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Abstract

Probiotics have been suggested as a potential intervention for improving outcomes, particularly ventilatory-associated pneumonia, in patients infected with COVID-19. However, with the rapid development of the COVID-19 pandemic, there is little direct evidence available in infected patients. The objective of this scoping review is to examine the availability and nature of literature describing the effect of probiotics in adults with conditions or infections similar to COVID-19 infection, on related health outcomes. MEDLINE, CINAHL and Cochrane Databases were searched for studies, published from 1999 to May 1, 2020, examining the effect of probiotics in conditions applicable to individuals infected with COVID-19, including, but not limited to, other forms of coronavirus, critical illness, and mechanical ventilation. The databases search identified 1,925 unique articles, 77 full-text articles were reviewed, and 48 studies were included in this scoping review, including 31 primary studies and 17 systematic reviews. Primary studies examined a range of interventions that varied by probiotic diversity and types, including eight studies which focused on synbiotics, which include both pre- and probiotics. Several systematic reviews examined the effect of probiotics on ventilator-associated pneumonia and other infections. While most systematic reviews concluded probiotics may improve these outcomes, most systematic review authors concluded that the evidence was low in quality and high in heterogeneity. In the absence of direct evidence with COVID-19 infected patients, studies in comparable populations are currently the best resource to guide probiotics interventions in conjunction with clinical expertise and multidisciplinary healthcare planning.

Introduction

As the COVID-19 pandemic unfolds, dietitians are moving quickly to determine best methods for preventing and treating the effects of COVID-19 infection.[1] Probiotics are living microorganisms that are consumed or applied for health benefits,[2] and have been suggested as a potential intervention to improve outcomes in patients infected with COVID-19. Probiotics may be delivered with in the form of a symbiotic, which also includes prebiotics to stimulate the growth or activity of probiotic microorganisms.[2] Specific to COVID-19, probiotics have been suggested as a possible method of: addressing the "cytokine storm" and inflammation caused by COVID-19; enhancing immune function; and decreasing infections common to patients in the intensive care unit (ICU), including ventilator-associated pneumonia.[3-6] In addition, literature has described the potential relationship between gut and lung microbiota and respiratory health.[7-10]

Because of the rapid spread of COVID-19 across the globe, there has been little time for research on the efficacy of probiotics and other nutrition-related interventions on the prevention and treatment of signs and symptoms from COVID-19 infection specifically. Thus, to inform evidence-based practice, dietitians must rely on indirect evidence in addition to clinical expertise and critical thinking. For example, findings on the efficacy of probiotics in individuals with other forms of coronavirus, acute respiratory distress syndrome (ARDS), critical illness, on ventilators, or with other viral infections may inform treatment decisions for adults infected with COVID-19. Evidence scoping reviews are a tool to determine if literature is available on a topic of interest,[11] including systematic reviews (SRs)[12] and evidence-based practice guidelines.[13] Identifying and mapping relevant studies can direct dietitians to the most current, applicable research with the highest-quality study designs to inform practice.

The objective of this scoping review was to answer the research question: In adults with conditions or infections similar to COVID-19 infection, what is the availability and nature of literature describing the effect of probiotics on health outcomes?

Methods

This scoping review was conducted based on the protocol by Arksey and O'Malley[11] and later developed by Levac et al[14] and the Joanna Briggs Institute.[15] The protocol for this scoping review adheres to the PRISMA checklist for scoping reviews[16] and was registered at Open Science Framework (osf.io/2etbd).[17]

Eligibility Criteria

The research question was formulated using the Population-Concept-Context approach.[15] A full description of the eligibility criteria can be found in **Table 1**. Studies were included if they included adults with conditions that were applicable to individuals with COVID-19 infection, including but not limited to, adults with other forms of coronavirus, ARDS, critical illness, and/or on mechanical ventilation. Use of probiotics to *prevent* viral infections, such as rhinovirus or influenza, in healthy individuals were not included in this scoping review. The major concept explored was the intervention of probiotics. Interventions with synbiotics, which contain both pre- and probiotics, were included. Though the primary focus of this scoping review was to report studies targeting individuals in the ICU, the context was left open to also include free-living individuals with respiratory or viral infections similar to COVID-19. Study design was limited to primary intervention studies, systematic reviews or evidence-based practice guidelines.

Studies were limited to those published in the English language due to resource constraints and since 1999 to capture studies that may have been conducting during or following severe acute respiratory syndrome (SARS) or middle east respiratory syndrome (MERS) outbreaks.

Search Strategy

The literature was searched using MEDLINE (EBSCO), CINAHL (EBSCO), Cochrane Databases of Controlled Trials and Systematic Reviews for articles published in the English language from January 1999 until the search date of May 1, 2020. Databases were searched using terms for both population and for probiotics. Search terms for COVID-19 were adapted from the National Institute for Health and Care Excellence .[18] The search plan for the MEDLINE database can be found in **Appendix 1**.

Study Selection and Data Charting

De-duplicated studies were uploaded onto Rayyan, an online title/abstract screening program.[19] Title/abstract screening was conducted in two phases. In the first phase, one reviewer (M.R.) excluded all studies that were conducted with animals or cells or did not examine the intervention of probiotics. All remaining eligible title/abstracts were screened independently by two reviewers using *a priori* eligibility criteria (**Table 1**) (M.R. and F.W.C.) and discrepancies were settled by consensus or a third review (D.H.). All potentially included title/abstracts progressed to full text review. For each potential study, a reviewer examined eligibility criteria and extracted data on the following: study design; disease condition of target population (ex: ICU, mechanically ventilated), intervention including the number and type of probiotic strains,[20]

whether the intervention was delivered in the context of a synbiotic, and mode of delivery; comparison treatment; and outcomes reported. Eligibility and data extraction were confirmed by a second reviewer, with questions and discrepancies determined by consensus or a third reviewer. As is customary for scoping reviews, eligibility criteria were clarified during the full-text review, and the authors determined that trauma, burn and acute pancreatitis were conditions or infections not applicable to the COVID-19 population. The search and selection process was documented on a PRISMA flowchart.[21] Results were synthesized narratively and were mapped using a heat map, pie chart and bar graph.

Results

The databases and hand searches identified 1,925 unique title/abstracts. Full texts of 77 studies were reviewed, and 48 studies were included in scoping review, including 17 SRs,[22-38] 26 RCTs,[39-64] and five NRCTs (including both non-randomized controlled trials and observational studies)[65-69] **(Figure 1)**.

Overview of Included Articles

Of the 48 included articles, twenty-three articles[23-26,30,31,36,37,40,43-47,49,50,52,53,55,58,60,64,69] focused on participants who were critically ill but not mechanically ventilated, twenty articles[22,27,28,32-35,38,39,41,42,51,59,61-63,66-69] targeted adults who were critically ill and mechanically ventilated, and five[29,54,56,57,65] included individuals with various conditions, such as respiratory tract infections or influenza (**Figure 2**). All articles focused on the adult population, which may include older adults, but none of them focused exclusively on older populations.

The most commonly reported outcomes were mortality, followed by development of ventilator-associated pneumonia, new infections, length of hospital, gastrointestinal symptoms, gastrointestinal microbiota, adverse events, inflammatory markers, days on ventilator, development of pneumonia, nutrition status, organ dysfunction/failure, quality of life, and severity of symptoms of viral symptoms. Availability and nature of included studies are demonstrated on a heat map (**Figure 2**), which illustrates the distribution of outcomes assessed in the included articles according to study design and patients' condition. For example, of the nine RCTs with critically ill and mechanically ventilated patients,[28,39,41,42,49,51,59,61,62] eight of them reported development of ventilator-associated pneumonia as an outcome. [28,39,41,42,49,51,59,61]

Primary Studies Included in Scoping Review

Of the 31 primary research studies included, sample sizes ranged from 15 to 259 participants and intervention durations ranged from two to 60 days. However, intervention durations were often variable even within a study depending on how long the participant was in the ICU or on mechanical ventilation. Eight of the included primary studies examined probiotics in the context of synbiotics (pre- and probiotics combined).[59-64,67,69] The number of probiotic strains varied between studies, with 42% of studies intervening with one probiotic strain and 16% intervening with 7-10 probiotic strains (**Figure 3**). The probiotic genus most frequently utilized in interventions was lactobacillus (90.3% of interventions), followed by bifidobacterium (32.2% of interventions) and streptococcus (19.4% of interventions) (**Figure 4**); several species of these genera was included across study interventions. Interventions were delivered enterally through a feeding tube due to the critical condition of nearly all participants in included studies, except in two studies each in which probiotics were ingested orally[56,57] or applied topically.[48,49]

In four studies, authors indicated multiple routes of probiotics delivery. Patients were given probiotics orally vs through a feeding tube depending on patient condition in Kwon et al,[50] McNaught et al[53] and Forestier, et al[46] and probiotics were administered topically in the oropharynx combined with enterally in Morrow et al.[54]

Systematic Reviews/Meta-Analyses and Guidelines Included in Scoping Review

Seventeen systematic reviews and guidelines were included in this scoping review.[22-38] The authors' conclusions and certainty of evidence for systematic reviews published from 2010-2020 are shown in **Table 2**. In these systematic reviews, authors' conclusions are heterogeneous, though there were no systematic reviews describing high-quality evidence examining the effect of probiotics in the populations of interest. Most of the systematic reviews describe that probiotics decreased incidence of VAP,[26-28,34-36] though other systematic reviews that specifically focused on VAP incidence concluded no beneficial effect from probiotics.[22,29,32] Several authors describe that intervention heterogeneity[22,25,26,29,32,34,36] and/or risk of bias[24-26,29,34,36] were a concern. While most systematic reviews did include an analysis of the risk of bias of included studies, [22,24-26,28-30,33-35,37,38] few reported on the certainty of evidence for outcomes.[30,34] The systematic review conducted by the Cochrane Collaboration in 2014 described low quality evidence for the effect of probiotics on ventilator-associated pneumonia.[34] There were fewer conclusions describing the effect of probiotics on other outcomes. Authors concluded that probiotics may decrease infections but had no effect on mortality. One systematic review focused specifically on the outcome of adverse events and found no increased risk for critically ill patients administered probiotics.[30]

Discussion

This scoping review elucidated that there was considerable research, including recent systematic reviews, on the use of probiotics to treat ventilator-associated pneumonia in critically ill patients on mechanical ventilation, which may be applicable to patients infected with COVID-19. There were also systematic reviews available describing the effect of probiotics on length of hospital stay, mortality, new infections and gastrointestinal symptoms in critically ill patients who were or were not mechanically ventilated. There were no systematic reviews or primary studies included that examined the effects of probiotics in patients infected with COVID-19 or other forms of the coronavirus, and there was little evidence regarding treating other viral infections such as influenza. There were important outcomes, including quality of life and severity of symptoms from a viral infection, that were not addressed in primary studies or systematic reviews.

Application to Practitioners in the Context of COVID-19 Pandemic

Evidence-based practice depends on practitioners staying abreast of the most recent evidence and interpreting and implementing it through the lens of clinical expertise and in consideration of each individual patient. The COVID-19 pandemic has developed so rapidly that practitioners are required to analyze indirect evidence in populations that may be comparable to determine which interventions will result in the most optimal outcomes.

This scoping review demonstrated that, at present, there are no systematic reviews or primary studies examining the effect of probiotics in patients with COVID-19 or other forms of

coronavirus. Therefore, there is currently no direct evidence to demonstrate that probiotics may be effective in reducing COVID-19 symptoms for patients with mild or moderate infections who are managing care at home. There is evidence available in patients with critical illness, particularly those who are mechanically ventilated, and this body of research may be applicable to individuals infected with COVID-19 in critical care. While there was one guideline describing probiotics use in mechanically-ventilated critically ill adults,[38] this guideline was from 2003 and described insufficient evidence to make a recommendation. Thus, for practitioners to find a starting point for guidance regarding probiotic interventions for patients with COVID-19, they may need to interpret findings from systematic reviews through the lens of clinical expertise, with consideration how the COVID-19 infection specifically may modify relationships observed in critically ill patients without COVID-19. In addition, practitioners will need to consider pragmatic considerations that are typically incorporated into guideline recommendations including feasibility and acceptability to other providers on the healthcare teams[70] as well as factors specific to individuals infected with COVID-19. For example, a recent COVID-19 report on nutrition therapy by the Society of Critical Care Medicine and the American Society for Parenteral and Enteral Nutrition describe that supplemental nutrition given in discrete doses, such as probiotics, should be given once per day to cluster care.[71]

Any intervention can result in unintended consequences, and the risk-benefit ratio must be considered when determining whether to intervene with probiotics. The mechanisms of probiotics in regards to modulating the immune system to prevent and treat infections is not well understood,[72] and thus, practitioners should proceed with caution when recommending probiotics to individuals infected with COVID-19.

Research Needs

The heterogeneity in findings described between systematic reviews may be indicative of the heterogeneous populations within critical care, or due to the variation in types and doses of probiotics delivered in the interventions. Most of the included systematic reviews regarded "probiotics" as the intervention, but as demonstrated in the primary studies, probiotics can be delivered in a variety of genera, species, dosages, modes, and durations. In fourteen studies, including eight primary studies[59-64,67,69] and six systematic reviews,[32-37] authors included interventions with synbiotics, which include a prebiotic along with the probiotic to stimulate, activate, or improve survival of probiotic microorganisms.[73] While there were no clear differences in systematic review conclusions according to if the intervention was delivered in a synbiotic vs probiotic alone, this difference in included primary studies may have contributed to the heterogeneity demonstrated between the systematic reviews. Therefore, future systematic reviews should stratify narrative and quantitative results according to the types or diversity of strains in the interventions of primary studies in order to determine it using specific probiotics or a greater diversity of probiotic organisms is advantageous in improving outcomes. In addition, more research is needed on patient-centered outcomes such quality of life and severity of symptoms from viral infections.

The greater research need is to understand the efficacy and risks of utilizing probiotics in COVID-19 infected patients specifically. Currently, research trials are underway to determine the effect of probiotics in treating COVID-19 infection.[74-76] Dietitians who are working with individuals infected with COVID-19 and who are using probiotics in care are encouraged to document experiences using the Academy of Nutrition and Dietetics Health Informatics

Infrastructure (ANDHII).[77] This forum allows practitioners to contribute experiences to an evidence base for nutrition practice, with the goal of improving patient care.

Strengths and Limitations

This scoping review examined the effects of probiotics on a wide range of conditions that may be applicable to COVID-19 infected patients. However, due to the rapid development of the COVID-19 pandemic, there has been little time for published research regarding the effect of probiotics in patients infected with COVID-19. Therefore, though the evidence reported in this scoping review is a good starting place for finding applicable literature on probiotics that may apply to COVID-19 infected patients, the specific pathology and secondary complications of COVID-19 infection require that practitioners assess the potential benefits and risk for each individual patient before recommending probiotics.

Conclusion

Probiotics have been suggested as a potential method of modulating the immune system to improve outcomes, such as ventilator-associated pneumonia, in patients infected with COVID-19. There is currently no direct evidence examining the use of probiotics in improving outcomes in patients infected with COVID-19 or other similar viral infections. There have been several systematic reviews examining the effects of probiotics in individuals with critical illness with or without mechanical ventilation on patient-centered outcomes such as mortality and new infections, including ventilator-associated pneumonia. However, risk of bias in these studies and heterogeneity between studies preclude consistent conclusions between systematic reviews, and

246 practitioners should consider these limitations when determining treatment priorities for critically
247 ill patients with COVID-19.

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458 **Figures**

459 Figure 1. PRISMA Flow Diagram for Scoping Review of Literature Examining the Effects of Probiotics
460 on COVID-19 Related Outcomes

461

462 Figure 2. Heat Map Describing Interventions and Outcomes According to Study Design in a
463 Scoping Study Investigating the Effect of Probiotics in Conditions Similar to COVID-19
464 infection on Health Outcomes. Red color = highest number of studies, yellow color = number of
465 studies at around 50 percentile, green color = lowest number of studies.

466

467 Figure 3. Proportion of Primary Research Studies Included in the Scoping Review According to
468 the Number of Probiotics Strains in the Study Interventions (N=31).

469

470 Figure 4. Frequency of Probiotic Genera in Interventions of Primary Research Studies Included
471 in the Scoping Review (N=31).

472 Appendix 1. Sample search strategy from MEDLINE database for Scoping Review Examining
473 the Effect of Probiotics on COVID-19 Related Outcomes.

474

Appendix 1. Sample search strategy from MEDLINE database for Scoping Review Examining the Effect of Probiotics on COVID-19 Related Outcomes.

#	Query	Limiters/Expanders	Last Run Via
S18	S16 AND S17	Limiters - Date of Publication: 19990101-20201231 Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete
S17	S1 OR S2 OR S3	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete
S16	S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete
S15	(MH "Influenza, Human") OR (MH "Virus Diseases+") OR (MH "Viremia+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete
S14	(MH "Sepsis+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete
S13	"acute respiratory distress syndrome" OR (MH "Respiratory Distress Syndrome, Adult")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete
S12	(MH "Respiratory Tract Infections+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete

S11	(MH "Critical Illness")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete
S10	(MH "Respiration, Artificial+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete
S9	(MH "Pneumonia, Ventilator-Associated") OR (MH "Pneumonia+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete
S8	(MH "Middle East Respiratory Syndrome Coronavirus")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete
S7	(MH "SARS Virus") OR (MH "Severe Acute Respiratory Syndrome")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete
S6	coronavirus* OR coronovirus* OR coronavirinae* OR Coronavirus* OR Coronovirus* OR Wuhan* OR Hubei* OR Huanan OR "2019-nCoV" OR 2019nCoV OR nCoV2019 OR "nCoV-2019" OR "COVID-19" OR COVID19 OR "CORVID-19" OR CORVID19 OR "WN-CoV" OR WNCoV OR "HCoV-19" OR HCoV19 OR CoV OR "2019 novel*" OR Ncov OR "n-cov" OR "SARS-CoV-2" OR "SARSCoV-2" OR "SARSCoV2" OR "SARS-CoV2" OR SARSCov19 OR "SARS-Cov19"	Search modes - SmartText Searching	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete

	OR "SARSCov-19" OR "SARS-Cov-19" OR Ncovor OR Ncorona* OR Ncorono* OR NcovWuhan* OR NcovHubei* OR NcovChina* OR NcovChinese*		
S5	((corona* OR corono*) N0 (virus* OR viral* OR virinae*)) OR ((corona* OR corono*) N0 (virus* OR viral* OR virinae*))	Search modes - SmartText Searching	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete
S4	(MH "Coronavirus+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete
S3	(MH "Bifidobacterium+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete
S2	(MH "Lactobacillus+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete
S1	(MM "Probiotics") OR "probiotics"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete

Table 1. Eligibility Criteria for Scoping Review of Studies Examining the Effect of Probiotics on COVID-19 Related Outcomes

Category	**Inclusion Criteria**	**Exclusion Criteria**
Study Type	Articles published in peer-reviewed journals	Conference abstracts, grey literature such as organizational reports, government documents and white papers.
Population	Adult humans who have ● shown signs and symptoms or tested positive for viral infections related to the coronavirus (COVID-19, SARS, MERS) ● acute respiratory disease (ARDS) ● pneumonia ● or are at risk for ventilator-associated pneumonia ● respiratory tract infections ● critical illness ● planned/mechanical ventilation ● sepsis ● viral diseases, specifically influenza	Animal studies Cell/In Vitro studies Children, healthy adults, athletes, pregnant women. Individuals who do not have an infection/condition of interest. Individuals with the following conditions: HIV/AIDS, HPV, Hepatitis, Post-surgery, Trauma/ brain injury/burn, COPD, Acute Pancreatitis
Intervention	Probiotics, synbiotics	Herbal supplements
Comparison	No limits	No limits
Outcomes	Outcomes including but not limited to: Mortality Quality of life Development of COVID-19 or ventilator-associated pneumonia or other pneumonia Hospital Admission Intubation Days on Ventilator Length of hospital stay Symptom severity Nutrition Status Gastrointestinal symptoms New Infections Inflammatory markers Gastrointestinal bacteria/microbiota	Outcomes not related to COVID-19 and/or nutrition
Setting	No limits	No limits

Sample Size	No limits	No limits
Study Designs	Intervention and observational primary studies Systematic review and meta-analyses	Narrative reviews, commentary, editorials, letters to the editor
Year Range	January 1999 to May 1, 2020	Articles published before 1999 or after the search on May 1, 2020
Language	English	Non-English

ARDS= acute respiratory distress syndrome; COPD= chronic obstructive pulmonary disease; COVID-19= 2019 novel coronavirus; HIV/AIDS= human immunodeficiency virus infection/acquired immune deficiency syndrome; HPV= human papillomavirus; MERS= Middle East Respiratory Syndrome; SARS= Severe Acute Respiratory Syndrome

Table 2. Authors conclusions in systematic reviews or guidelines published from 1999-2020 examining the effect of probiotics in individuals with conditions comparable to COVID-19 infection.

Systematic Review or Guideline	**Target Population/ Context**	**Authors Conclusion**	**Grade for Certainty of Evidence**
Fan et al 2019[35]	Prevention of VAP	"Based on efficacy ranking, "B. longum + L. bulgaricus + S. thermophiles" should be the first [symbiotic] choice for prevention of VAP, while Synbiotic 2000FORTE has the potential to reduce in-hospital mortality and ICU mortality."	NR. Efficacy of interventions was ranked in network meta-analysis.
Manzanares et al 2016[36]	Critical Illness	"Probiotics show promise in reducing infections, including VAP in critical illness. Currently, clinical heterogeneity and potential publication bias reduce strong clinical recommendations and indicate further high quality clinical trials are needed to conclusively prove these benefits."	NR
Bo et al 2014[34]	Prevention of VAP	"Evidence suggests that use of probiotics is associated with a reduction in the incidence of VAP. However, the quality of the evidence is low… The available evidence is not clear regarding a decrease in ICU or hospital mortality with probiotic use… The results of this meta-analysis do not provide sufficient evidence to draw conclusions on the efficacy and safety of probiotics for the prevention of VAP in ICU patients."	Incidence of VAP: low ICU and Hospital Mortality: very low
Barraud et al 2013[33]	Critical Illness	"The present meta-analysis suggests that the administration of probiotics did not significantly reduce ICU or hospital mortality rates but did reduce the incidence of ICU-acquired pneumonia and ICU length of stay."	NR

Wang et al 2013[29]	Prevention of VAP	"Probiotic prophylaxis of [VAP] remained inconclusive and it failed to improve the prognosis of general mechanically ventilated patients. It was noteworthy that infections caused by P. aeruginosa was reduced by administration of probiotics. In further, it is recommended that advanced studies should exploit transformation in pathogenic microorganisms owing to administration of probiotics as well as the specific population."	NR
Gu et al 2012[22]	Prevention of VAP	"The limited evidence suggests that probiotics show no beneficial effect in patients who are mechanically ventilated; thus, probiotics should not be recommended for routine clinical application. However, the results of this meta-analysis should be interpreted with caution because of the heterogeneity among study designs. Future studies should focus on the safety of probiotics.	NR
Liu et al 2012[25]	Critical Illness	"The use of probiotics was associated with a statistically significant reduction in the incidence of nosocomial pneumonia in critically ill patients. However, large, well-designed, randomized, multi-center trials are needed to confirm any effects of probiotics clinical endpoints such as mortality and length of ICU and hospital stay."	NR
Petrof et al 2012[26]	Critical Illness	"Probiotics appear to reduce infectious complications including [VAP] and may influence [ICU] mortality. However, clinical and statistical heterogeneity and imprecise estimates preclude strong clinical recommendations. Further research on probiotics in the critically ill is warranted."	NR

Bailey et al 2011[32]	Prevention of VAP	"Clinical trials have failed to demonstrate a consistent beneficial effect of probiotics in mechanically ventilated patients; thus, they are not recommended for routine clinical use. However, heterogeneity among study designs may hinder this assessment and the designs should be unified in future research."	NR
Hempel et al 2011[30]	Includes Critical Illness	"There is a lack of assessment and systematic reporting of adverse events in probiotic intervention studies, and interventions are poorly documented. The available evidence in RCTs does not indicate an increased risk; however, rare adverse events are difficult to assess, and despite the substantial number of publications, the current literature is not well equipped to answer questions on the safety of probiotic interventions with confidence."	Insufficient, but critical illness not examined separately
Schultz et al 2011[27]	Prevention of VAP	"Prophylactic use of antibiotics in critically ill patients is effective in reducing the incidence of VAP. Probiotic strategies deserve consideration in future well-powered trials. Future studies are needed to determine if preventive… probiotic strategies are safe with regard to development of … probiotic infections. It should be determined whether the efficacy of probiotics improves when these agents are provided to the mouth and the intestines simultaneously."	NR
Siempos et al 2010[28]	Prevention of VAP	"Administration of probiotics is associated with lower incidence of [VAP] than control. Given the increasing antimicrobial resistance, this promising strategy deserves consideration in future studies, which should have active surveillance for probiotic-induced diseases."	NR
Jack et al 2010[23]	Critical Illness	"Evidence to support probiotic use in the management of [enteral tube feeding] diarrhea in critically ill patients remains unclear. This paper	NR

		argues that probiotics should not be administered to critically ill patients until further research has been conducted to examine the causal relationship between probiotics and mortality, irrespective of the patient's disease state or projected prophylactic benefit of probiotic administration."	
Koretz et al 2009[24]	Critical Illness	"Probiotics did not appear to influence mortality or duration of hospitalization. However, the recipients of the probiotics had fewer infectious episodes… it is not clear that probiotics are beneficial (and they may even be harmful) in the critically ill patient group."	NR
Isakow et al 2007[31]	Prevention of HAP	"There is no current clinical evidence to support the use of probiotics to … reduce HAP rates."	NR
Watkinson et al 2007[37]	Critical Illness	"The use of pre- pro- or synbiotics in adult critically ill patients confers no statistically significant benefit [for nosocomial infections, length of ICU stay, hospital mortality and specifically pneumonia]. There is currently a lack of evidence to support the use of pre- pro- or synbiotics in patients admitted to adult ICUs, and a large well-designed trial is needed in this area."	NR
Heyland et al 2003[38a]	Critical Illness, Mechanically Ventilated	"There are insufficient data to make a recommendation on the use of probiotics in critically ill patients."	NR

HPA= Hospital-Associated Pneumonia; ICU= Intensive Care Unit; NR=Not Reported; RCTs= Randomized Controlled Trials; VAP= Ventilator-Associated Pneumonia

[a] Evidence-based practice guideline

Figure 1. PRISMA Flow Diagram for Scoping Review of Literature Examining the Effects of Probiotics on COVID-19 Related Outcomes

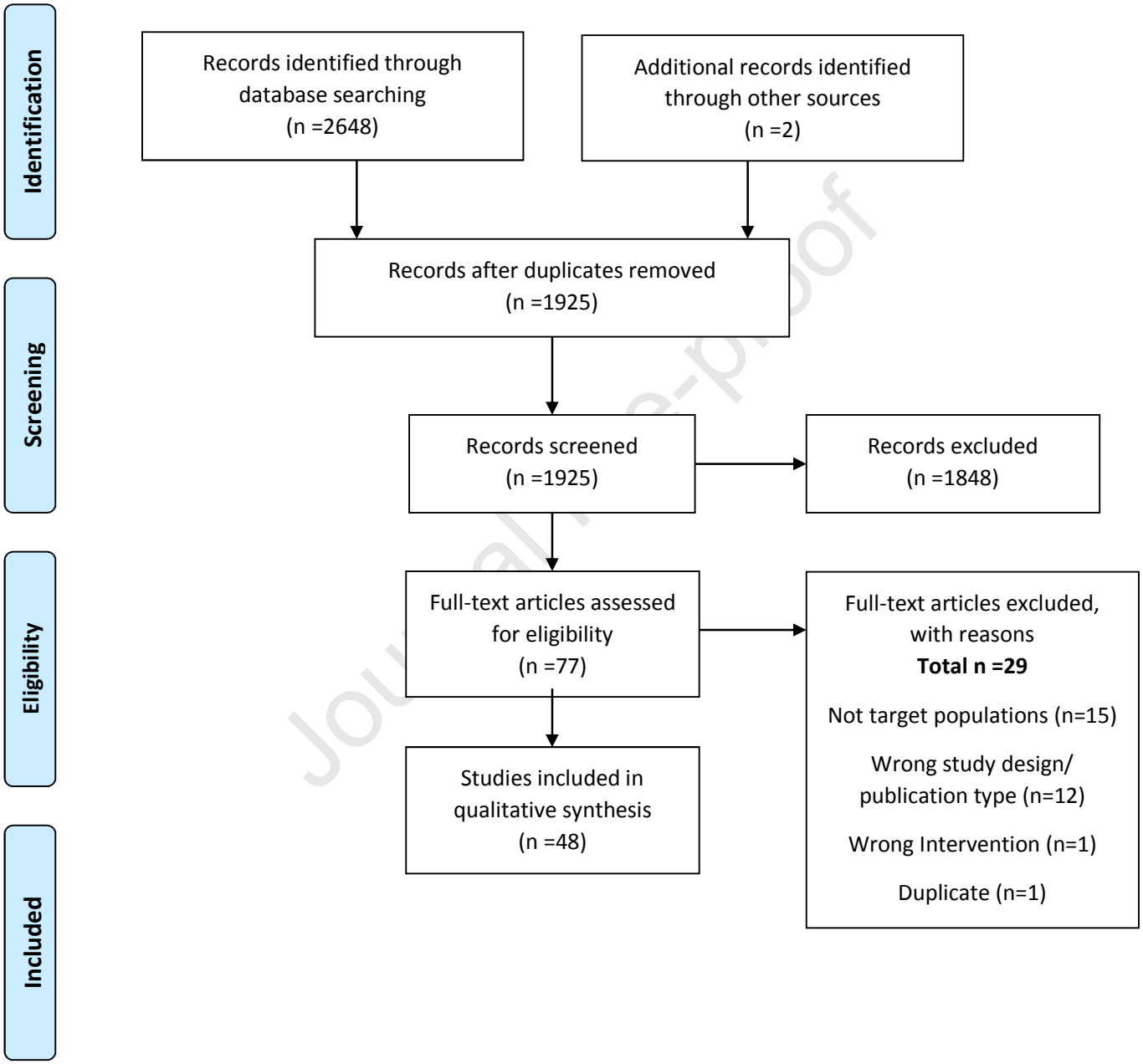

Figure 2. Heat Map Describing Interventions and Outcomes According to Study Design in a Scoping Study Investigating the Effect of Probiotics in Conditions Similar to COVID-19 infection on Health Outcomes. Green cells indicate few included studies for the indicated population, outcome and study design, with yellow, orange and red cells indicating progressively more available evidence.

		Critical illness + mechanically ventilated			**Critical illness + not mechanically ventilated**			**Others**		
	Total number of studies by RCT, NRCT, SR/M/G	RCT n=9	NRCT n=3	SR/ M/G n=8	RCT n=14	NR CT n=1	SR/ M/G n=8	RC T n=3	NR CT n=1	SR/ M/G n=1
Outcomes	Adverse events	2	1	2	2	0	4	1	0	0
	Days on ventilator	2	1	4	2	0	0	0	0	0
	Development of pneumonia	0	1	0	1	0	3	0	0	0
	Development of ventilator-associated pneumonia	8	2	7	3	0	2	1	0	1
	GI microbiota	3	1	1	6	1	0	1	1	0
	GI symptoms	4	1	2	5	1	3	2	0	0
	Inflammatory markers	2	0	0	6	1	0	0	1	0
	Length of hospital stay	7	1	3	3	0	5	0	0	1
	Mortality	7	2	5	4	0	6	0	0	1
	New infections	6	3	2	4	1	5	1	1	1
	Nutrition status	1	0	0	2	0	0	0	0	0
	Organ dysfunction/failure	1	0	0	2	0	0	0	0	0
	Quality of life	0	0	0	0	0	1	0	0	0
	Severity of symptoms of viral infection	1	0	0	0	0	0	0	0	0

RCT=Randomized controlled trial; NRCT=Non-randomized controlled study;

SR/M/G=Systematic review/Meta-analysis/Guideline

Figure 3. Proportion of Primary Research Studies Included in the Scoping Review According to the Number of Probiotics Strains in the Study Interventions (N=31).

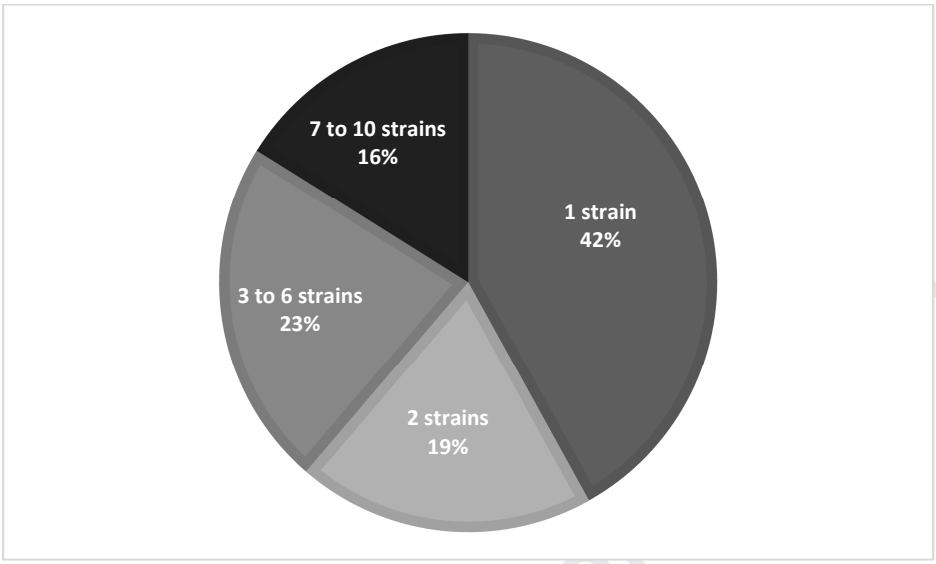

Figure 4. Frequency of Probiotic Genera in Interventions of Primary Research Studies Included in the Scoping Review (N=31).