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Role of probiotics in prevention of hospital acquired pneumonia in Egyptian children admitted to Pediatric Intensive Care Unit of Mansoura University Children's Hospital

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The objective of the study is to evaluate the effect of probiotics to reduce the risk of hospital-acquired pneumonia in Pediatric Intensive Care Unit. The study is a double-blinded randomized placebo-controlled study. Patients were evenly and randomly assigned in two groups. The first group was 50 randomly selected patients who formed the placebo group, while the second group was 70 patients selected randomly to form the intervention group that received the probiotic capsules; *Lactobacillus rhamnosus* strain GG, once a day. The study site was Pediatric Intensive Care Unit in a university-affiliated children's hospital. Fifteen (30%) patients in the placebo population developed hospital-acquired pneumonia. Of the 15 patients, infections in 22% were caused by Gram-negative organisms. In the intervention group, 10% developed hospital-acquired pneumonia. The causative agents were predominantly Gram-negative organisms (22% Gram-negative vs. 7% Gram-positive; *P*–value; 0.01). After 72 h of study, significantly higher oral and gastric colonization rates were observed in patients who were given placebo treatment, compared with those given *Lactobacilli*. The current study is the first to report these higher significant variations. The current study found an influence of probiotic supplementation on the rate of hospital-acquired pneumonia.

Key words: Peiatric intensive care unit, probiotics, hospital-acquired, pneumonia.

INTRODUCTION

Health care-associated infections (HCAIs), hospital-acquired urinary tract infection, blood stream infection,

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pneumonia, and meningitis in Critical Care Units are correlated with increased mortality and morbidity (Sohn et al., 2001). Blood stream infection, with the potential cerebro-spinal fluid infection, lung and other sterile sites in the body may result from transfer of enteric pathogenic organisms through the intestinal wall (Duffy, 2000).

Probiotics may prevent or reduce infections in a variety of ways by altering intestinal permeability and interacting with pathogenic and commensal microorganisms in the gut mucosal system. Their administration may stimulate the host immune system in cases of infectious diarrhea. Furthermore, probiotics may compete with potential pathogens for nutrients or binding sites and subsequently inhibit growth and invasion of pathogenic organisms (Wang et al., 2016).

The use of probiotics like *Lactobacillus rhamnosus* GG (LGG) and *Saccharomyces boulardii* (strong recommendation, low quality of evidence), may be considered in the treatment of children with acute gastroenteritis besides rehydration therapy. Less imperative evidence is available for *Lactobacillus reuteri* DSM 17938 (weak recommendation, low quality of evidence) (Szajewska and van Goudoever, 2014). A 2011-meta-analysis of three randomized clinical trials comprising, 1092 children, reported that, there were significantly lower rates of diarrhea in placebo management compared with LGG administration (Szajewska, 2011). Children attending daycare centers are at high exposure of respiratory infections (Hao et al., 2011). Therefore, a systematic review evaluated the impact of probiotics on preventing upper respiratory tract infections (URTIs). Many outcome measures were reported in different trials on children (Rio et al., 2002; Sanz et al., 2006; Rautava et al., 2009; Hojsak et al., 2010; Merenstein et al., 2010; Rerksuppaphol and Rerksuppaphol, 2012). Honeycutt et al. (2007) conducted a randomized, placebo-controlled trial, using *L. rhamnosus* strain GG that was not shown to be effective in reducing the incidence of nosocomial infections (Honeycutt et al., 2007).

Prevention of life-threatening infections can be achieved through gastrointestinal (GI) tract colonization with probiotics (anaerobic, nonpathogenic bacteria) which competitively inhibits the binding of bacterial pathogens, reducing their possibility for colonization and translocation (Honeycutt et al., 2007). Hospital-acquired pneumonia (HAP) is the leading risk of death due to hospital-acquired infections in the United States with an incidence of 5 to 10 cases per 1000 hospital admissions. Hospital-acquired pneumonia, determined as pneumonia occurs 48 h or more after hospital admittance, and has not been incubating at the time of admission. Hospital-acquired pneumonia adds excess medical costs ranging from $12,000 to $40,000 per patient and prolongs hospital stays for an average of 7 to 9 days. Mortality attributed to HAP is estimated to be between 33 and 50% with the highest mortality occurring in patients with bacteremia or infections with drug resistant *Acinetobacter or Pseudomonas aeruginosa* species (Griffiths et al., 2004). Although, there is theoretical possibility, there is insufficient evidence that probiotic products decrease the incidence of HAP.

The aim of this study is to evaluate the clinical impact of probiotics in decreasing the rates of HAP compared with standard conventional therapy alone in cases admitted to Pediatric Intensive Care Unit (PICU) of Mansoura University Children's Hospital (MUCH).

STUDY DESIGN AND METHODS

A total of 2,050 patients were admitted to PICU of MUCH, Mansoura, Egypt, between October, 2012 and December, 2015. The study is a parallel assignment, placebo controlled, randomized (on PICU admission, according to computer generated randomized numbers list) and double blind study (microbiology laboratory subject, investigator, primary care clinicians, outcomes assessor, bedside nurses, were blinded to group assignments). The patients were considered eligible on admission to PICU.

Patients were excluded if they had suspicion or evidence of perforated intestine, mechanical GI obstruction, absolute neutrophil count < 0.5×10^9 cells/L; been admitted to the PICU for more than 72 h; had use probiotics in the week before study accession; had no parental presence, or consent.

All the 2,050 patients were screened. Of the total number, 1,900 were excluded due to one exclusion criteria or the other and unavailability of parental consent on the first day of admission. There were 150 patients in this prospective, double-blinded, randomized, placebo-controlled trial. The 150 cases were equally and randomly assigned into two groups (75 cases in each of placebo and the intervention group). Then, the first placebo and the second intervention groups were reduced to 50 and 70 cases respectively due to further exclusions at randomization due to death, discharge from the hospital (transferred to another hospital) or the patient's parents no longer wished to participate (Figure 1).

The intervention group received one *L. rhamnosus* strain GG capsule once a day (Culturelle, 10×10^9 cells/capsule, ConAgra Foods, Omaha, NE) for the duration of hospitalization. Probiotic capsules were prepared in a suspension of (5 ml) of 5% dextrose. They were administered by oro-gastric, naso-gastric tube or by mouth in the patients who could be fed orally. More than two doses of *Lactobacillus* GG missing by any patient, excluded the patient from probiotic regimen. Daily clinical and demographic data were obtained prospectively by the study investigators (Honeycutt et al., 2007; Banupriya et al., 2015).

Information was collected on a daily basis from all participants. This information was then, entered into a Microsoft Excel database for subsequent statistical analysis. Patients received all routine care, including antibiotic therapy as deemed necessary, HAP preventive measures as per hospital protocols, under their physician direction.

All the study participants were subjected to careful history taking, clinical examination, other demographic information, pediatric risk of mortality; (PRISM) score (Taori et al., 2010), laboratory investigations including complete blood count and C-reactive protein, monitoring for HAP, blood cultures, tracheal aspirates and quantitative broncho-alveolar lavage cultures. Tracheal aspirate cultures, blood cultures, and complete hemogram, were emitted every three day. Outcome variables studied in both groups included the mechanical ventilation use, ICU stay duration, HAP duration,

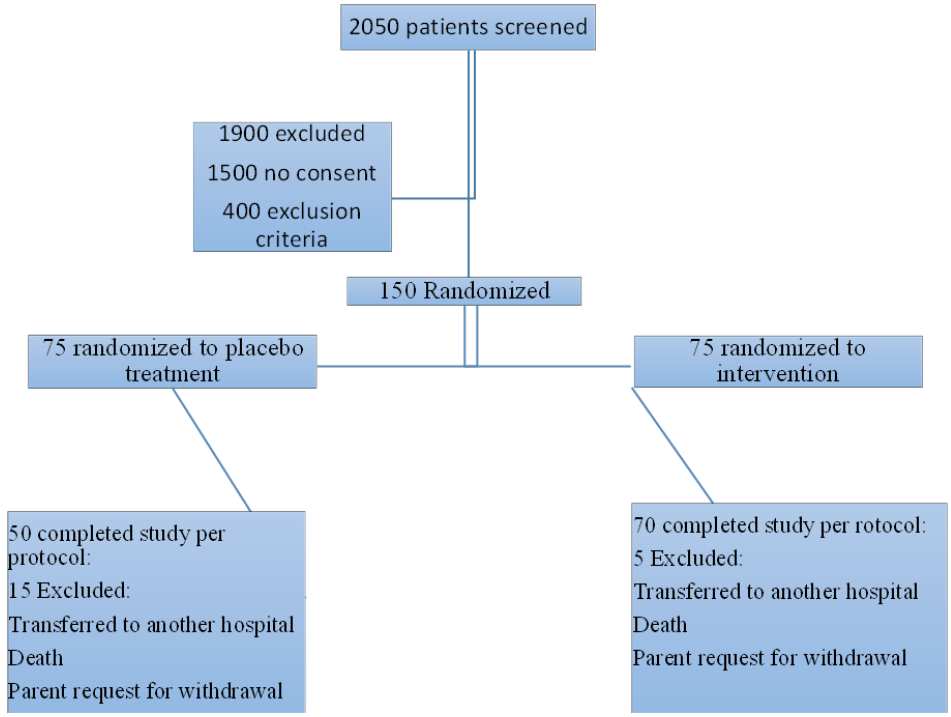

Figure 1. Participants of the study.

duration of antibiotic use and mortality.

The diagnostic criteria for HAP were determined as any pneumonia contracted by a patient in the hospital, within at least 48 to 72 h, after admission with x-ray evidence of consolidation, a new infiltrate, or cavitations (Cernada et al., 2014).

In HAP diagnosis, the patient also should have either, increased difficulty in breathing or tachypnea, new onset or increased purulent sputum, isolation of a known respiratory pathogen on blood culture, isolation of known respiratory virus by antigen detection, or evidence of pneumonia histopathologically (which were done in the MUCH laboratory) (Foglia et al., 2007).

Study protocol was approved by Institutional Review Board (IRB) of Mansoura University. Approval was taken from the management of hospital in which the study was conducted. Informed verbal consent was obtained from each participant sharing in the study. Confidentiality and personal privacy were respected in all levels of the study.

Statistical analysis

All statistical tests were conducted using the IBM Statistical Package for Social Sciences; version 23 (IBM SPSS, Chicago, IL). Fisher's exact test (2-tailed) was used for comparison between the categorical variables. The Mann-Whitney U test was used to compare continuous variables between the two groups. Chi square was used for comparison between the categorical variables. Significance was set at *P*-value < 0.05.

RESULTS

All the 2,050 patients were screened (Figure 1); 1,900 were not enrolled due to one exclusion criteria or the other; or informed consents could not be obtained on the first day of admission. One hundred and fifty patients were evenly distributed between two groups (75 patient per each group) based on baseline and demographic characteristics (Table 1).

The study is a prospective, randomized, double-blinded, placebo-controlled trial. Fifty patients (children) were randomly selected to the placebo group and 70 to the intervention group. The clinical features of the infected patients in both the placebo and intervention groups are recorded in Table 2. There were no cases of bacteremia caused by *Lactobacilli* found in the intervention group. There were no known serious adverse effects observed in any subject during the study period.

Out of the 75 patients of the placebo and intervention groups; 43 (57.3%) and 38 (50.6%) were male, respectively. The mean age was 5.3 ± 2.7 (1-12) years in placebo group and 5.7± 4.9 (1-10) years in the randomized intervention group (*p*-value < 0.05); a statistical significance without any clinical significance since the mean age in both groups was 5.3 and 5.7. In PRISM score, the mean range was 33.9 ±13.9 and 34.2 ±15.6 in randomized placebo and intervention groups respectively (68.3% Confidence level). Also, the reasons for PICU admission were mainly respiratory problems. Fifteen (30%) patients in the placebo population developed HAP. Overall, of the 15 infections, 11 (22%) were caused by Gram-negative organisms (Table 2).

Table 1. Demographic and study population characteristics.

Parameter	Placebo (*n = 75*)	*Intervention* (*n = 75*)	*P* -value
Male sex	43(57.3%)	38(50.6%)	0.41
Age, mean ± SD (range), years	5.3± 2.7 (1-12)	5.7±4.9 (1-10)	0.00
PRISM score, mean ± SD (range)	33.9±13.9 68.3%Confidence level	34.2±15.6 63.3%confidence level	0.08
Reasons for ICU admission			
Respiratory	30	32	
Cardiovascular (shock, resuscitation, arrhythmias)	5	4	
Gastrointestinal	20	19	
Neurologic	4	4	
Hematology/Oncology	8	7	
Endocrine/Metabolic	3	4	
Renal	3	3	
Multisystem	2	2	

SD, Standard deviation; PRISM, pediatric risk of mortality; ICU, intensive Care Unit.

Table 2. Incidence and microbiology of HAP.

Microbiology	Placebo	Intervention	Chi- square	P- value
	15/50	**7/70**	**7.79**	**0.005**
Subjects with Gram-positive HAP	3/50(6%)	2/70(2.9%)	0.72	0.39
Subjects with Gram-negative HAP	11/50(22%)	5/70(7%)	5.57	0.01
Gram-positive pathogens isolated	3	2		
MSSA	1	1		
MRSA	1	0		
Streptococcus species	1	1		
Gram-negative pathogens isolated	11	5		
Pseudomonas	3	1		
Haemophilus influenza	2	1		
Acinetobacter	1	1		
Klebsiella	1	1		
Proteus	1	1		
Escherichia coli	1	0		
Serratia	1	0		
Citrobacter	1	0		
Yeast	1	0		

HAP, Hospital-acquired pneumonia; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus.*

Gram-positive bacteria accounted for 3 (6%) of HAP. Candida species were responsible for one (2%) of the infections. Of the 70 patients of the intervention group, 7(10%) developed HAP. Overall of the 7 infections, 5 (7%) were caused by Gram negative organisms. Gram positive bacteria accounted for 2 (2.9%) of HAP. There was statistically significant variation between the studied arms regarding the microbiology of the HAP (*P*-value; 0.005), and the causative agents were predominantly Gram negative organisms (22 vs 7%; *P*- value; 0.01). There was no difference in case of Gram positive organisms (6 vs 2.9%; *p*-value; 0.39). The relative risk of developing HAP in the placebo group was 3.3 (confidence interval; CI, 1.44 to 7.51(95%), *p*-value; 0.004). Thus, patients of placebo group would be 3.3 times as likely as the intervention group to develop HAP.

In this study, death rate significantly varied between both groups (24% in the placebo group and 14.3% in the

Table 3. Secondary outcomes.

Parameter	Placebo (n = 50)	Intervention (n=70)	Chi-square	*P*-value
Death	15 (24%)	10 (14.3 %)	4.36	0.03
Days of ICU-associated pneumonia, mean ± SD	6.9 ± 3.8	4.1 ± 3.7	2.4	0.12
Total antibiotic-days, mean ± SD	17.3 ± 14.4	13.3 ± 10.4	3.7	0.05
ICU length of stay in days, mean ± SD	15.6 ± 11.6	14.8 ± 11.8	1.7	0.19
No of patients who needed MV	20 (40%)	10 (14.3%)	10.28	0.001

ICU, intensive Care Unit; SD, standard deviation; MV, mechanical ventilation.

Table 4. Surveillance of culture.

Parameter	Non*	Rare	Few	Moderate	Many	Chi-squre	*P* Value
Oral swab pathogen+ (density at baseline)							
Placebo (50)	17 34%	2	2	10 66%	19	0.2	0.65
Intervention (70)	22 31.4%	19	8	12 68.6%	9		
Gastric aspirate pathogen+ (density at baseline)							
Placebo (50)	18 36%	2	2	10 64%	18	0.56	0.45
Intervention (70)	22 31.4%	16	10	13 68.6%	9		
Oral swab (pathogen density at 72 h)							
Placebo (50)	10 20%	2	2	10 80%	27	39.7	0.00001
Intervention (70)	45 64.3%	9	2	5 35.7%	9		
Gastric aspirate (pathogen density at 72 h)							
Placebo (50)	10 20%	6	5	12 80%	17	43.16	0.00001
Intervention (70)	46 65.7%	7	7	5 34.3%	5		

*None if no growth is seen; rare if growth is restricted to only the first quadrant; few if growth extends into the second quadrant; moderate if growth extends into the third quadrant; many if growth extends into the fourth quadrant. + Pathogens from oral swabbing and gastric as pirates included Enterobacteriaceae, non-fermenting Gram-negative bacteria and Staphylococcus aureus (including methicillin-resistant strains).

probiotic group; *P*-value*;* 0.03). Also, there was a statistical variation between 2 groups regarding the mean duration of antibiotic use (17.3 ± 14.4 vs. 13.3 ± 10.4; *P*-value*;* 0.05). On the contrary, probiotics administration resulted in non-significant difference in mean duration of PICU associated pneumonia; in addition, the mean duration of PICU was not statistically variable between the mentioned groups. Moreover, patients in placebo group showed a strong trend toward increased probability of using mechanical ventilation, compared with patients in intervention group (40 vs. 14.3% *P*-value; 0.001) (Table 3). No cases of pneumonia or bacteremia caused by *Lactobacillus* in the patients of the intervention group were observed.

The oral colonization, rates of microbial species, was not significantly variable at baseline between the 2 groups, (66% for placebo vs. 68.6% for *Lactobacillus*; *P*–value; 0.66) (Table 4). The gastric colonization rates at baseline were also non-significantly variable (64% for placebo vs. 68.6% for *Lactobacillus*; *P*–value; 0.45). Patients given placebo had significantly higher rates of oral colonization of pathogenic bacteria after 72 h of study compared with those who were given *Lactobacillus* (80.0% for placebo vs. 35.7% for *Lactobacillus*; *P*–value;

0.00001).

The rates of gastric colonization with pathogenic bacteria were also increased after 72 h in placebo patients (80.0% for placebo vs. 34.3% for *Lactobacillus*; *P*-value; 0.00001).

DISCUSSION

Evaluation of the use of probiotics in preterm infants and children indicates a valuable influence for enterocolitis prevention and mortality, but less suggestion for HCAIs (Alfaleh et al., 2014). The present study aims to check the clinical impact of probiotics in decreasing HAP rates compared with standard conventional therapy alone, in cases admitted to PICU of MUCH, Mansoura, Egypt.

In this study, probiotic treatment showed a statistically significant decline in HAP rate depending on strict diagnostic criteria that require microbiological confirmation using respiratory samples beside the other mentioned diagnostic criteria. Probiotic treatment also exhibited less duration of antibiotic prescribed for therapy. Generally, these data considered that *Lactobacillus* may represent a unique, cheap, and non-antibiotic intervention to prevent hospital-acquired infections in properly selected PICU patients.

Previous studies demonstrated in voluntary humans reported that *Lactobacillus rhamnosus* colonized the bowel tract when 10^8 CFUs/day were administered [Griffith et al., 2004); therefore, a dosage of 10^9 CFUs/12 h was chosen.

150 patients were used in this prospective, which was a double-blinded, randomized, placebo-controlled study distributed evenly between 2 groups (75 each). Out of the 75 patients that were randomly selected to the placebo treatment, 25 were excluded thus leaving 50 placebo patients. From those who were randomly selected to the intervention treatment, 5 patients were excluded, leaving 70 (that is, 70 intervention patients). These secondary exclusions (that is, occurred after randomization of both placebo and intervention groups) was due to death, transference to another hospital or parental request to withdraw from the study. In this study, death before fulfilling adequate duration in the PICU was an exclusion since adequate time space to assess the secondary outcomes (days of ICU-associated pneumonia, total antibiotic days, ICU length of stay, number of patients needed MV, and finally death was required (Table 3). There were statistically significant variations regarding child age, yet, no clinically significant difference between both groups (Age range in randomly selected placebo group from 1-10 and in intervention group from 1-12). Likewise, statistically significant variations were observed between groups regarding the microbiology of the HAP (*P*-value; 0.005), and the causative agents were predominantly Gram negative organisms (*P*-value; 0.01).

This was not in accordance with the study of Honeycutt et al. (2007) who evaluated the impact of probiotics in decreasing the rates of HCAIs in PICU. Sixty-one patients were randomly selected, 31 in the *Lactobacillus* treatment group and 30 in the placebo group. In the control group of the same study, three patients had 4 infections and 6 patients in the treatment group had 11 infections with a trend towards increased infections rate in the group receiving probiotics (Honeycutt et al., 2007).

In another study, Mihatsch et al. (2010), investigated whether *Bifidobacterium lactis* decreases the incidence of HCAIs in infants with very low birth weight (VLBW; <1,500 g) of <30 weeks of gestation. In that randomized controlled trial, there were 90 in the placebo group and 93 infants in the *B. lactis* group that showed no significant variation with regard to the incidence of HCAIs (Mihatsch et al., 2010).

Moreover, Rojas et al. (2012) designed a large double-blinded placebo-controlled trial using *Lactobacillus reuteri* to test the effect of probiotics on infant HCAIs and death rate. However, primary outcome, death, or HCAI frequency, were similar in the probiotic and placebo groups (Rojas et al., 2012).

On the contrary, the study of Hojsak et al. (2010) conducted a double-blind, randomized placebo-controlled trial of hospitalized children receiving *Lactobacillus* GG (n = 376) and placebo (the same post-pasteurized milk, deprived of *Lactobacillus* GG, placebo group, n = 366). They found a significantly reduced risk for respiratory tract and GI infections, in *Lactobacillus* GG group, compared with the placebo group (Hojsak et al., 2010).

Most recently, the study of Hojsak et al. (2015) aimed to investigate the role of *Bifidobacterium animalis*; subsp. lactis in preventing HCAIs. They organized a randomized, double-blind, placebo-controlled trial in 727 hospitalized children. The children were randomly assigned to receive placebo therapy (n = 365) or *Bifidobacterium animalis* subsp. lactis in a dose of 10^9 CFU, once daily for the entire duration of the hospital stay (intervention group, n = 362). There was no statistical difference in primary outcome or incidence of common hospital acquired GI and respiratory tract infections between both groups and no statistical variation regarding the duration of HCAIs, the secondary outcomes.

Many trials were conducted in children and found that probiotics showed benefit in decreasing the number of children that experienced URTI episodes (Rio et al., 2002; Sanz et al., 2006; Rautava et al., 2009; Hojsak et al., 2010; Merenstein et al., 2010; Rerksuppaphol and Rerksuppaphol, 2012; Caceres et al., 2010).

These mentioned previous studies had different results from the present one and this may be due to the significant difference in their criteria of inclusion, the probiotic administration rout, dosing, probiotic agent(s) used, populations studied, the HAP diagnostic criteria and probiotic treatment mechanisms that are, inherently,

based on capability to alter the microbial flora (Klarin et al., 2008). Significant variations were also seen in respiratory colonization with Gram negative bacteria and the duration of ICU stay. Also, there was significant reduction in oropharyngeal and gastric colonization, in this study, after probiotic administration. Changes in colonization were significantly parallel to the HAP development that was confirmed microbiologically in the current study.

Probiotic intake had dramatical effects on decreasing the rates of microbiologically confirmed HAP caused by Gram-negative pathogens (22 vs. 7%; *P*-value; 0.01). On the contrary, HAP caused by gram-positive organisms was not variable between groups (6 vs. 2.9%; *p*-value; 0.39). The inadequacy of realizing probiotic mechanisms, made this observation difficult to be explained. However, the changes in the host flora were consistent based on the information on microbial colonization from the current study (Forestier et al., 2008; McNabb and Isakow, 2008)

The oral colonization rates of microbial species were not significantly variable at baseline between 2 groups (66% for placebo vs. 68.6% for *Lactobacillus*; *P*–value; 0.66) (Table 4). The gastric colonization rates at baseline were also non-significantly variable (64 for placebo vs. 68.6% for *Lactobacillus*; *P*–value; 0.45).

Patients given placebo had significantly higher rates of oral colonization of pathogenic bacteria after 72 h of study compared with those given *Lactobacillus* (80.0% for placebo vs. 35.7% for *Lactobacillus*; *P*-value; 0.00001). The rates of gastric colonization with pathogenic bacteria were also increased after 72 h in placebo patients (80.0% for placebo vs. 34.3% for *Lactobacillus*; *P*–value; 0.00001). Oral colonization changes were correlated significantly with the existence of microbiologically confirmed HAP.

The pathogenesis of HAP is complicated, but, the involvement of aerodigestive tract colonization with pathogenic bacteria is one of the pathogenesis mechanisms. Enteric bacteria colonize the GI tract in increasing numbers from the stomach to the colon. There is a debate whether or not colonization and adherence of the GI tract is necessary for probiotics to provide biological activity (Klingberg and Budde, 2006).

Respiratory sampling with quantitative cultures to reach the microbiologic HAP diagnosis was used in this study (Caceres et al., 2010). This study also differ from others, in that, high-risk patients were chosen as subjects, as recognized by the high PRISM score. A particular probiotic agent (*L. rhamnosus* GG) which was a different type was also selected. This agent was chosen because it had little information indicating that it may have favorable activity in the upper airways and strong safety data (Brandtzaeg, 1992; Gluck, 2003). It remains unknown whether other agents would have the same or remarkable results because of the short plan of comparative data in this field.

These data should be viewed as introductory and cannot be generalized to the general PICU population given the prolonged period of enrolment, the large number of exclusion criteria, the small number of patients included, and the strict inclusion criteria. Moreover, the current study carries multiple defects. That is because, these data were collected from one hospital and has inherent biases related to the patients served and the habits of local practice.

Mansoura University Children's Hospital has a patient population with many risk factors for colonization with hospital-acquired pathogens and serves an urban community with limited resources. This explains the high colonization rate seen in the baseline cultures.

Furthermore, like most other existing HAP preventive strategies, probiotic treatment requires compliance (Pitsouni et al., 2009; Wolvers et al., 2010). Such compliance is difficult to achieve in routine practice. Eventually, the delivery of probiotics to the oro/naso-pharynx and the stomach (that is, anatomically different sites), the delivery site is not known. Additionally, the differences in antibiotic use information are restricted by the methods used to calculate antibiotic prescription (antibiotic-days).

Contrary to the iatrogenic infection safety concern, the high death rate seen in the probiotic side of PROPATRIA was attributable to intestinal ischemia (Besselink et al., 2008).

Moreover, their effects may vary in disease and health, in distinct disease states, and in various age groups. Thus, this clinical trial in this certain population that results from specific probiotic strain cannot be generalized to other populations or strains.

Additional work is required to clear up the relative significance of strain-specific effects in different scenarios and the nature of interactions between probiotics.

Conclusion:

The current study found an influence of probiotic supplementation on the rate of HCAIs, including HAP. Further studies are necessary to display further mechanistic concerns and probiotic interactions. Clinicians have to be aware of the benefits and risks of these treatments, because of the increasing use of probiotics as therapeutic agents and health supplements.

Conflict of Interests

The authors have not declared any conflict of interests.

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