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## Systematic Review

# THE EFFECTS OF PROBIOTICS, PREBIOTICS AND SYNBIOTICS ON INFECTIONS AND CLINICAL OUTCOMES IN CRITICAL ILLNESS: A SYSTEMATIC REVIEW

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### Abstract

**Background:** Critically ill patients treated in intensive care units (ICU) are characterized by a qualitative and quantitative change in the composition of their intestinal microflora, leading to a reduction in commensal flora and an overgrowth of potentially pathogenic bacteria, which increase susceptibility to nosocomial infections and compromise their outcome. Probiotics are live, non-pathogenic microorganisms that can provide health benefits to the host, such as restoring the balance of the microbiota and positive effects on immune function and gastrointestinal tract structure and function, when ingested in sufficient quantities. This systematic review aimed to evaluate the effects of probiotics/prebiotics and synbiotic mixtures on infections and clinical outcomes in critically ill patients.

**Method and Material:** Randomized clinical trials (RCTs) were reviewed in PubMed, EMBASE, CINAHL, CENTRAL and COHRANE from January 2004 to November 2024. Initially, 81 RCTs were selected, which evaluated the effects of probiotics or synbiotics versus placebo or prebiotics on clinical outcomes in adult ICU patients. Following the implementation of the PRISMA statement, 25 studies were finally included in this systematic review, and 5.106 patients were identified for analysis. The total number of new infections was the primary outcome. Secondary outcomes included mortality, ICU-acquired pneumonia, duration of mechanical ventilation (MV), length of stay (LOS) in the ICU, hospital and diarrhea.

**Results:** Probiotics were associated with a significant reduction in infections and ventilator-associated pneumonia (VAP), shorter duration of MV, ICU and hospital LOS and fewer episodes and shorter duration of diarrhea. No effect on ICU or hospital mortality was observed. Moreover, the greatest improvement in most outcomes was seen with probiotics alone compared to synbiotics mixtures, with a higher dose of probiotics ( $\geq$ 5 × 109 CFU/day) and with at least 14-15 days of supplementation.

**Conclusion:** Probiotics appear to reduce infectious complications, including ventilator-associated pneumonia, in critically ill patients and positively influence ICU and hospital LOS, days on MV and diarrhea. However, clinical heterogeneity and potential publication bias limit a clear clinical recommendation. Further research on probiotics in critically ill patients and more high-quality clinical trials are needed to demonstrate these benefits.

Keywords: Probiotics, prebiotics, synbiotic, critically ill patients, enteral nutrition.

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#### INTRODUCTION

Infections are the most common cause of death in adult patients admitted to Intensive Care Units (ICUs) in Europe, Asia, and America. Despite the heterogeneity of the clinical picture in critically ill patients, ICU patients have been found to exhibit a change in the composition of the gut microflora, i.e. the microbes that colonize the gut, with a reduction in "normal" bacteria and an increase in potentially pathogenic bacteria, a phenomenon known as 'dysbiosis', which increases the predisposition to developing hospital-acquired infections while compromising outcome.<sup>1</sup> Systemic infections can lead to an increased risk of complications and burdensome outcomes. Systemic infections include infections of the respiratory tract, urinary tract and bacteremia<sup>2</sup> and it has been shown that microbiome dysbiosis is not implicated as the cause of them, but as a critical mediator between external stimuli and systemic infections. Possible explanations for the dysbiosis of the microbiome in the severely ill are rapid changes in feeding parenteral and enteral nutrition, the stress they are under, the drugs that inhibit gastric acidity, antibiotics, mechanical ventilation etc.

As the intestinal mucosa been hypothesized to play a vital role in the progression of severe disease, sepsis and multiorgan dysfunction syndrome (MODS)<sup>3</sup>, the maintenance of a healthy/physiological mucosa, possibly through probiotic administration, is of great interest in the literature. According to the World Health Organization (WHO), probiotics are defined as live non-pathogenic microorganisms, which when administered in sufficient quantity have shown beneficial effects in the prevention and treatment of various pathological conditions.<sup>4</sup>

To date, the mechanisms by which probiotics have been described through which they may exert beneficial effects include modification of the gut microbiome by enhancing antimicrobial peptide production, release of antimicrobial factors, suppression of immune cell proliferation, activation of mucus and IgA production, enhancement of the immune response and activation of various protective actions of the epithelial barrier. Considering that the gut plays an important role in the progression of severe disease, sepsis and MODS<sup>3</sup>, strengthening the intestinal barrier and maintaining a normal intestinal microbiota, possibly through the administration of congenital bacteria (probiotics), has been shown by many studies to optimize the course of severely ill patients.<sup>5,6,7</sup> However, at the same time there are studies which have shown no improvement.<sup>8</sup>

As the administration of probiotics in the ICU remains widespread, while current guidelines are not completely clear, and at the same time there are a significant number of new clinical trials with the use of probiotics in critically ill patients, we considered it necessary to conduct a systematic review on the efficacy of probiotics use in the ICU. We aim to evaluate the efficacy of probiotic / prebiotic and /or synbiotic administration on both infections and overall outcomes in adult patients hospitalized in the intensive care unit.

#### METHODOLOGY

#### Protocol

This systematic review meets the relevant criteria of the Preferred Reporting Items for Systematic Reviews (PRISMA)<sup>9</sup> (Figure 1).

#### Eligibility criteria

The research question and the inclusion and exclusion criteria were defined as a priori and developed using a PICOS structure (Patient, Intervention/Exposure, Comparators, Outcome, Study Design). Only studies with clear information from the authors about their design were considered. The inclusion criteria were: (1) randomized, controlled, parallel, group-controlled trials; (2) adults aged  $\geq$  18 years, ICU patients; (3) probiotics or synbiotics or in combination compared with a control group (placebo or prebiotics) and (4) prespecified clinical outcomes in critically ill ICU patients such as primarily total infections and ventilator-associated pneumonia (VAP) and secondarily ICU and hospital mortality, ICU and hospital length of stay, ventilator length of stay, and incidence of diarrhea. We excluded studies that examined different outcomes, e.g., only nutrition-related, or only biochemical markers.

#### Information sources and search strategy

A literature search was conducted in the National Institutes of Health (NIH) via PubMed and EMBASE, CINAHL, CENTRAL and COHRAINE to find all randomized clinical trials (RCTs) published from January 2004 to November 2024. The literature search combined the terms "enteral nutrition" as well as "probiotics" OR "prebiotics" OR "synbiotics" AND "critically ill patients". Only articles in English were considered.

#### Study selection and data extraction

Two reviewers (OK, VL) conducted the primary screening independently. Secondary screening in full text was also performed by two reviewers (OK, VL) to assess eligibility and exclude studies that did not meet the inclusion criteria.

#### Quality assessment

The methodological quality of the studies was assessed using the Jadad Score,<sup>10</sup> which consists of a point system from 1 to 5 according to the following criteria: (1) the study was described as randomized (this includes the use of words such as random, randomization), (2) the study was described as double-blind, (3) there was a description of subjects who dropped out or withdrew from the study. The first two questions can be scored 0 to 2 and the third 0 to 1. Regarding the comparison between groups, in the studies where p values were used, we considered statistically significant differences as those with p < 0.05 and the variables with p < 0.10 were considered as indicating a trend.

#### Clinical outcomes - subgroup analysis

As mentioned above, the main clinical outcomes studied were total infections, VAP, ICU/hospital mortality, length of ICU/hospital stay, duration of MV and incidence of diarrhea. Our secondary aim is to report the results of the studies on the above key outcomes to important intervention modifiers, such as (1) the administration of a probiotic, a prebiotic or a combination of both, i.e. a synbiotic, (2) the dose administered, with a high dose defined as the higher of 5 billion colony forming units (CFU) / day and a low dose defined as the lower of 5 billion CFU / day (73), and (3) the days of microbial administration in 7-day intervention, 14-15-day intervention and intervention longer than 15 days.

A total of eighty-five relevant citations of randomized clinical trials were identified by searching computerized bibliographic databases and reviewing reference lists of related articles. Of these, we excluded fifty-three studies for the following reasons: 43 articles were systematic reviews, 7 were Meta- analyses, 1 was a letter to the editor and 2 were pilot studies. Of the 32 remaining studies, 7 additional studies were excluded because 2 involved a pediatric population, 2 clinical trials had only one intervention group and no second control group, 1 other study administered only a diet and no probiotics, and 2 studies examined different outcomes, i.e., had only nutritional and biochemical markers as outcomes (Figure 1).

#### Characteristics of the Clinical Trials

Finally, twenty-five randomized clinical trials <sup>(7,8,11–33)</sup> met the standards to be included in our systematic review. All trials were published after 2004 and included 5106 patients treated in the ICU (Tables 1 and 2). The average methodological quality of the studies was 4.12 with a maximum of 5 and a minimum of 2. Details of the qualitative analysis of the studies can be found in Table 1. All but 9 of the studies were conducted at a single research center. 16 studies were double-blind studies, 6 were single-blind studies and the remaining 3 were non-blind studies. The number of patients also varied, ranging from 17<sup>13</sup> to 2650<sup>31</sup> with a mean of 204 patients.

The probiotic interventions - treatments - used in the studies varied widely between studies. 18 studies administered probiotics alone, while 7 studies chose to administer synbiotics and 0 studies with prebiotics alone. 11 studies administered lactobacilli alone, 2 lactobacilli and enterococci, 3 lactobacilli and bifidobacteria, 7 lactobacilli, bifidobacteria and streptococci, 1 enterococcus alone, 1 clostridium butyricum alone. The probiotics were administered either orally or through gastric tube GT, orogastric tube OG or nasogastric tube NGT and the daily dose of probiotics administered ranged from 5\*10<sup>7 8</sup> to 2\*10<sup>11</sup> CFU.<sup>17</sup> The control groups received enteral nutrition and/or parenteral nutrition with or without placebo (4 groups received enteral nutrition and prebiotics).<sup>18,20,22,25</sup>

#### RESULTS

Identification and selection of clinical studies

#### **Primary results**

#### New infections overall

Treatment with probiotics led to a lower incidence of infections in the group receiving the probiotics than in the control group. When we summarize the results of the 25 studies, we find that 12 studies reported on the total number of infections that occurred during hospitalization in the ICU and 5 of them<sup>12,14,15,17,24</sup> showed a statistically significant lower incidence of infections in the intervention group. At the same time, 4 of the remaining 7 studies<sup>8,20,21,22</sup> showed a lower tendency to develop infections in the intervention group, 1 showed no difference<sup>31</sup> and only 2 showed a greater tendency.<sup>11,30</sup>

#### Ventilator-associated pneumonia

Treatment with probiotics resulted in a lower incidence of ventilator-associated pneumonia in the group receiving probiotics than in the control group. Of the total of 25 studies, 15 reported on VAP and 9 of them<sup>7,15,17,18,24,25,26,28,32</sup> showed a statistically significant lower incidence of VAP in the intervention group. At the same time, 4<sup>16,21,27,33</sup> of the remaining studies showed a lower tendency to develop VAP in the intervention group and only 2 studies<sup>20,31</sup> showed a greater tendency, but these differences were not statistically significant.

#### Mortality in the intensive care unit

Treatment with probiotics does not appear to affect ICU mortality, as none of the 19 out of 25 studies comparing the probiotictreated group with the control group showed statistically significant results. The trends between the studies were also different: 12 studies<sup>13,14,16,17,18,20,21,24,25,27,31,33</sup> showed lower patient mortality in the intervention group, 3 studies showed the same values in both groups<sup>8,29,30</sup> and 4 studies<sup>7,15,19,26</sup> showed increased mortality in the intervention group.

#### In-hospital mortality

The results on in-hospital mortality were presented in 7 studies, none of which showed statistically significant differences between the group receiving probiotics and the group not receiving probiotics. However, we note that 5 studies<sup>7,11,13,16,31</sup> showed a lower mortality rate in the intervention group, 1 study<sup>22</sup> showed the same mortality rate and only 1 study<sup>30</sup> showed a higher mortality rate in both groups.

#### Length of stay with mechanical ventilation.

The administration of probiotics appeared to have a positive effect on MV, as out of the 14 studies<sup>7,12-18,23,25,27,28,31,33</sup> that reported on the duration of MV between patients in the intervention and control groups, 8 studies<sup>7,12,13,15,17,23,25,33</sup> showed that the group receiving probiotics spent fewer days on mechanical ventilation and 5 of them<sup>12,14,17,23,25</sup> with a statistically significant difference. 5 out of the rest studies showed the same duration of MV between patients in the intervention and control groups<sup>16,18,28,31,33</sup> only 1 of them<sup>27</sup> showed more days of MV, but these differences were not statistically significant.

#### Length of stay in the intensive care unit.

Treatment with probiotics appeared to reduce the days of ICU stay. The length of ICU stay was examined in 22 of 25 studies and the results of 9 of the studies<sup>12,14,17,21,23,25,26,29,32</sup> showed a statistically significant reduction in ICU days in the probiotic group. The results of the remaining studies that did not show statistical significance were different: 7 studies<sup>7,13,14,16,19,20,24,28</sup> showed a shorter ICU stay for the intervention group, 4 studies<sup>8,11,22,27</sup> showed a longer ICU stay and 2 studies<sup>18,31</sup> showed the same duration.

*Length of hospital stay.* The length of hospital stay in the intensive care unit was investigated in 11 clinical studies, whereby the results of 10 studies were not statistically significant and differed from each other. However, one study showed statistically significantly fewer days of hospitalization for the group in which probiotics were administered.<sup>25</sup>

#### Incidence of diarrhea

The administration of probiotics to ICU patients appears to have a positive effect on the incidence of diarrhea, as of the 8 clinical trials, 2<sup>18,19</sup> showed a lower incidence of diarrhea episodes or fewer days with diarrhea in the group receiving probiotics, and another trial<sup>25</sup> showed a trend towards similar results.

#### Secondary results

Intervention with probiotics or synbiotic

Among the 25 randomized clinical trials, there was considerable heterogeneity in terms of the type of intervention, with 18 trials exclusively administering probiotics and the remaining 7 trials administering synbiotics. As for the statistically significant results:

- In the occurrence of fewer infections in the intervention group, 4 had administered synbiotics<sup>14,15,17,24</sup> and one had administered probiotics.<sup>12</sup>
- In the occurrence of fewer cases of ventilator-associated pneumonia in the intervention group, 4 studies<sup>15,17,24,28</sup> had administered synbiotics, while the other 5<sup>7,18,25,26,28,32</sup> had administered probiotics.
- With the shorter duration of mechanical ventilation in the intervention group, 6 studies<sup>7,12,13,23,25,33</sup> had administered probiotics and only 2 studies<sup>15,17</sup> had administered synbiotics.
- With the shorter length of stay in the intensive care unit in the intervention group, 7 studies<sup>12,21,23,25,26,29,32</sup> had administered probiotics and only 2 studies<sup>14,17</sup> synbiotics.
- Probiotics were administered for the shortest length of hospital stay in the intervention group.<sup>25</sup>
- Fewer episodes of diarrhea occurred in the intervention group that was administered probiotics<sup>18,19</sup> while the study showing a tendency for fewer episodes of diarrhea had also administered probiotics.<sup>25</sup>

Probiotics have a statistically significant effect on more of the primary endpoints assessed than synbiotics.

#### The dosage used.

Among the 25 randomized clinical trials, there was also great heterogeneity in the dosage of the administered bacteria. 18 studies<sup>7,11,14-17,29-33,25,26,28,30-33</sup> administered a high dose of microbiota  $\geq$  5 billion CFU colony forming units/day and the remaining 7<sup>8,12,13,18,24,27,29</sup> studies administered a dose  $\leq$  5 billion CFU/day.

Regarding the statistically significant results:

- In the occurrence of fewer infections in the intervention group, 2 had administered a small dose<sup>12,24</sup> and the other 3 a large dose.,14,15,17
- In the occurrence of fewer cases of ventilator-associated pneumonia in the intervention group, 2 studies<sup>18,24</sup> had administered a small dose, while the other 7 had administered a larger dose<sup>7,15,17,25,26,28,32</sup>
- On the shorter duration of stay on mechanical ventilation in the intervention group only 2 studies had administered a small dose<sup>12,13</sup>, whereas the other 6 administered a large dose<sup>7,15,17,23,25,33</sup>
- On the shorter duration of stay in the ICU in the intervention group in 2 studies<sup>12,29</sup> had administered a small dose, while the other 7 had administered a large dose.<sup>14,17,21,23,25,26,32</sup>
- On the shorter length of hospital stay in the intervention group a large dose was administered.<sup>25</sup>
- In the occurrence of fewer episodes of diarrhea in the intervention group, one study administered a large dose<sup>19</sup> and the other a small dose<sup>18</sup>, while the study showing a tendency for fewer episodes of diarrhea had administered a large dose of probiotics.<sup>25</sup>

Larger doses have a statistically significant effect on more of the primary endpoints tested than lower doses.

#### The length of administration of probiotic

Among the 25 randomized clinical trials, there was also great heterogeneity in terms of the days of administration of the microbiota. 2 studies<sup>22,23</sup> administered probiotics for 7 days, 6 studies for 10-15 days<sup>7,11,12,14,17,25</sup> and the remaining 17 studies for >15 days<sup>8,13,15,16,18-21,24,26-34</sup>

As for the statistically significant results:

- Regarding the occurrence of fewer infections in the intervention group, 3 studies<sup>12,14,17</sup> administered the microbiota for 14 or 15 days, 2 studies<sup>15,24</sup> administered the probiotics for longer than 15 days.
- With fewer cases of ventilator-associated pneumonia in the intervention group, 3 studies<sup>7,17,25</sup> administered probiotics for 10-15 days and 6 studies<sup>15,18,24,26,28,32</sup> and 6 studies<sup>15,18,24,26,28,32</sup> for >15 days.

- With the shorter duration of mechanical ventilation in the intervention group, 4 studies<sup>12,14,17,25</sup> administered probiotics for 10-15 days and 1 study<sup>23</sup> for 7 days.
- On the shorter duration of ICU stay in the intervention group, 4 studies<sup>12,14,17,25</sup> had administered probiotics for 10-15 days, other 4 studies<sup>21,16,29,32</sup> had administered probiotics for >15 days, while only 1 study<sup>23</sup> had administered probiotics otics for 7 days.
- On the shorter duration of hospitalization in the intervention group, probiotics had been administered for 14 days.<sup>25</sup>
- Regarding the occurrence of fewer episodes of diarrhea in the intervention group, both studies had administered probiotics for >15 days<sup>18,19</sup>, while the study showing a trend towards fewer episodes of diarrhea<sup>25</sup> had administered probiotics for 14 days.

As you can see from the above, most of the statistically significant results were related to the number of probiotics given for 14 days or longer.

#### Safety issues

Safety issues regarding the administration of probiotics were investigated in 7 RCTs. Treatment with probiotics/synbiotics proved to be safe in the group of critically ill patients in the intensive care unit in 6 out of 7 RCTs.<sup>7,15,18,20,21,25</sup> Neither adverse effects associated with probiotics nor infections or bacteremia due to the strains used in these studies were reported. Only in 1 large RCT<sup>31</sup> 16 patients (15 of them were receiving probiotics (1.1%) compared with 1 patient (1.1%) receiving placebo) experienced either an adverse event or a serious adverse event -2 patients who had a serious adverse event died.

#### DISCUSSION

In this systematic review of 5106 ICU patients, the association between treatment with microbials, i.e., probiotics and/or synbiotics and the outcome of these patients was investigated. The administration of probiotics/synbiotics was associated with a statistically significant reduction in overall ICU infections, including ventilator-associated pneumonia, which is the most common infection in critically ill patients. Our findings on reducing overall infections and VAP are consistent with previous large systematic reviews.<sup>35-41</sup> However, there have been other large systematic reviews in the past, such as that by Barraud et al<sup>42</sup>, which did not show a positive contribution of probiotic administration to overall infections but also indicated a positive effect of probiotic treatment on VAP. The administration of probiotics may contribute to the reduction of VAP and other nosocomial infections by restoring non-pathogenic bacteria in the gut microflora that compete with pathogenic nosocomial microbes by inhibiting their proliferation, modifying local and systemic immune responses, and improving intestinal barrier function<sup>43</sup>. Despite reducing nosocomial infections and VAP, probiotics do not appear to influence ICU or hospital mortality, as none of the trials found such an effect. This may seem contradictory, but after all, mortality due to VAP is lower than previously thought.<sup>44</sup> However, Lou et al.<sup>39</sup> reported that probiotic and synbiotic supplements are beneficial for ICU mortality, but they also wrote that sensitive analysis showed that no single study qualitatively altered the pooled mortality of ICU, providing evidence for the stability of the meta-analysis.

Another important finding of the present review is that 5 studies showed a reduction in the length of stay on the ventilator in the group in which probiotics were administered. It has been shown that treatment with probiotics reduces colonization with pathogenic bacteria in both the oropharynx and the stomach in mechanically ventilated patients. Alexandre et al.<sup>44</sup> from 2014 also confirmed our findings by attributing this effect of probiotic treatment to the effect on the immune system through the effect on mucosa-associated lymphoid tissue, lymphoid tissue in the bronchi and lymphoid tissue in the gut.

In addition, 9 studies showed that treatment with probiotics shortened the length of stay in the intensive care unit and one study showed that the length of hospital stay was also shortened. Some previous studies with similar results attributed this to the ability of lactobacilli to degrade arginine to nitric oxide, which is involved in several important gastrointestinal functions, such as bacteriostasis, mucus secretion, regulation of motility and visceral blood flow, and stimulation of immune functions of the gastrointestinal system.<sup>45</sup> In our review, 2 studies showed a statistically significant reduction in episodes of diarrhea and their duration in days. Our finding is consistent with previous systematic reviews that have also shown that probiotics can reduce the incidence of antibiotic- and Clostridium difficile-associated diarrhea<sup>46</sup> and the same was shown to a recent review.<sup>41</sup> The secondary results were also interesting. Probiotics alone had a better effect than synbiotics and microbial doses of ≥5 billion colony-forming units (CFU) per day and duration of probiotic therapy of at least 14 days or longer were associated with statistically significant results. Both results need to be considered and reviewed to see if they can be verified in future studies. Finally, it should be mentioned that 6 out of 7 RCTs that reported on the safety of probiotic administration found no adverse effects associated with probiotics. Although one recent RCT found that the same percentage (1.1%) of the group receiving probiotics and of the group receiving placebo had adverse events, thus safety should be better investigated. A more recent review also showed that probiotics had higher adverse events than control.<sup>47</sup> Administration of probiotics to critically ill patients should be assessed in many well-designed new clinical trials, so that their positive results can be verified many times over and clear guidelines for their effective administration will be established.

#### Limitations

However, like any systematic review, this study has several limitations. First, the population was heterogeneous and included general ICU patients, surgical ICU patients, patients with multiple injuries, patients with head injuries, etc. In addition, there were many different exclusion criteria in each clinical trial such as immunosuppression, malignancies, prior antibiotic use, liver, gastroenterological and respiratory diseases. The type of intervention in each study varied in terms of the strains administered, their combinations, their dosage and the duration of administration. Finally, the degree of quality of the studies also varied, with some meeting all criteria to the maximum, such as double-blind study, computer randomization, detailed description of subjects who were rejected or dropped out of the study and some others without any randomization, which did not include the exact type of randomization and were qualitatively weak.

#### Conclusions and recommendations

Our systematic review found that probiotics reduce infectious complications, including ventilator-associated pneumonia, in critically ill patients and positively influence ICU and hospital LOS, days on MV and diarrhea. Furthermore, probiotics seemed to have better effect than synbiotics and microbial doses of  $\geq$ 5 billion colony-forming units (CFU) per day and duration of probiotic therapy of at least 14 days or longer were associated with statistically significant results. However, clinical heterogeneity and potential publication bias limit a clear clinical recommendation. Further research on probiotics in critically ill patients and more high-quality clinical trials are needed to demonstrate these benefits.

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# ANNEX

# **TABLE 1.** Randomized studies evaluating probiotics in critically ill patients.

	Authors/	Country	Study	Quality	Participants	Modalities	Intervention/	Control	Primary
	Year		Design	Score	intervention	of	Dose/		outcome
					vs control	treatment	Duration		
						administrati			
						on			
1	Jain et	Germany	SC,	5	90 ICU	Btd through	Trevis capsule (Chr	NR	Incidence
	al, 2004		RCT,		patients	NGT	Hansen), 3/d		and nature
	(11)		DB		(45		4_10 <sup>9</sup> CFU L. aci-		of gastric
			(SYN)		intervention/		dophilus La5, B. lac-		coloniza-
					45 control)		tis Bb-12, S. ther-		tion
							mophilus and L.		
							bulgaricus + Oli-		
							gofructose (7.5 g		
							Raftilose powder,		
							2/d) for 10d		
2	Arruda	Brazil	SC,	5	20 ICU	Btd through	Polymeric diet with	Polymeric	Incidence
	et		RCT,		patients	NGT	30 g of	Diet	of ICU ac-
	Aguilar-		DB		(10		glutamine and 240		quired in-
	Nascime		(PRO)		intervention /		ml of fermented		fections,
	nto,				10 control )		milk with the		LOS in ICU
	2004						probiotic strain Lac-		& duration
	(12)						tobacillus johnsoni		of MCV
							(La 1) 10 <sup>5</sup> (LC 1 ®,		
							Nestle, Sao Paulo,		
					47.1011		Brazil), 5 to 14 d		1 000
3	Klarin et	Sweden	SC,	3	17 ICU pa-	Btd through	Fermented oatmeal	EN (Impact	Lp 299v
	al, 2005		RCT, SB		tients on anti-	NGT	10 <sup>9</sup> CFUL m 2004	or Nutro-	survivai
	(13)		(PRO)		blotics		10° CFU Lp 299V	arip fiber).	through
					(9		(Probl AB, Lund,	Some	the
					( 8 control)		50 ml ovory 6 h x 2		from the
					7 8 (011101)		dave	needed Fix	stomach to
							then 25 ml overv 6 h		the rectum
							until ICII discharge		the rectain
4	McNaug	United	SC PCT	2	103 (CL)	Btd through	EN or PN + Proviva	EN or PN	Systemic
-	ht et al	Kingdom	Onen	5	natients (52	Oral NIT	(oatmeal and fruit	alone	inflammato
	2005	Ringdonn	label		interventions /		drink) 5 x 10 <sup>7</sup>	uione	ry response
	(8)		(PRO)		51 control)		CEU/ml of L planta-		
	(0)		()				$rum 299 v \times 500$		
							mls until		
							hospital discharge		
							or beyond		
5	Kotzamp	Greece	MC.	5	65 severe mul-	Btd throuah	Synbiotic 2000Forte	The pla-	Systemic
	assi et al.		RCT,DB	-	tiple trauma	GT or NGT	Medipharm, Swe-	cebo prep-	infection
	2006		(SYN)		ICU patients	_	den, (10 <sup>11</sup> CFU,	aration	rate (SIRS
	(14)				(35 interven-		Pediococcus pen-	consisted	and
					tion /30 con-		toseceus, Leuconos-	of	MODS)
					trol)		toc	identical	and Mor-
					mesenteroides, L.	doses of	tality		
							paracasei ssp 19,	powdered	-

							and L. plantarum	glucose	
							2362), 1 sachet/d +	polymer	
							2.5 g inulin, oat	(maltodex-	
							bran,pectin, and re-	trin,	
							sistant starch.for 15	Caloreen,	
							days diluted in 100	Nestle, UK).	
							ml of tap water.		
6	Spindler	Slovenia	SC,	2	113 multiple	Btd through	Synbiotic 2000;	3 different	Incidence
	et al,		RCT,		trauma ICU	NGT	Medipharm Swe-	formulas of	of ICU ac-
	2007		Open		patients re-		den, (10 <sup>10</sup> CFU of	enteral	quired in-
	(15)		label		ceiving		Pediococcus pento-	feeding	fections
			(SYN)		MV>4d		saceus, Lactococcus		
					(26 interven-		raffinolactis , Lacto-		
					tion /87 con-		bacillus paracasei		
					trol)		19, Lactobacillus		
							<i>plantarum</i> )once a		
							day diluted in 100		
							ml of lukewarm		
							sterile water until		
							ICU discharged or		
							death		
7	Knight	United		5	259 general	Btd through	Synbiotic 2000Forte,	A crystal-	Incidence
	et al,	Kingdom	SC,		ICU patients	NGT or OGT	Medipharm, Swe-	line cellu-	of VAP
	2009	5	RCT, DB		, reauirina MV		den. (at a dose of	lose-	
	(16)		(SYN)		for>48 h		10 <sup>10</sup> bacteria per sa-	based pla-	
	()		(2)		(130		chet, twice a day +	cebo twice	
					intervention /		Betaglucan, Inulin,	a dav	
					129 control)		Pectin and Resistant		
					,		starch (2.5 g of each		
							as prebiotics diluted		
							in 50–100 ml of		
							sterile water for 28		
							d or ICU discharge		
							or death Incidence		
8	Giamarel	Greece	MC.	3	72 multiple	Btd through	Synbiotic 2000	NR	Incidence
-	los-		RCT. DB	-	trauma ICU	GT or NGT	Forte, Medipharm,		of ICU ac-
	Bourbou		(SYN)		patients		Sweden, (10 <sup>11</sup> CFU)		auired in-
	lis et al.		· · /		(36 interven-		for 15 days diluted		' fections
	2009				tion / 36 con-		in 100 ml of tap wa-		and VAP
	(17)				trol)		ter		
9	Morrow	United	SC,	5	138 general	Btd through	EN (routine care) +	EN (routine	Incidence
	et al,	States	RCT, DB		ICU patients	Oropharynx	Lactobacillus rham-	care) + in-	of VAP
	2010		(PRO)		,	and	nosus GG, $2 \times 10^9$	ert plant	
	(18)		/		(68 interven-	NGT	BID aslubricant and	starch inu-	
	. /				tion / 70 con-		mixed with water	lin (prebi-	
					trol)		until extubation	otic) BID as	
					- /			lubricant	
								and mixed	
								with water	

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10	Frohmad	Australia	SC,	5	45 General ICU	Btd through	EN (Standard) + VSL	EN (Stand-	Number of
	er et al,		RCT, DB		patients	NGT or NJT	#3 (VSL Pharmaceu-	ard) + pla-	episodes of
	2010		(SYN)		on antibiotics		ticals,	cebo	liquid
	(19)						Gaithersburg, Mary-	mixed in	stool in en-
					(20 interven-		land, 450 10 <sup>9</sup> CFU	50ml nutri-	teral fed
					tion / 25 con-		Bifidobacterium	tional	patients
					trol)		breve, Bifidobacte-	supple-	
							rium	ment (Sus-	
							longum	tagen),	
							(>10x10 <sup>9</sup> /g),	twice daily	
							Bifidobacterium in-	until hospi-	
							fantis (>10x10 <sup>9</sup> /g), L	tal dis-	
							acidophilus, Lacto-	charge	
							bacillus plantarum,		
							Lactobacillus casei, L		
							bulgaricus, Strepto-		
							coccus thermophilus		
							(>100 x 10 <sup>9</sup> /g)		
							mixed in 50ml nutri-		
							tional supplement		
							(Sustagen),		
							twice daily until		
							hospital discharge		
11	Barraud	France	SC,	5	167 Mechani-	Btd through	EN (Fresubin) +	EN	Assess the
	et al,		RCT, DB		cally ventilated	NGT	capsule 2 * 10 <sup>10</sup> of	(Fresubin)	effects of
	2010		(PRO)		ICU		revivable bacteria	+ placebo	prophylac-
	(20)				patients		(Lactobacillus rham-	capsules	tic
					(87 interven-		nosus GG, Lactoba-	(excipient	probiotic
					tion / 80 con-		cillus casei, Lactoba-	of potato	administra-
					trol)		cillus acidophi-	starch) 5	tion in pa-
							lus,and Bifidobacte-	cap-	tients ven-
							rium bifidum) + po-	sules/day	tilated for
							tato starch (Nu-	diluted in	up to 2
							tergia, Capdenac,	20 mL of	days
							France)	water for	
							5 capsules/day di-	28 days	
							luted in 20 mL of		
				-			water for 28 days		
12	Tan et al,	China	SC,	3	52 ICU pa-	Btd through	EN (standard), total	EN (C)	Assess the
	2011		RCT, SB		tients with	NGI	of 10 <sup>°</sup> bacteria i.e., 7	(Standard)	effects of
	(21)		(PRO)		closed		sachets each 0.5 ×		probiotics
					nead injury		10° Bifidobacterium		to the
					(20				imbalar -
					intervention /				
		26 0		26 control)		garicus and 0.5 ×			
							thermonkilus for 21		outcomes
						dave discolved in 20		штыра-	
					m storilized distilled		uents		
1			1	1		1	water		1

13	Ferrie et al, 2011 (22)	Australia	SC, RCT, DB (PRO)	5	36 ICU pa- tients enterally fed adults with di- arrhea (18 intervention / 18 control)	Btd through OGT	EN (Standard) + Culturelle (Lactobacillus rham- nosus GG), 10 <sup>10</sup> species/capsule +280 mg inulin powder for 7 days, diluted in 50 mL sterile water	EN (Stand- ard) + Raftiline, gelatin capsule with 280 mg inulin powder (prebiotic) for 7 days, diluted in 50 mL ster- ile water diluted in 50 mL ster- ile water	Duration of diarrhea
14	Malik et al, 2016 (23)	Malaysia	SC, RCT, DB (PRO)	i,       5       60 ICU       Btd through       3gr granule of       3         DB       patients       NGT       30*10 <sup>9</sup> CFU of Lac-       ull         O)       (30       tobacillus acidophi-       ull         intervention /       30 control)       sei, Lactobacillus ca-       tw         30 control)       Iactis, Bifidobacte-       rium bifidum,       Bifidobacterium         longum and       Bifidobacterium in-       fantis diluted in 5mL       twice a day for 7		3gr Gran- ule diluted in 5mL twice a day for 7 days	Duration until re- turning to normal gut function		
15	Zeng et al, 2016 (7)	China	MC, RCT, Open label (PRO)	3	235 ICU patients (117 intervention / 118 control)	Btd through NGT	1 capsule (Medilac- S, China) 0.5 g three times daily. Each probiotic capsule contained active Bacillus sub- tilis and Enterococ- cus faecalis at a concentration of 4.5 $\times$ 10 <sup>9</sup> /0.25 g and 0.5 $\times$ 10 <sup>9</sup> /0.25 g, Respectively for 14 days	EN (standard)	Preventive effect of probiotics on VAP
16	Shimizu et al, 2018 (24)	Japan	MC, RCT, SB (SYN)	3	72 ICU septic patients (35 interven- tion / 37 con- trol)	Btd through NGT	The probiotics used were Yakult BL Seichoyaku (Yakult Honsha, Tokyo, Ja- pan), 1 × 10 <sup>8</sup> CFU B. breve /g and 1 × 10 <sup>8</sup> CFU L. casei /g + prebiotics	NR	Incidence of ICU ac- quired in- fections and VAP and gut microbiota modulation

							3g/d galactooligo- saccharides &		
							10g/d galactooligo-		
							saccharides (Oligo-		
							mate S-HP,		
							Yakult Honsha) were		
							used as SYNbiotic		
							therapy until oral in-		
							take was initiated or		
							4 weeks		
17	Mahmoo	Iran	MC,	5	100 ICU	Btd through	1 capsule of 10 <sup>10</sup>	Placebo	Incidence
	dpoor et		RCT, DB		patients	NGT	CBU of Lactobacillus	capsule	of VAP
	al, 2019		(PRO)		(48		species (casei, aci-	contained	
	(25)				intervention /		dophilus, rhamno-	sterile	
					52 control)		sus,	starch	
							bulgaricus),	powder,	
							Bifidobacterium spe-	visually	
							cies (breve, longum)	identical	
							and Streptococcus	twice a day	
							thermophilus. (Lac-	for 14d	
							tocare, Zist-Takhmir,		
							Tehran, Iran) twice a		
							day for 14d		
18	Tsaousi	Greece	SC,	3	58 ICU multi-	Btd through	A four-probiotic for-	Placebo	Positive ef-
	et al,		RCT, SB		trauma pa-	NGT or OGT	mula was applied		fect on the
	2019		(PRO)		tients, requir-		and each patient re-		incidence
	(26)				ing mechanical		ceived two capsules		of VAP or
					ventilation for		per day from Day1		other ICI I-
							, , ,		
					>10 days.		to Day 15 post ICU		acquired
					>10 days. (28		to Day 15 post ICU admission. The con-		acquired
					>10 days. (28 intervention /		to Day 15 post ICU admission. The con- tent of one capsule		acquired infections and ICU
					>10 days. (28 intervention / 30		to Day 15 post ICU admission. The con- tent of one capsule was given as an		acquired infections and ICU stay in crit-
					>10 days. (28 intervention / 30 placebo)		to Day 15 post ICU admission. The con- tent of one capsule was given as an aqueous suspension		acquired infections and ICU stay in crit- ically ill
					> 10 days. (28 intervention / 30 placebo)		to Day 15 post ICU admission. The con- tent of one capsule was given as an aqueous suspension by nasogastric tube,		acquired infections and ICU stay in crit- ically ill multi-
					>10 days. (28 intervention / 30 placebo)		to Day 15 post ICU admission. The con- tent of one capsule was given as an aqueous suspension by nasogastric tube, while the other one		acquired infections and ICU stay in crit- ically ill multi- trauma pa-
					> 10 days. (28 intervention / 30 placebo)		to Day 15 post ICU admission. The con- tent of one capsule was given as an aqueous suspension by nasogastric tube, while the other one was spread to the		acquired infections and ICU stay in crit- ically ill multi- trauma pa- tients.
					>10 days. (28 intervention / 30 placebo)		to Day 15 post ICU admission. The con- tent of one capsule was given as an aqueous suspension by nasogastric tube, while the other one was spread to the oropharynx after		acquired infections and ICU stay in crit- ically ill multi- trauma pa- tients.
					>10 days. (28 intervention / 30 placebo)		to Day 15 post ICU admission. The con- tent of one capsule was given as an aqueous suspension by nasogastric tube, while the other one was spread to the oropharynx after being mixed up with		acquired infections and ICU stay in crit- ically ill multi- trauma pa- tients.
					> 10 days. (28 intervention / 30 placebo)		to Day 15 post ICU admission. The con- tent of one capsule was given as an aqueous suspension by nasogastric tube, while the other one was spread to the oropharynx after being mixed up with water-based lubri-		acquired infections and ICU stay in crit- ically ill multi- trauma pa- tients.
					>10 days. (28 intervention / 30 placebo)		to Day 15 post ICU admission. The con- tent of one capsule was given as an aqueous suspension by nasogastric tube, while the other one was spread to the oropharynx after being mixed up with water-based lubri- cant. The follow-up		acquired infections and ICU stay in crit- ically ill multi- trauma pa- tients.
10					> 10 days. (28 intervention / 30 placebo)	Diskthere wh	to Day 15 post ICU admission. The con- tent of one capsule was given as an aqueous suspension by nasogastric tube, while the other one was spread to the oropharynx after being mixed up with water-based lubri- cant. The follow-up period was 30 days		acquired infections and ICU stay in crit- ically ill multi- trauma pa- tients.
19	Habib et	Egypt	SC,	4	> 10 days. (28 intervention / 30 placebo) 65 adult multi-	Btd through	to Day 15 post ICU admission. The con- tent of one capsule was given as an aqueous suspension by nasogastric tube, while the other one was spread to the oropharynx after being mixed up with water-based lubri- cant. The follow-up period was 30 days 32 patients received	33 Patients	Evaluate
19	Habib et al, 2020	Egypt	SC, RCT, DB	4	> 10 days. (28 intervention / 30 placebo) 65 adult multi- ple trauma pa- tionte on ma	Btd through NGT or OGT	to Day 15 post ICU admission. The con- tent of one capsule was given as an aqueous suspension by nasogastric tube, while the other one was spread to the oropharynx after being mixed up with water-based lubri- cant. The follow-up period was 30 days 32 patients received one Lacteo Forte ®	33 Patients received	Evaluate the role of
19	Habib et al, 2020 (27)	Egypt	SC, RCT, DB (PRO)	4	> 10 days. (28 intervention / 30 placebo) 65 adult multi- ple trauma pa- tients on me-	Btd through NGT or OGT	to Day 15 post ICU admission. The con- tent of one capsule was given as an aqueous suspension by nasogastric tube, while the other one was spread to the oropharynx after being mixed up with water-based lubri- cant. The follow-up period was 30 days 32 patients received one Lacteo Forte® sachet (Lactobacil-	33 Patients received similar reg-	Evaluate the role of probiotics
19	Habib et al, 2020 (27)	Egypt	SC, RCT, DB (PRO)	4	> 10 days. (28 intervention / 30 placebo) 65 adult multi- ple trauma pa- tients on me- chanical venti-	Btd through NGT or OGT	to Day 15 post ICU admission. The con- tent of one capsule was given as an aqueous suspension by nasogastric tube, while the other one was spread to the oropharynx after being mixed up with water-based lubri- cant. The follow-up period was 30 days 32 patients received one Lacteo Forte ® sachet (Lactobacil- lus delbrueckii and	33 Patients received similar reg- imen of	Evaluate the role of probiotics in prophy-
19	Habib et al, 2020 (27)	Egypt	SC, RCT, DB (PRO)	4	> 10 days. (28 intervention / 30 placebo) 65 adult multi- ple trauma pa- tients on me- chanical venti- lator (expected	Btd through NGT or OGT	to Day 15 post ICU admission. The con- tent of one capsule was given as an aqueous suspension by nasogastric tube, while the other one was spread to the oropharynx after being mixed up with water-based lubri- cant. The follow-up period was 30 days 32 patients received one Lacteo Forte ® sachet (Lactobacil- lus delbrueckii and Lactobacillus fer- montum (10 *10 <sup>3</sup> ) a	33 Patients received similar reg- imen of placebo	Evaluate the role of probiotics in prophy- laxis of
19	Habib et al, 2020 (27)	Egypt	SC, RCT, DB (PRO)	4	> 10 days. (28 intervention / 30 placebo) 65 adult multi- ple trauma pa- tients on me- chanical venti- lator (expected ≥48 h) (22	Btd through NGT or OGT	to Day 15 post ICU admission. The con- tent of one capsule was given as an aqueous suspension by nasogastric tube, while the other one was spread to the oropharynx after being mixed up with water-based lubri- cant. The follow-up period was 30 days 32 patients received one Lacteo Forte® sachet (Lactobacil- lus delbrueckii and Lactobacillus fer- mentum (10 *10 <sup>9</sup> ), 3 times daily during	33 Patients received similar reg- imen of placebo sachets	Evaluate the role of probiotics in prophy- laxis of VAP after multiple
19	Habib et al, 2020 (27)	Egypt	SC, RCT, DB (PRO)	4	> 10 days. (28 intervention / 30 placebo) 65 adult multi- ple trauma pa- tients on me- chanical venti- lator (expected ≥48 h) (32	Btd through NGT or OGT	to Day 15 post ICU admission. The con- tent of one capsule was given as an aqueous suspension by nasogastric tube, while the other one was spread to the oropharynx after being mixed up with water-based lubri- cant. The follow-up period was 30 days 32 patients received one Lacteo Forte® sachet (Lactobacil- lus delbrueckii and Lactobacillus fer- mentum (10 *10 <sup>9</sup> ), 3 times daily during their ICU stay	33 Patients received similar reg- imen of placebo sachets	Evaluate the role of probiotics in prophy- laxis of VAP after multiple
19	Habib et al, 2020 (27)	Egypt	SC, RCT, DB (PRO)	4	> 10 days. (28 intervention / 30 placebo) 65 adult multi- ple trauma pa- tients on me- chanical venti- lator (expected ≥48 h) (32 intervention / 33 placebo)	Btd through NGT or OGT	to Day 15 post ICU admission. The con- tent of one capsule was given as an aqueous suspension by nasogastric tube, while the other one was spread to the oropharynx after being mixed up with water-based lubri- cant. The follow-up period was 30 days 32 patients received one Lacteo Forte ® sachet (Lactobacil- lus delbrueckii and Lactobacillus fer- mentum (10 *10 <sup>9</sup> ), 3 times daily during their ICU stay	33 Patients received similar reg- imen of placebo sachets	Evaluate the role of probiotics in prophy- laxis of VAP after multiple trauma.

20	Nazari et al, 2020 (28)	Iran	MC, RCT, SB (SYN)	4	147 Neurosur- gical ICU pa- tients on me- chanical venti- lator ≥48 h (73 intervention / 74 placebo)	Btd through NGT	2 Daily Lactocare capsules (Zist Tak- mir Company Ter- han -Iran) with 20cc distilled water twice a day	2 Starch capsules with 20cc distilled water twice a day	The effects of probiot- ics on the prevalence of VAP in multi- trauma pa- tients in neurosur- gical ICU
21	Wang et al, 2021 (29)	China	SC, RCT, SB (PRO)	4	61 Respiratory ICU patients (28 interven- tion / 33 placebo)	Btd orally or through NGT or OGT	One tablet MIYA- BM® (Miyarisan pharmaceutical Co., Ltd., Tokyo, Japan), contains Clostridium butyricum at 10 <sup>6</sup> CFU bacteria per sa- chet) was adminis- tered thrice daily	A placebo tablet was adminis- tered thrice daily	Whether exogenous probiotics could im- prove the intestinal barrier function effect via attenuating inflamma- tion and im- munomo- dulation to improve the clinical outcomes in critically ill patients.
22	Litton et al, 2021 (30)	Australia	MC, RCT, DB (PRO)	5	228 ICU patients (110 intervention / 108 placebo)	Btd through NGT or OGT	The study drug (contained 2×10 <sup>10</sup> colony-forming units (CFUs) of L. plantarum 299v per capsule) was admin- istered once daily, for 60 days	The pla- cebo pa- tients re- ceived an identical capsule containing microcrys- talline cel- lulose	Whether early and sustained L. planta- rum 299v therapy adminis- tered to adult ICU patients in- creased days alive and at home.
23	Johnston e et al, 2021 (31)	Canada, USA and Saudi Ara- bia	MC, RCT, DB (PRO)	4	2650 ICU pa- tients ≥18 years old, an- ticipated to be mechanically ventilated ≥72 hours	Btd through NGT or OGT	One capsule, 1×10 <sup>10</sup> colony forming units of L. rhamno- sus GG (i-Health, Inc.) in suspended in tap water or ster- ile water (depend-	Patients in the pla- cebo group re- ceive an identical capsule containing	Develop- ment of VAP

					(1318		ent on local prac-	microcrys-	
					intervention /		tices), administered	talline cel-	
					1332		through a nasogas-	lulose.	
					Placebo)		tric or orogastric		
							feeding tube up to		
							60 days or until dis-		
							charge from the		
							ICU.		
24	Tsilika et	Greece	MC,	4	112 multi-	Btd through	2 sachets twice daily		The aim of
	al, 2022		RCT, DB		trauma pa-	NGT or OGT	for 15 days (Lacto-		this study
	(32)		(PRO)		tients, ex-		bacillus acidophilus		was to as-
					pected to re-		LA-5 [1.75 × 10 <sup>9</sup>		sess the ef-
					quire mechan-		colony-forming		ficacy of a
					ical ventilation		units (CFU)], Lacto-		probiotic
					for >10 days		bacillus plantarum		regimen
					(59		(0.5 × 10 <sup>9</sup> CFU),		for VAP
					intervention /		Bifidobacterium lac-		prophylaxis
					53		tis BB12 (1.75 ×10 <sup>9</sup>		in mechan-
					Placebo)		CFU) and Saccharo-		ically venti-
							myces boulardii (1.5		lated
							× 10 <sup>9</sup> CFU) twice		multi-
							daily for 15 days		trauma pa-
									tients
25	Lu et al,	China	SC,	5	24 ICU pa-		The probiotic group	The control	The effect
	2024		RCT, DB		tients ≥18		was given Bifco	group re-	of mixed
	(33)		(PRO)		years old, an-		(Shanghai Shinji	ceived	probiotics
					ticipated to be		Pharmaceutical Fac-	conven-	on the di-
					mechanically		tory Co., Ltd., Si-	tional	versity of
					ventilated $\geq /2$		nopharm quasizu	treatment	the pulmo-
					hours		s10950032, specifi-	only	nary fora in
					(12		cation: 210		critically ill
					intervention /		mg/grain) twice		patients re-
					12		daily until leaving		quiring
					Placebo)		the ICU		mechanical
									ventilation
									by analyz-
									ing the
									changes in
									iung mi-
									crobes

**Notes:** SC=single center, MC=multi center, ICU= intensive care unit, DB= double blind, RCT=randomized controlled trial, SYN = synbiotics, PRO =probiotics, PRE=prebiotics, NGT= nasogastric tube, GT= gastrostomy tube, MV=mechanical ventilation, OGT= orogastric tube, CFU=colony forming units, VAP= ventilator-associated pneumonia, BID= twice daily

TABLE 2. Reported clinical outcomes in RCT	s evaluating probiotics in crit	ically ill patients
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	Authors/	ICU	Hospital	Incidence	Incidence of	Duration of	ICU LOS	Hospital	Diarrhea
	Year	Mortality	Mortality	of ICU-	ICU-Acquired	Mechanical	(days)	LOS (days)	(days)
		Control	Control	Acquired	Pneumonia	Ventilation	Control	Control	Control
		vs	vs	Infections	Control	(days)	vs	vs	vs
		Intervention	Intervention	Control	vs Intervention	Control	Intervention	Intervention	Intervention
				vs		VS			
				Intervention		Intervention			
1	Jain et al,	NR	22/45 (49%)	26/45 (58%)	NR	NR	5 (3–14)	15 (9–26)	NR
	2004 (11)		vs	vs			vs	vs	
			20/45 (45%)	33/45 (73%)			7 (3–16)	14 (9–29)	
2	Arruda et	0	NR	10 (100 %)	NR	14 (3–53)	22 (7–57)	NR	NR
	Aguilar-			vs		VS	vs		
	Nascimento			5 (50 %)		7 (1–15)	10 (5–20)		
	,2004			(p=0.03)		(p=0.04)	(p<0.01)		
	(12)								
3	Klarin et al,	2/7 (29%	2/7 (29%)	NR	NR	17 (13–28)	16.3 ± 15.7	34.3 ± 15.4	NR
	2005	VS	VS			VS	VS	VS	
	(13)	1/8 (12%)	2/8 (25%)			12 (7–20)	14.2 ± 10.6	48.3 ± 30.4	
4	McNaught	18/51 (35%)	NR	Septic	NR	NR	4 (2–7)		
	et al, 2005	VS		morbidity			VS	NR	NR
	(8)	18/52 (35%)		22/51(43%)			5 (2–9)		
				VS					
				21/52 (40%)					
5	Kotzampass	9/30 (30%)	NR	90%	NR	26 ( 7–60)	43 (17–82)	NR	NR
	i et al, 2006	VS		VS		VS	VS		
	(14)	5/35 (14.3%)		63%		15 ( 5–32)	25 (13–54)		
				(p = 0.01)		(p = 0.001)	(p= 0.01)		
6	Spindler et	5/87 (6%) vs	NR	46/87 (53%)	46/87 (53%)	34/87 (39%)	NR	NR	NR
	al, 2007	2/26 (8%)		VS	vs 5/26 (19%)	VS			
	(15)			5/26 (19%)	(p =0.032)	4/26 (15%)			
				(p =0.003)					
7	Knight et	34/129 (26%)	42/129	NR	17/129 (13%)	5 (3-11)	7 (3-14)	18 (7-32)	
	al, 2009	VS	(33%)		VS	VS	VS	VS	
	(16)	28/130 (22%)	VS		12/130 (9%)	5 (2-9)	6 (3-11)	19 (8-36)	
			35/130						
	<u>.</u>		(27%)	000/	10 (00 000)	207 277	44.0 07.0		
8	Giamarellos	10/36 (27.8%)	NR	90%	12 (33.3%)	29.7 vs 16.7	41.3 vs 27.2	NR	NR
	-Bourboulis	VS		VS	VS	(p=0.001)	(p= 0.01)		
	et al, 2009	5/36 (13.9%)		63%	5 (13.9%)				
	(17)	04.407		( p= 0.01)	(p=0.047)	0.0		017 17 1	
9	Worrow et	21.4%	NK	NK	33 (45.2%)	9.6 ± 7.2	14.6 ±11.6	21./±1/.4	Non C. dit-
	ai, 2010	VS			VS	VS	VS	VS	TICILE
	(10)	17.6%			17 (23.3%)	9.5 ±6.3	14.8 ±11.8	21.4± 14.9	diarrhea
					(p=0.005)				44 (62.9%)
									vs 42 (61.8%)
									C. difficile
									diarrhea,

									9.8± 4.9 vs
									13.2 ±7.4,
									ICU-associ-
									ated diar-
									rhea
									5.9 ±3.8 vs
									4.1 ± 3.7,
									(p=0.03)
10	Frohmader	3/25 (12%)	NR	NR	NR	NR	8.1 ± 4	NR	Diarrhea
	et al, 2010	VS					VS		episodes/
	(19)	5/20 (25%)					7.3 ± 5.7		pt/day
									1.05± 1.08
									vs
									0.53 ± 0.54
									(p=0.03)
11	Barraud et	21 (26.2%)	NR	30 (37.5%)	15 (18.7%)	NR	20.2 ± 20.8	28.9 ± 26.4	42 (52.5%)
	al, 2010	VS		vs	VS		VS	VS	VS
	(20)	21 (24.1%)		30 (34.4%)	23 (26.4%)		18.7 ± 12.4	26.6 ± 22.3	48 (55.2 %)
12	Tan et al,	28 days	NR	15/26 (58%)	13/26 (50%)	NR	10.7 ± 7.3	NR	NR
	2011	5/26 (19%)		VS	VS		vs		
	(21)	VS		9/26 (35%)	7/26 (27%)		6.8 ± 3.8		
		28 days 3/26					(p=0.034)		
		(12%)							
13	Ferrie et al,	NR	2/18 (11%)	16/18 (89%)	NR	NR	29.75 ± 18.81	59.04 ±	2.56 ±
	2011		VS	VS			VS	33.92	1.85) vs
	(22)		2/18 (11%)	14/18 (78%)			32.04 ± 24.46	VS	3.83 ± 2.39
								54.50 ±	
								31.26	
							45.04 7.0		
14	Malik et al,	NR	NR	NR	NR	14.0(±8.0)	15.8(±7.8)	NR	NR
	2016					VS	VS		
	(23)					8.4(±3.5)	$10.9(\pm 3.9)$		
45	7	0 (117 (7 7 0()	10/100	ND	FO (117 (FO 40())	(p<0.01)	(p<0.01)	10.0 + 10.2	ND
15	Zeng et al,	9/11/(7.7%)	16/108	NR	59/11/ (50.4%)	17 (13–28)	22 (11–56)	10.6 ± 10.2	NR
	2016	VS	(14.8 %)		VS	VS	VS		
	(7)	15/116 (12.7	VS		43/110 (30.4%)	12 (7-20)	16 (14–32)	$13.5 \pm 12.4$	
		70)	(10,7,9%)		(P = 0.031)				
16	Chimizu of	4 (10 99/)	(10.7 %)	25 (67 60/)	10 (40 60/)	ND	20 (17 AE)	ND	ND
10	Shimizu et	4 (10.0%)	INK	25 (07.0%)	10 (40.0%)	INK	20 (17-45)		
	al, 2018 (24)	VS 2 (8 6%)		vs 10 (28 6%)	VS 5 (1/ 2%)		VS 22 (12 /2)		
	( )	5 (0.078)		(p < 0.05)	(n < 0.05)		23 (13-43)		
17	Mahmoodn	6 (11 1%)	NID	(p< 0.03)	(p< 0.03)	200 + 171	186 + 63	211 + 57	15 (27.8)
17		U (11.170) Ve	INIT		0.34		10.0 ± 0.5	Δ1.1 ± J.1	15 (21.0) Ve
	2010 et al,	vs 5 (10 4%)			0.66	vs 210 ± 115	vs 116 ± 9	vs 1/1 2 + 8.6	vs 7 (1/ 6%)
	(25)	5 (10.470)			(n - 0.04)	(n - 0.02)	(n < 0.07)	(n < 0.02)	(n=0.08)
	()				(p=0.04)	(p=0.02)	(p < 0.07)	(p < 0.02)	(p=0.00)
18	Tsaousi et	30-dav	NR	NR	53 3%	NR	C   stay > 30	NR	NR
	al. 2019 (26)	mortality	i vi v		VS		davs		
	, (20)	6.78%			32.1%		401%		
					(n - 0.001)				

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-									
		10.7%					vs 7.1%		
							(p=0.002)		
19	Habib et al,	12 (36.36%)	NR	NR	7 (21.21%)	9.10±3.642	12.63±3.681	NR	NR
	2020 (27)	VS			VS	VS	VS		
		11 (34.38%)			5 (15.63%)	11.60±4.775	14.60±4.775		
20	Nazari et al,	NR	NR	NR	33 (44.59%)	8.00+01.51	14.88+01.79	NR	NR
	2020 (28)				VS	VS	VS		
					9 (12.32%)	8.19+01.21	13.35+01.45		
					(p=0.001)				
21	Wang et al,	21.43%	NR	NR	NR	NR	12.94 vs 4.85	19 (14- 26)	66.67%
	2021 (29)	Vs					(p=0.00)	VS	vs. 60.71%
		21.21%						19 (12.5 -	
								28.5)	
22	Litton et al,	4 (3.7%)	4 (3.7%)	5 (4.6%)	NR	NR	NR	NR	NR
	2021 (30)	VS	VS	vs					
		4 (3.6%)	5 (4.6%)	8 (7.3%)					
23	Johnstone	296 (22,2%)	381 (28.6%)	418 (31.4%)	284 (21.3%)	7 (4-13)	12 (8-18)	22 (13-40)	787 (59.1%)
	et al, 2021	VS	vs	vs	VS	VS	vs	VS	Vs
	(31)	279 (21.2%)	363 (27.5%)	414 (31.4%)	289 (21.9%)	7 (4-13)	12 (7-19)	22 (13-42)	785 (59.6%)
24	Tsilika et al,	NR	NR	NR	15 (28.3)	NR	(11-28)	(11-28)	2 (3.8%)
	2022 (32)				VS		VS	VS	Vs
					7 (11.9)		(8-28)	(12-27)	0
					(p=0.034)		(p=0.01)	(p=0.08)	
25	Lu et al,	28-day	NR	NR	1 vs 0	11.75±6.283	NR	NR	NR
	2024 (33)	mortality				VS			
		rate				10.92±4.209			
		4 (33.33%)							
		VS							
		2 (16.67%)							

Notes: vs=versus, NR=not reported, p=p-value, C. difficile = Clostridium difficile

Figure 1. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram. RCT= Randomized Controlled Trial.

