrhea.

In this study, *S. boulardii* prevented diarrhea in critically ill tube-fed patients. The percentage of days with diarrhea during tube feeding was reduced by 25%, from 18.9 % in controls to 14.2 % in *S. boulardii*-treated patients. This effect was also highly significant after adjustment for risk factors. There was a trend to a more important reduction, up to 52%, when a risk factor enhanced the frequency of diarrhea. If our study population had been larger this effect in subgroups might have reached significance. It is notable that this was

nearly the case for the two larger subgroups (infection site, fever or hypothermia).

The preventive effect of *S. boulardii* may be due to its role in antibiotic-associated diarrhea, as observed by Surawicz et al. in a prospective trial [9]. In this study of patients treated with antibiotics, 22% of those who received a placebo had diarrhea compared with 9.5% of those who received preventive treatment with *S. boulardii* . Tempe et al., in a study in the ICU, has demonstrated the efficacy of *S. boulardii* for the prevention of diarrhea in critically ill patients receiving enteral nutrition [29]. Similarly, Schlotterer et al., in a unit for burned patients, found the same results [30]. But these were one-center studies, they included a limited number of patients, and they were not adjusted for risk factors. Our data confirm these previous studies.

Bacterial overgrowth in the intestine is a cause of diarrhea. In ICU patients, numerous factors favor bacterial overgrowth: use of nonsterile feeds, treatment with antacid or antisecretory drugs, and impairment of gastric acid secretion and digestive mobility. For these conditions, *S. boulardii* may also be effective. The way in which *S. boulardii* works is not well understood. Some mechanisms have been experimentally demonstrated: inhibitory effect on intestinal secretion induced by bacterial toxins [31], stimulation of intestinal secretion of immunoglobulins [32], stimulation of brush border membrane enzymes (hydrolases) of intestinal cells [33], endoluminal release of polyamines explaining the two previous modifications, and antagonistic effect against the overgrowth of pathogenic microorganisms in the intestine [34]. This study offers no additional explanation to the mechanism of action.

In conclusion, *S. boulardii* reduces by 25% the frequency of diarrhea in critically ill tube-fed patients. Beneficial effects may be estimated in terms of reduction in electrolyte losses, pressure sores, and nursing workload, but also in terms of patient comfort and dignity. Moreover, efficacy might be enhanced in patients with risk factors. Therefore, preventive administration of *S. boulardii* appears justified in critically ill tube-fed patients, especially in those with risk factors for diarrhea.

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