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Interventions for reducing late-onset sepsis in neonates: an umbrella review

https://doi.org/10.1515/jpm-2022-0131
Received March 11, 2022; accepted August 17, 2022;
published online October 31, 2022

Abstract

Objectives: Neonatal sepsis is one of the leading causes of neonatal deaths in neonatal intensive care units. Hence, it is essential to review the evidence from systematic reviews on interventions for reducing late-onset sepsis (LOS) in neonates.
Methods: PubMed and the Cochrane Central were searched from inception through August 2020 without any language restriction. Cochrane reviews of randomized clinical trials (RCTs) assessing any intervention in the neonatal period and including one or more RCTs reporting LOS. Two authors independently performed screening, data extraction, assessed the quality of evidence using Cochrane Grading of Recommendations Assessment, Development and Evaluation, and assessed the quality of reviews using a measurement tool to assess of multiple systematic reviews 2 tool.
Results: A total of 101 high-quality Cochrane reviews involving 612 RCTs and 193,713 neonates, evaluating 141 interventions were included. High-quality evidence showed a reduction in any or culture-proven LOS using antibiotic lock therapy for neonates with central venous catheters (CVC). Moderate-quality evidence showed a decrease in any LOS with antibiotic prophylaxis or vancomycin prophylaxis for neonates with CVC, chlorhexidine for skin or cord care, and kangaroo care for low birth weight babies. Similarly, moderate-quality evidence showed reduced culture-proven LOS with intravenous immunoglobulin prophylaxis for preterm infants and probiotic supplementation for very low birth weight (VLBW) infants. Lastly, moderate-quality evidence showed a reduction in fungal LOS with the use of systemic antifungal prophylaxis in VLBW infants.
Conclusions: The overview summarizes the evidence from the Cochrane reviews assessing interventions for reducing LOS in neonates, and can be utilized by clinicians, researchers, policymakers, and consumers for decision-making and translating evidence into clinical practice.

Keywords: infection; late-onset sepsis; neonatal sepsis; neonate; overview; sepsis.

Introduction

Sepsis is traditionally defined as the isolation of the pathogen from sterile body fluid such as blood or cerebrospinal fluid. In adults, the consensus definition includes life-threatening organ dysfunction caused by a dysregulated response to infection [1]. However, in neonates, no such consensus definition is available [2]. Sepsis manifesting in neonates within the first 72 h of life is classified as early-onset, whereas it is considered late-onset if the manifestations appear beyond 72 h of life. Advances in obstetric care and prophylactic intrapartum antibiotics have reduced the risk of early-onset sepsis [3, 4]. However, the incidence of late-onset sepsis (LOS) has increased in parallel with the improved survival of extremely premature (gestational age <28 weeks) and very low birth weight (VLBW, birth weight <1,500 g) neonates [3, 4]. It affects 0.61–14.2 percent of hospitalized newborn infants and is inversely related to the degree of prematurity [5].

Sepsis remains the major contributor to global mortality, and the World Health Organization has declared it a global health priority [6]. Despite effective treatment strategies, including appropriate antimicrobial treatment, it remains a leading cause of neonatal death and a significant contributor to neonatal morbidities in neonatal intensive care units and the community. It is therefore imperative to identify the preventive measures that reduce the risk of sepsis in the neonatal period. Randomized clinical trials (RCTs) and their systematic reviews investigating a broad range of interventions realize the potential for interventions of interest to reduce

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the risk of neonatal sepsis. Given that several risk factors impact the risk of neonatal sepsis, there is a need to systematically examine all potentially relevant interventions that can contribute to the prevention of neonatal sepsis. To our knowledge, no published overview has compiled and summarized the evidence from systematic reviews on interventions for preventing neonatal sepsis in one coherent document. This overview will help clinicians, researchers, policymakers, funding bodies, and consumers assist decision-making and evidence translation.

Materials and methods

We conducted this systematic review as per Preferred Reporting Items for Overviews of Systematic Reviews including Harms (PRIO-harms) guideline [7] and the approach outlined in the Cochrane Handbook for Systematic Reviews of Interventions [8]. We registered the protocol for the systematic review with PROSPERO (registration number CRD42020192513), the international prospective register for systematic reviews (https://www.crd.york.ac.uk/PROSPERO).

Search strategy

We conducted a comprehensive search of the literature using appropriate pre-specified search terms within the following databases: PubMed and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception (Supplemental Information) through August 6, 2020. We did not apply language restrictions. We also read the reference lists of included systematic reviews to identify eligible studies. Finally, we searched the "related articles" feature in PubMed and hand searched in Cochrane Neonatal (https://neonatal.cochrane.org) for missing reviews.

Study selection (eligibility criteria)

Type of studies: In this overview, we included Cochrane reviews RCTs or quasi-RCTs assessing neonatal interventions. The Cochrane review must consist of one or more RCTs reporting at least one of the pre-specified outcomes of this review. We excluded non-Cochrane reviews, Cochrane reviews of non-randomized studies, and Cochrane reviews with no RCTs reporting the outcome.

Population: We included Cochrane reviews assessing interventions in term and preterm neonates. We also included reviews reporting data on mixed infant (age less than one year) populations as long as separate data was provided for neonates.

Interventions and comparisons: We considered all types of interventions following the birth of the newborn infant (delivery room interventions) or interventions in the neonatal period (neonatal interventions within 28 days from the birth) in a neonatal intensive care unit or community, compared with placebo, no treatment, or an alternative treatment. We excluded Cochrane reviews assessing non-neonatal interventions (interventions in pregnancy or before childbirth) and interventions beyond the neonatal period. However, interventions initiated in the neonatal period and continued beyond the neonatal period were also included.

Outcomes

Primary outcomes:

1. Any LOS: Clinically suspected or microbiologically confirmed LOS, as defined by the Cochrane review authors.
2. Culture-proven LOS: Microbiologically confirmed LOS, as defined by the Cochrane review authors.

Secondary outcomes:

1. Bacterial LOS: LOS caused by a bacterial organism, as defined by the Cochrane review authors.
2. Fungal LOS: LOS caused by a fungal organism, as defined by the Cochrane review authors.

We excluded Cochrane reviews evaluating early-onset sepsis as our overview focuses on neonatal interventions and not childbirth or pregnancy interventions. However, we included Cochrane reviews evaluating both early-onset and late-onset sepsis as long as reviews reporting separate data on LOS were available.

Study selection and data extraction

The author (A.R.) performed the literature search across the databases using pre-specified terms (Supplementary Information). We managed the citations retrieved through the search using Covidence. Authors, J.A. and O.A., independently performed the titles and abstracts screening, independently evaluated the full-text articles of the short-listed reports, and independently extracted the information, including review title and authors, date last assessed as up-to-date, number of trials, number of participants and their characteristics, interventions and comparisons, outcomes relevant to this overview, and quality of RCTs assessed by review authors, and summary intervention effects (relative risks (RR), odds risk or absolute risk differences and their 95% confidence intervals (CI), model used for meta-analysis) for all neonates and subgroup of neonates (preterm and term neonates).

Assessment of methodological quality of included reviews

Quality of included reviews: Two authors (J.A. and A.R.) independently assessed the methodological quality of each Cochrane systematic review using the AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews 2) instrument [9]. AMSTAR 2 evaluates the review methodology against 16 distinct domains, of which 7 are critical domains. Eleven domains on AMSTAR 2 are rated as yes or no, and five domains are rated as yes, partially yes, and no. The overall confidence in the results of the review was rated as high (no or one non-critical weakness), moderate (more than one non-critical weakness), low (one critical flaw with or without non-critical weaknesses), and critically low (more than one critical flaw with or without non-critical weaknesses).

Quality of included studies within reviews: We reported, instead of reassessing, the quality of included RCTs within reviews according to the review authors' judgment.

Quality of evidence in the included reviews: We reported the quality of evidence using the Cochrane Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach according to the review authors' judgment as high certainty, moderate certainty, low certainty, or very low certainty [10]. Two authors (J.A. and O.A.) independently assessed the evidence certainty using the Cochrane GRADE if the Cochrane review authors did not provide the assessment of the evidence certainty. Discussions and consensus with the third author (A.R.) resolved discrepancies in the review process.

Data synthesis

We summarized the results of included reviews in the summary of the findings table. We categorized the interventions into 5 categories: effective interventions (high certainty in the evidence of effectiveness), possible effective interventions (moderate certainty in the evidence of effectiveness), ineffective interventions (high certainty in the evidence of lack of effectiveness (or harm)), possible ineffective interventions (moderate certainty in the evidence of lack of effectiveness (or harm)), and no conclusions possible (low or very low certainty in the evidence) [8].

Results

The database search results and study selection log are shown in Figure 1. The search yielded 1,047 from databases and 1 article from other sources. After removing the duplicates and unrelated articles by title and abstract screening, we included 286 reviews for full-text screening. Finally, 101 Cochrane reviews were included after excluding 185 reviews [11–111]. All the 101 included Cochrane reviews were of high quality, and the detailed evaluation as per AMSTAR 2 tool is provided in Table 1 of the Supplementary Information.

Table 1 provides the details of the included reviews, including the summary assessment of the primary and secondary outcomes of the study. The subgroup and sensitivity analysis details are provided in Table 2 of the Supplementary Information. Most reviews evaluated one intervention, but few evaluated two or more interventions. Overall, 101 included reviews evaluated 141 interventions with LOS as one of the primary or secondary outcomes. Few

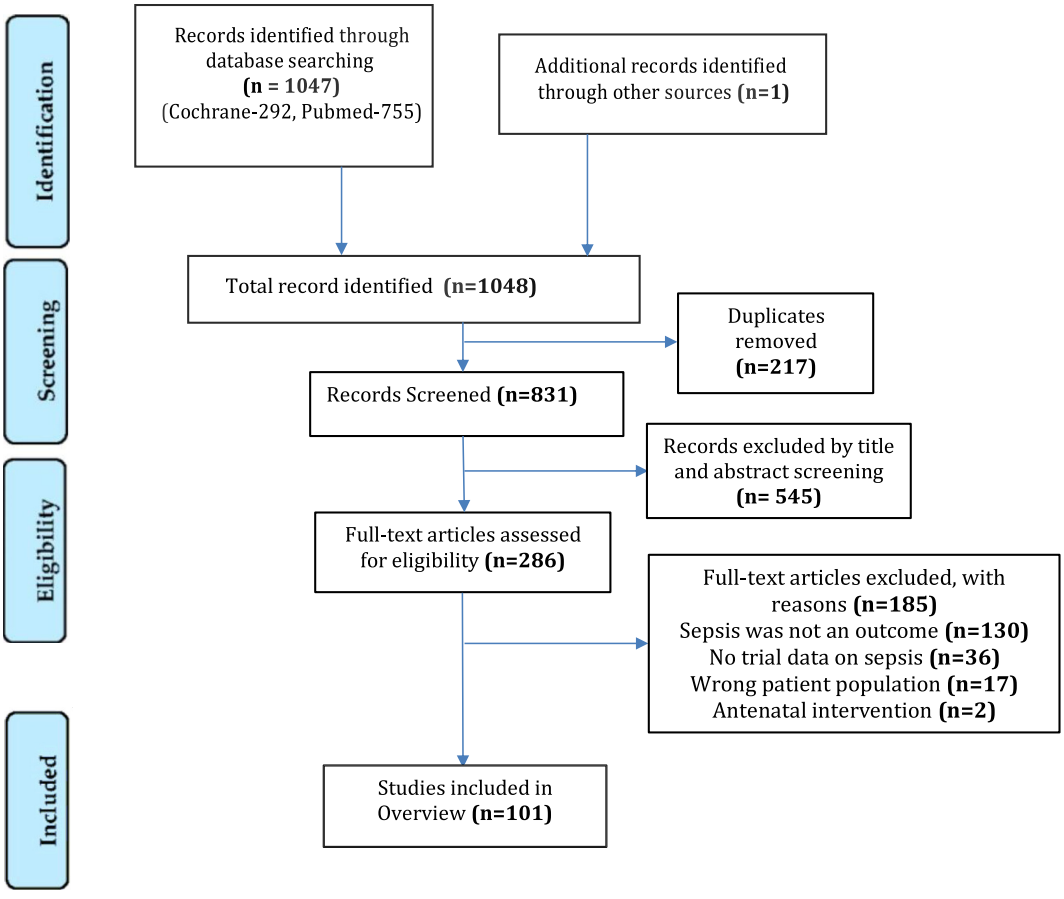

Figure 1: Study Flow diagram outlining stages of search results and filtering process.

Table 1: Summary of Cochrane reviews assessing intervention on late-onset neonatal sepsis.

Review ID	Population	Intervention	Comparison	Sepsis	No. of RCTs	No. of patients included in the RCTs	Summary of measure	Estimate (95% CI)	Certainty of evidence, GRADE
Abiramalatha 2019	<37 w	Routine monitoring of gastric residuals	No monitoring	CP	2	141	RR, fixed	1.46 [0.85, 2.52]	Low[1,3,a]
		Criteria 1 gastric residue monitoring	Criteria 2 gastric residue monitoring	CP	1	87	RR, fixed	5.35 [0.26, 108.27]	Low[1,3,a]
Aher 2020	<37 w or LBW	Late ESAs	P/NI	CP	5	551	RR, fixed	0.75 [0.52, 1.09]	Low[1,3,a]
Ainsworth 2015	Neonates requiring PN	Percutaneous CVC	Peripheral cannula	CP	6	549	RR, fixed	0.95 [0.72, 1.25]	Moderate[1,a]
Ardell 2015	<37 w	Animal derived surfactant	Protein free synthetic surfactant	Bacterial	10	5,219	RR, fixed	1.00 [0.91, 1.10]	Moderate[1,a]
Ardell 2018	<37 w	0.2 mg IV vit K	0.2 mg IM	Any	1	52	RR, fixed	1.0 [0.28, 3.58]	Low[1,3]
			0.5 mg IM	Any	1	54	RR, fixed	0.86 [0.26, 2.86]	Low[1,3]
			Any IM	Any	1	80	RR, fixed	0.92 [0.31, 2.72]	Low[1,3,a]
Austin 2015	<32 w or VLBW	Oral/topical antifungal	P/NI	Fungal	4	1800	RR, fixed	**0.20 [0.14, 0.27]**	Low[1,2,a]
			Systemic	Fungal	3	326	RR, fixed	1.89 [0.66, 5.39]	Low[1,3,a]
Bahadue 2012	RDS	Early surfactant (animal derived surfactant)	Delayed	Bacterial	1	75	RR, fixed	1.14 [0.81, 1.60]	Low[1,3,a]
Balain 2015	Neonates with CVC	Antimicrobial-impregnated CVC	Non-impregnated CVC	CP	1	86	RR, fixed	**0.11 [0.01, 0.87]**	Low[1,3,a]
Bottino 2011	<32 w or VLBW	Insulin infusion	No glucose reduction	Bacterial	1	23	RR, fixed	0.61 [0.29, 1.25]	Low[1,3,a]
			Glucose reduction	Bacterial	1	23	RR, fixed	0.46 [0.10, 2.03]	Low[1,3,a]
				Fungal	1	23	RR, fixed	0.18 [0.01, 3.47]	Low[1,3,a]
Brion 2003	<37 w	Vitamin E	P/NI	Any	4	1,009	RR, fixed	**1.52 [1.13, 2.04]**	Moderate[1,a]
			Another vitamin E	Any	1	44	RR, fixed	0.33 [0.04, 2.96]	Low[1,3,a]
Brown 2014	Neonates with severe GI disease	Glutamine	P/NI	CP	3	263	RR, fixed	1.37 [0.89, 2.11]	Moderate[3,a]
Carr 2003	Neonates requiring NICU	G-CSF or GM-CSF prophylaxis	P/NI	CP	1	75	RR, fixed	0.66 [0.36, 1.20]	Low[1,3,a]
				Any	2	284	RR, fixed	1.02 [0.76, 1.37]	Low[1,3,a]
Cleminson 2015	<32 w or VLBW	Systemic antifungal	P/NI	Fungal	10	1,371	RR, fixed	**0.43 [0.31, 0.59]**	Moderate[1,a]
			Oral/Topical	Fungal	3	326	RD, fixed	−0.03 [-0.07, 0.02]	Low[1,3,a]
Cleminson 2016	<37 w	Topical ointment or cream (sunflower seed oil, aquaphor, petroleum jelly, beiersdorf inc., bepanthen, 70% lanolin, 30% olive oil, eucerin crème)	Routine care	CP	8	2086	RR, fixed	1.13 [0.97, 1.31]	Low[1,3]
				CoNS	6	1839	RR, fixed	**1.30 [1.03, 1.65]**	Moderate[1,a]
				Other bacteria	6	1839	RR, fixed	0.84 [0.63, 1.12]	Moderate[1,a]
				Fungal	6	1839	RD, fixed	0.01 [-0.01, 0.03]	Moderate[1,a]
		Topical oil (sunflower oil, sunflower seed oil, aquaphor, coconut oil, mineral oil, soybean oil, sunflower seed oil)	Routine care	CP	6	844	RR, fixed	0.71 [0.51, 1.01]	Low[1,3]
				CoNS	5	775	RR, fixed	0.15 [0.02, 1.16]	Low[1,3,a]
				Other bacteria	5	775	RR, fixed	0.70 [0.47, 1.05]	Very low[1,2,3,a]
				Fungal	5	775	RR, fixed	1.93 [0.42, 8.78]	Very low[1,2,3,a]

Table 1: (continued)

Review ID	Population	Intervention	Comparison	Sepsis	No. of RCTs	No. of patients included in the RCTs	Summary of measure	Estimate (95% CI)	Certainty of evidence, GRADE
		Topical ointment or cream (sunflower seed oil, aquaphor)	Topical oil (sunflower seed oil, aquaphor)	CP	1	316	RR, fixed	0.91 [0.57, 1.46]	Low[1,3,a]
				Other bacteria	1	316	RR, fixed	0.90 [0.53, 1.50]	Low[1,3,a]
				Fungal	1	316	RR, fixed	1.35 [0.31, 5.94]	Low[1,3,a]
Collins 2015	<37 w	Early discharge (on gavage feeds)	Late discharge (once full suckling is established)	Any	1	88	RR, fixed	**0.35 [0.17, 0.69]**	Low[1,a]
Collins 2016	<37 w	Breast feeding, with supplements without bottle feeding	BF + supplementary feeding by bottle	Infection (any)	3	500	RR, fixed	0.70 [0.35, 1.42]	Moderate[1,4]
Conde 2016	LBW infant	Kangaroo care	Conventional care	Any (latest follow up)	8	1,463	RR, fixed	**0.50 [0.36, 0.69]**	Moderate[1]
				Any (at discharge or 40–41 w)	5	1,239	RR, fixed	**0.35 [0.22, 0.54]**	Moderate[1,a]
		Early kangaroo care	Late kangaroo care	Any	1	73	RR, fixed	0.42 [0.12, 1.49]	Low[1,3,a]
Craft 2000	Neonates <1,500 g or with CVC requiring PN	Prophylactic vancomycin	P/NI	Any	4	290	RR, fixed	**0.11 [0.05, 0.24]**	Moderate[1, a]
				CoNS	4	221	RR, fixed	**0.33 [0.19, 0.59]**	Low[1,2,a]
Darlow 2003	<37 w or <2000 g	Selenium supplementation	P/NI	Bacterial	3	583	RR, fixed	**0.73 [0.57, 0.93]**	Low[1,3,a]
Darlow 2016	<32 w or VLBW	Vitamin A	P/NI	Any	3	947	RR, fixed	0.89 [0.76, 1.04]	Low[1,3,a]
		High dose vit A	Standard dose	Any	1	80	RR, fixed	No difference b/w groups	Low[1,3,a]
		Once a week vit A	Standard dose	Any	1	80	RR, fixed	No difference b/w groups	Low[1,3,a]
De paoli 2008	<37 w requiring CPAP	Short binasal prongs	Single nasal prong	CP	1	87	RR, fixed	1.02 [0.66, 1.58]	Low[1,3,a]
				Suspected	1	87	RR, fixed	0.93 [0.60, 1.44]	Low[1,3,a]
		Infant flow driver	Medicorp prong	CP	1	100	RR, fixed	1.09 [0.53, 2.24]	Low[1,3,a]
Doyle 2017 (early PNCS)	Preterm at risk of BPD	Early corticosteroids (dexamethasone and hydrocortisone)	P/NI	Infection (LOS, any)	25	4,101	RR, fixed	1.05 [0.96, 1.15]	Moderate[1,a]
Doyle 2017 (late PNCS)	Preterm at risk of BPD	Late corticosteroids (dexamethasone or hydrocortisone)	P/NI	Infection (LOS, any)	18	1,349	RR, fixed	1.14 [0.97, 1.34]	High
Fenton 2020	LBW	High protein intake (>3 g/kg)	Low (<3 g/kg)	CP	1	30	RR, fixed	0.44 [0.04, 4.32]	Low[1,3,a]
Flenady 2003	Neonates	Radiant warmers	Incubators	Any	2	90	RR, fixed	0.93 [0.66, 1.30]	Low[1,3,a]
				CP	1	60	RR, fixed	0.6 [0.16, 2.29]	Low[1,3, a]
Foster 2015	Neonates with IV	IV filter	P/NI	CP	2	530	RR, fixed	0.86 [0.59, 1.27]	Moderate[1]
Foster 2017	Term or preterm	Routine oro-or-nasopharyngeal suction at birth	No	Infection (LOS (<7 days), any)	1	509	RR, fixed	0.76 [0.42, 1.36]	Low[1]

Table 1: (continued)

Review ID	Population	Intervention	Comparison	Sepsis	No. of RCTs	No. of patients included in the RCTs	Summary of measure	Estimate (95% CI)	Certainty of evidence, GRADE
Gordon 2017	Neonates with UVC	Early planned UVC removal	Later planned UVC removal	CP	1	210	RR, fixed	0.65 [0.35, 1.22]	Low[1,3]
				CoNS	1	210	RR, fixed	0.49 [0.19, 1.26]	Low[1,3]
				Other bacteria	1	210	RR, fixed	0.61 [0.21, 1.81]	Low[1,3]
				Fungi	1	210	RR, fixed	1.96 [0.18, 21.31]	Low[1,3]
Gray 2011	<37 w	Cot-nursing	Incubator	Any	2	108	RR, fixed	0.27 [0.01, 6.41]	Low[1,3]
Howlett 2019	<37 w or LBW	Inositol (IV followed by PO)	P/NI	Bacterial	2	701	RR, fixed	1.33 [1.00, 1.75]	High
		Inositol (repeat dose)	P/NI	Bacterial	4	1,067	RR, fixed	1.21 [0.95, 1.54]	Moderate[3]
		Inositol (single dose)	P/NI	Bacterial	1	74	RR, fixed	1.46 [0.71, 2.97]	Moderate[3,a]
Ibrahim 2011	<37 w (primary treatment for hypotension)	Steroids	P/NI	Bacterial	1	18	RR, fixed	0.33 [0.09, 1.23]	Moderate[3,a]
			Other drug (e.g. inotrope)	Bacterial	1	40	RR, fixed	0.60 [0.20, 1.82]	Low[1,3,a]
	<37 w (treatment for refractory hypotension)	Steroids	P/NI	Bacterial	2	65	RR, fixed	1.09 [0.29, 4.10]	Low[1,3,a]
Imdad 2013	Neonates	Antiseptics (chlorhexidine)	Antiseptics (salicylic acid powder)	Any	1	213	RR, random	1.11 [0.07, 17.50]	Low[1,3,a]
Inglis 2005 (antibiotics for UVC	Neonates with UVC	Any prophylactic antibiotic	P/NI	Any	1	29	N/A	N/A (no difference between groups/no events)	Low[1,3,a]
Inglis 2007 (antibiotics for UAC)	Neonates with UAC	Any prophylactic antibiotic	P/NI	Any	2	212	N/A	Not done (one trial reported no significant difference whereas another trial reported significant difference between groups)	Low[1,3,a]
Inglis 2007 (antibiotics for ventilated neonates)	Ventilated neonates	Antibiotic	P/NI	Any	2	N/A	N/A	Meta-analysis for sepsis is N/A (one trial reported no difference in LOS)	Low[1,3,a]
Jacobs 2013	>35 w	Therapeutic hypothermia	P/NI	CP	8	1,222	RR, fixed	0.87 [0.60, 1.26]	Moderate[1,a]
Jardine 2008	Neonates with CVC	Antibiotics (vancomycin, amoxicillin)	P/NI	Bacterial	2	201	RR, fixed	**0.38 [0.18, 0.82]**	Moderate[1,a]
				Any	2	201	RR, fixed	**0.40 [0.20, 0.78]**	Moderate[1,a]
Kabra 2005	Neonates with UVC	ML-UVCs	SL-UVCs	Suspected	2	56	RR, fixed	0.89 [0.29, 2.78]	Low[1,3,a]
Kapoor 2019 (lipid for term and late preterm)	>37 w with surgical problems	Fish oil LE	Non-fish oil LE	CP	2	51	RR, fixed	1.05 [0.47, 2.34]	Very low[1,3]
				Any	3	93	RR, fixed	1.04 [0.53, 2.02]	Low[1,3,a]
	>37 w cholestasis	Fish oil LE	Non-fish oil LE	Any	2	40	RR, fixed	1.21 [0.50, 2.92]	Very low[1,3]

Table 1: (continued)

Review ID	Population	Intervention	Comparison	Sepsis	No. of RCTs	No. of patients included in the RCTs	Summary of measure	Estimate (95% CI)	Certainty of evidence, GRADE
Kapoor 2019 (lipid for preterm)	<37 w	Fish oil LE	Non-fish oil LE	CP	7	774	RR, fixed	1.16 [0.91, 1.48]	Low[1,3]
			Another fish oil LE	Any	1	55	RR, fixed	1.69 [0.56, 5.11]	Low[1,3]
		Alternative LE	Another alternative-LE	Any	1	59	RR, fixed	1.93 [0.65, 5.73]	Low[1,3]
		Alternative LE	Soybean LE	CP	2	164	RR, fixed	1.22 [0.54, 2.78]	Low[1,3]
Kelly 2017	Asymptomatic newborns with MSAF	Antibiotics	P/NI	CP	1	250	RD, fixed	−0.01 [-0.07, 0.04]	Low[1,3]
				Suspected	1	250	RD, fixed	−0.03 [-0.10, 0.05]	Low[1,3]
	Symptomatic newborns with MSAF	Antibiotics	P/NI	CP	3	445	RD, fixed	0.00 [-0.02, 0.03]	Low[1,3]
Kuti 2021	Pregnant women, mothers, other caregivers, and HCWs	2% chlorhexidine gluconate	Alcohol hand sanitizer	CP	1	2,932	RR, fixed	2.26 [1.73, 2.93]	Very low[1,3]
				Any	1	2,932	RR, fixed	2.19 [1.79, 2.69]	Very low[1,3]
		4% chlorhexidine gluconate	Triclosan 1%	Any	1	1916	RR, fixed	6.01 [3.56, 10.14]	Low[1,3,a]
Lai 2016 (antimicrobial dressing for CVC)	Neonates with CVC	Chlorhexidine dressing	Polyurethane dressing	CP	1	655	RR, fixed	1.18 [0.53, 2.65]	Moderate[3]
				Suspected	1	705	RR, fixed	1.06 [0.75, 1.52]	Moderate[3]
Lai 2016 (co bedding)	<37 w, twins	Co-bedding	P/NI	Any	2	59	RR, fixed	0.45 [0.07, 2.86]	Very low[1,3,a]
				CP	3	65	RR, fixed	0.84 [0.30, 2.31]	Very low[1,3]
Lassi 2019	Neonates	Maternal and neonates care education	P/NI	Infection, including sepsis (any)	2	42,043	RR, random	0.88 [0.72, 1.08]	Moderate[1,a]
Lemyre 2016	<37 w	NIPPV for RDS	NCPAP for RDS	Any	2	136	RR, fixed	0.78 [0.36, 1.70]	Moderate[1]
Malviya 2013	<37 w or LBW with symptomatic PDA	Surgical ligation	Medical treatment	Any	1	154	RR, fixed	1.14 [0.62, 2.09]	Low[1,3,a]
McCall 2018	<37 w or LBW	Plastic wrap or bag	Routine care	Bacterial	2	830	RR, fixed	0.88 [0.70, 1.10]	Low[1,3,a]
		Thermal mattress	Routine care	Bacterial	1	102	RR, fixed	0.92 [0.48, 1.79]	Low[1,3,a]
McMullan 2018	Neonates undergoing CVC removal	Cephazolin	P/NI	CP	1	88	RR, fixed	0.09 [0.01, 1.60]	Low[1,3]
				Suspected	1	88	RR, fixed	0.33 [0.01, 7.97]	Low[1,3]
Meyer 2018	<37 w	Respiratory support before cord clamping	P/N	CP	1	150	RR, fixed	1.67 [0.41, 6.73]	Low[1,3,a]
Moe-Byrne 2016	<37 w	Glutamine	P/NI	CP	11	2,815	RR, fixed	0.94 [0.86, 1.04]	Moderate[2,4]
Moon K 2020	>34 w	Early PN	Late PN	CP	1	209	RR, fixed	0.22 [0.05, 1.01]	Low[1,3]
				Any	1	209	RR, fixed	**0.53 [0.32, 0.89]**	Low[1,3]
Morgan 2013	VLBW or <32 w	Early trophic feeding	No trophic feeds	CP	3	237	RR, fixed	1.06 [0.72, 1.56]	Low[1,3,a]
Morgan 2014	VLBW or <32 w	Delayed feeds (4/> days after birth)	Early feeds	CP	2	457	RR, fixed	1.27 [0.95, 1.70]	Low[1,3,a]
Muelbert 2019	<37 w	Smell and taste of milk	P/NI	CP	1	51	RR, fixed	2.46 [0.27, 22.13]	Low[1,3]
Nasuf 2018	<37 w	OPC	P/NI	CP	6	335	RR, fixed	0.86 [0.56, 1.33]	Very low[1,3]

Table 1: (continued)

Review ID	Population	Intervention	Comparison	Sepsis	No. of RCTs	No. of patients included in the RCTs	Summary of measure	Estimate (95% CI)	Certainty of evidence, GRADE
Ng 2016	<37 w at risk of CLD	Salbutamol	P/NI	CP	1	173	RR, fixed	1.06 [0.54, 2.06]	Low[1,3,a]
Ng 2017	<37 w	Cromolyn sodium	P/NI	Any	2	64	RR, fixed	0.82 [0.41, 1.63]	Low[1,3,a]
Ng 2019	<37 w	Hydrolyzed formula	Standard formula	CP	1	60	RR, fixed	1.50 [0.27, 8.34]	Low[1,3,a]
Oddie 2017	<32 w or VLBW	Slow feeding advancement	Faster feed advancement	CP	8	3,392	RR, fixed	**1.15 [1.00, 1.32]**	Low[1,3]
Ohlsson 2020 (ibuprofen for prevention of PDA)	<37 w and LBW EOS	Ibuprofen	P/NI	Bacterial	2	201	RR, fixed	**2.70 [1.10, 6.59]**	Low[1,3,a]
Ohlsson 2020 (ibuprofen for treatment of PDA)	<37 w or LBW	Ibuprofen	Indomethacin	Bacterial	7	735	RR, fixed	1.22 [0.84, 1.76]	Low[1,3,a]
		Ibuprofen, PO	Indomethacin, IV/PO	Bacterial	2	53	RD, fixed	0.03 [-0.22, 0.28]	Low[1,3,a]
		Ibuprofen, PO	Ibuprofen, IV	Bacterial	3	236	RR, fixed	0.82 [0.54, 1.25]	Low[1,3,a]
		High dose ibuprofen	Standard dose ibuprofen	Bacterial	1	70	RR, fixed	0.93 [0.51, 1.68]	Low[1,3,a]
		Early ibuprofen	Expectant	Bacterial	1	105	RR, fixed	0.90 [0.58, 1.41]	Moderate[3,a]
Ohlsson 2020 (IVIG for prevention of infection)	Preterm and LBW	IVIG	P/NI	CP	10	3,975	RR, fixed	**0.85 [0.74, 0.98]**	Moderate[2]
				CP 'serious infection'	16	4,986	RR, fixed	**0.82 [0.74, 0.92]**	Moderate[2]
Ohlsson 2020 (paracetamol for PDA)	PDA <37 w or LBW	Paracetamol	Ibuprofen	Bacterial	4	472	RR, fixed	0.88 [0.64, 1.21]	Low[1,3,a]
			P/NI	Bacterial	1	48	RR, fixed	1.45 [0.36, 5.79]	Moderate[3,a]
			Indomethacin	Bacterial	2	277	RR, fixed	1.14 [0.59, 2.19]	Low[1,3,a]
Ohlsson 2020 (early EPO)	<37 w and/or LBW	Erythropoietin	P/NI	CP	12	2,180	RR, fixed	0.87 [0.74, 1.02]	Moderate[1,a]
		Darbepoetin alfa	P/NI	CP	1	62	RR, fixed	1.13 [0.38, 3.30]	Low[1,3,a]
Onland 2017 (late inhaled steroid for prevention of BPD)	<36 w	Inhaled corticosteroids (budesonide, fluticasone, beclomethasone)	P/NI	Any	5	107	RR, fixed	0.90 [0.50, 1.64]	Low[1,3,a]
Onland 2017 (systemic steroid for prevention of BPD)	Preterm at risk of BPD	Lower cumulative dexamethasone dose	Higher cumulative dexamethasone dose	CP	6	230	RR, fixed	0.91 [0.60, 1.38]	Low[1,3,a]
				Suspected	2	72	RR, fixed	1.03 [0.62, 1.70]	Low[1,3,a]
Osborn 2007	<37 w	Thyroid hormone therapy	P/NI	Any	3	278	RR, fixed	0.78 [0.53, 1.16]	Moderate[3,a]
Osborn 2018	Neonates requiring PN	High amino acid	Low	Bacterial	15	1,255	RR, fixed	0.96 [0.79, 1.18]	Low[1,4,a]
		High amino acid (at the start)	Low	Bacterial	5	319	RR, fixed	0.94 [0.65, 1.38]	Low[1,3,a]
		High amino acid (at max dose)	Low	Bacterial	1	127	RR, fixed	0.94 [0.63, 1.41]	Moderate[3,a]
Pammi 2020	<37 w	Lactoferrin	P/NI	Any	12	5,425	RR, fixed	**0.80 [0.72, 0.89]**	Low[1,4]
				CP	12	5,425	RR, fixed	**0.83 [0.72, 0.94]**	Low[1,2]
				Bacterial	8	3,565	RR, fixed	**0.86 [0.74, 1.00]**	Low[1,2]
				Fungal	6	3,266	RR, fixed	**0.23 [0.10, 0.54]**	Low[1,2]
		Lactoferrin + probiotics		Any	3	564	RR, fixed	**0.25 [0.14, 0.46]**	Low[1,3]

Table 1: (continued)

Review ID	Population	Intervention	Comparison	Sepsis	No. of RCTs	No. of patients included in the RCTs	Summary of measure	Estimate (95% CI)	Certainty of evidence, GRADE
				Bacterial	1	319	RR, fixed	**0.28 [0.11, 0.72]**	Low[1,3]
				Fungal	2	494	RR, fixed	**0.24 [0.08, 0.71]**	Low[1,3]
Pfister 2009	<37 w or LBW	Protein with surfactant	Protein-free surfactant	CP	1	1,036	RR, fixed	1.00 [0.87, 1.14]	Moderate[1,a]
Premkumar 2019	<37 w	Human milk fortifier	Bovine milk fortifier	CP	1	125	RR, fixed	0.54 [0.25, 1.21]	Low[1,3]
Quigley 2019	<37 w or LBW	Formula	Donor human milk	CP	5	1,025	RR, fixed	0.94 [0.79, 1.12]	Moderate[1,a]
Rojas-Reyes 2012	<32 w	Prophylactic surfactant	Rescue surfactant	Bacterial	6	2,438	RR, fixed	0.83 [0.64, 1.08]	Low[1,2,a]
Schulzke 2014 (pentoxifylline for BPD)	<32 w or VLBW	Nebulized pentoxifylline	P/NI	CP	1	100	RR, fixed	1.22 [0.63, 2.36]	Low[1,3,a]
Schulzke 2014 (physical activity for bone mineralization)	<37 w	Physical activity	P/NI	CP	1	16	N/A	The trial reported no difference in sepsis between the groups	Low[1,3,a]
Seger 2009	<37 w	Animal surfactant	P/NI	Any	4	1,012	RR, fixed	1.14 [0.87, 1.48]	Moderate[1,a]
Shah 2008	Term or preterm requiring CVC	Heparin infusion	P/NI	Any	3	477	RR, fixed	0.82 [0.43, 1.57]	High[a]
Shah 2009	<32 w or VLBW	Anti-staphylococcal immunoglobulin INH A-21	P/NI	CoNS	2	2,488	RR, fixed	1.07 [0.94, 1.22]	Moderate[1,a]
				Other bacterial	2	2,488	RR, fixed	0.87 [0.72, 1.06]	Moderate[1,a]
				Any	2	2,488	RR, fixed	1.00 [0.91, 1.09]	Moderate[1,a]
		Anti-staphylococcal immunoglobulin altastaph	P/NI	CoNS	1	206	RR, fixed	0.86 [0.32, 2.28]	Moderate[3,a]
				Other bacterial	1	206	RR, fixed	0.93 [0.53, 1.64]	Moderate[3,a]
				Any	1	206	RR, fixed	0.93 [0.54, 1.62]	Moderate[3,a]
Shah 2017 (prevention of BPD)	VLBW neonates	Early inhaled steroids	P/NI	CP	6	1,121	RD, fixed	1.17 [0.99, 1.38]	Moderate[1,a]
Shah 2017 (prevention of BPD)	VLBW or <32 w	Inhaled steroid	Systemic corticosteroids	Any	1	278	RR, fixed	1.04 [0.73, 1.49]	Low[1,3,a]
Shah 2017 (treatment of BPD)	VLBW or <32 w	Inhaled steroid	Systemic corticosteroids	CP	2	368	RR, fixed	1.07 [0.79, 1.45]	Low[1,3,a]
Shah 2018	Neonates requiring RBC transfusion	Short transfusion	Longer transfusion	Suspected	1	52	RR, random	**1.25 [1.00, 1.56]**	Low[1,3,a]
Sharif 2020	<32 w	Probiotics	P/NI	CP	47	9,762	RR, fixed	**0.89 [0.82, 0.97]**	Moderate[1]
Sinclair 2011	<32 w or VLBW	Early parenteral lipid	Delayed	CP	1	29	RR, fixed	0.81 [0.13, 5.01]	Low[1,3,a]
		Insulin infusion for hyperglycemia	Standard care	CP	1	386	RR, fixed	0.92 [0.63, 1.34]	Low[1,3,a]

Table 1: (continued)

Review ID	Population	Intervention	Comparison	Sepsis	No. of RCTs	No. of patients included in the RCTs	Summary of measure	Estimate (95% CI)	Certainty of evidence, GRADE
Singh 2015	<32 w	Bovine lung lavage surfactant extract (prophylaxis)	Modified bovine minced lung surfactant extract	Bacterial	2	1,123	RR, fixed	1.08 [0.91, 1.28]	Moderate[1,a]
	<37 w	Bovine lung lavage surfactant extract (rescue)	Modified bovine minced lung surfactant extract	Bacterial	6	2,228	RR, fixed	1.00 [0.87, 1.15]	Moderate[1,a]
		Modified bovine minced lung (rescue)	Porcine minced lung	Bacterial	6	526	RR, fixed	1.13 [0.87, 1.46]	Low[1,3,a]
Sinha 2015	Term or late preterm	Chlorhexidine for skin or cord care, in hospital	P/NI	Any	2	13,033	RR, fixed	0.98 [0.82, 1.16]	Moderate[1,a]
		Chlorhexidine for skin or cord care in the community	P/NI	Any	1	203	RR, fixed	**0.69 [0.49, 0.95]**	Moderate[3,a]
Soll 1997	<30 w	Animal surfactant	P/NI	CP	4	914	RR, fixed	1.06 [0.81, 1.38]	Low[1,2,a]
Soll 2009	<30 w <1,250 g with RDS or at risk	Multiple doses of surfactant (synthetic surfactant, curosurf)	Single dose	Bacterial	2	1,169	RR, fixed	0.85 [0.70, 1.04]	Moderate[1,a]
Spence 1999	Neonates who required endotracheal intubation	Nasal intubation	Oral	CP	1	86	RR, fixed	1.0 [0.15, 6.78]	Low[1,3,a]
				Suspected	1	91	RR, fixed	2.1 [0.89, 4.91]	Low[1,3,a]
Subramaniam 2016	<32 w or VLBW	Prophylactic CPAP	Supportive care	Any	3	568	RR, fixed	1.04 [0.64, 1.69]	Moderate[1, a]
			Assisted ventilation	Any	1	425	RR, random	0.59 [0.33, 1.04]	Low[1,3,a]
Symington 2006	<37 w	NIDCAP	P/NI	Any	1	21	RR, fixed	0.92 [0.71, 1.18]	Low[1,3,a]
Taylor 2015	Neonates with CVC	Antibiotic lock	P/NI	CP	3	271	RR, fixed	**0.15 [0.06, 0.40]**	High
				Any	3	271	RR, fixed	**0.25 [0.12, 0.49]**	High
Ullman 2013	Neonate with any IV/arterial catheter	Less frequent for intravenous administration set replacement	Frequent	CP	1	148	RR, fixed	0.58 [0.25, 1.35]	Low[1,3,a]
Ungerer 2004	Term born to mothers with risk of infection (GBS)	Prophylactic antibiotic (intramuscular penicillin G)	Selective antibiotics use	CP	1	67	RD, fixed	0.00 [-0.06, 0.06]	Low[1,3,a]
	Term with other risk factors, PROM, fever)	Prophylactic antibiotics (intramuscular penicillin and kanamycin)	Selective antibiotics use	CP	1	49	RR, fixed	0.12 [0.01, 2.04]	Low[1,3,a]
Walsh 2019	<37 w	Iodine supplementation	P/NI	Any	1	1,259	RR, fixed	1.09 [0.96, 1.24]	High[a]
Webster 2003	Visitors	Over gowns	No gowns	Any	4	3,979	RR, random	0.95 [0.40, 2.23]	Low[1,2,a]
Whitelaw 2001	Infants <3 months with severe IVH	Acetazolamide + furosemide	Standard therapy	CNS infection	1	117	RR, fixed	1.20 [0.57, 2.52]	Low[1,3,a]
Whitelaw 2017	Infants with IVH	Repeated lumbar/Ventricular tapping	Conservative	CNS infection	2	195	RR, fixed	1.73 [0.53, 5.67]	Low[1,3]

Table 1: (continued)

Review ID	Population	Intervention	Comparison	Sepsis	No. of RCTs	No. of patients included in the RCTs	Summary of measure	Estimate (95% CI)	Certainty of evidence, GRADE
Wilkinson 2016	<37 w	HFNC	CPAP (primary respiratory support after birth)	CP	4	439	RR, fixed	1.29 [0.66, 2.54]	Low[1,3,a]
			CPAP (post-extubation)	CP	2	529	RR, fixed	0.92 [0.59, 1.43]	Low[1,3,a]
			NIPPV (primary respiratory support after birth)	CP	1	76	RR, fixed	1.33 [0.32, 5.56]	Low[1,3,a]
Zupan 2004	Neonates	Topical cord antiseptics	P/NI	Any	7	N/A	RR, fixed	No meta-analysis was conducted; No sepsis was noted in either arm in all the trials	Low[1,a]

[a]Cochrane reviews, where evidence's certainty was unavailable, were evaluated by two independent authors based on Grading of Recommendations, Assessment, Development and Evaluation (1, Risk of bias; 2, heterogeneity, 3, imprecision/wide confidence interval; 4, publication bias (asymmetry in funnel plot)/other reasons; 5, indirectness), with conflicts resolved by consensus and discussion with the third author; The effect estimates highlighted in bold represent statistically significant differences between the groups; BPD, bronchopulmonary dysplasia; CC, catheter colonization; CLD, chronic lung disease; CoNS, coagulase-negative staphylococcus; CP, culture-proven; CPAP, continuous positive airway pressure; CVC, central venous catheter; DBM, donor breast milk; ESAs, erythropoiesis-stimulating agents; GBS, group B *streptococcus*; G-CSF, granulocyte colony stimulating factor; GI, gastrointestinal; GM-CSF, granulocyte-macrophage colony stimulating factor; GRADE, grading of recommendations,assessment development and evaluation; HFNC, high flow nasal cannula; IVH, intraventricular hemorrhage; IVIG, intravenous immunoglobulin; IV, intravenous infusions; LBW, low birth weight; LE, lipid emulsion; ML-UVCs, multiple lumen umbilical venous catheters; MSAF, meconium-stained amniotic fluid; N/A: not available; NCPAP, nasal continuous positive airway pressure; NICU, neonatal intensive care unit; NIDCAP, neonates individualized developmental care and assessment program; NIPPV, nasal intermittent positive pressure ventilation; OPC, oropharyngeal colostrum; PCVC, percutaneous central venous catheters; PDA, patent ductus arteriosus; PO, per oral; PN, parenteral nutrition; P/NI: placebo/no intervention; PNCS, postnatal corticosteroids; PSBI, possible serious bacterial infection; RBCs, red blood cells; RDS, respiratory distress syndrome; RCTs, randomised clinical trials; RR, risk ratio; RD, risk difference; SL-UVCs, single lumen umbilical venous catheters; UAC, umbilical artery catheters; UVC, umbilical venous catheters; VLBW, very low birth weight.

reviews assessed various types of LOS (any, bacterial or fungal), and the majority of them evaluated LOS as culture-positive sepsis (n=65), followed by any sepsis (n=55), bacterial sepsis (n=34), and fungal sepsis (n=10).

The number of RCTs in 101 reviews ranged from one to 47. The number of neonatal participants in each trial ranged from 16 to 42,043. In total, there were 612 RCTs involving 193,713 term and preterm neonates. Of the 101 included reviews, 28 provided GRADE assessments for one or more LOS outcomes. For the remainder of the reviews (n=73), two study authors performed the GRADE assessment independently for all the primary and secondary outcomes. The details are provided in Table 1. The interventions on LOS were categorized into five categories based on the effectiveness and certainty of the evidence, as summarized in Table 2.

Effective interventions

High-quality evidence showed reduced LOS (any sepsis, RR (95% CI) 0.15 (0.06, 0.40) [103] or culture-proven sepsis, RR (95% CI) 0.25 (0.12, 0.49)) [103] when antibiotic lock therapy, compared with placebo, was used for neonates with central venous catheters (CVC). We found no high-quality, effective intervention for reducing bacterial or fungal sepsis.

Possible effective interventions

Any sepsis

Moderate-quality evidence showed antibiotic prophylaxis for neonates with CVC (RR (95% CI) 0.38 (0.18, 0.82)) [47], vancomycin prophylaxis for neonates requiring parenteral nutrition or neonates with CVC (RR (95% CI) 0.11 (0.05, 0.24)) [28], chlorhexidine for skin or cord care (RR (95% CI) 0.69 (0.49, 0.95) [97], and kangaroo care for low birth weight babies (RR (95% CI) 0.50 (0.36, 0.69)) [27] reduced any LOS.

Culture-proven sepsis

Moderate-quality evidence showed intravenous immunoglobulin prophylaxis (RR (95% CI) 0.85 (0.74, 0.98)) [72] for preterm infants and probiotic supplementation for VLBW infants (RR (95% CI) 0.89 (0.82, 0.97) [94]) reduced culture-proven sepsis.

Bacterial sepsis

Moderate-quality evidence showed antibiotic prophylaxis for neonates with CVC (RR (95% CI) 0.40 (0.20, 0.78)) [47] reduced bacterial LOS.

Fungal sepsis

Moderate-quality evidence showed systemic antifungal prophylaxis VLBW infants (RR (95% CI) 0.43 (0.31, 0.59)) [23] reduced fungal LOS.

Ineffective interventions

High-quality evidence showed no difference in LOS with use of late postnatal corticosteroids for bronchopulmonary dysplasia prevention (RR (95% CI) 1.14 (0.97, 1.34)) [32], heparin infusion for neonates with CVC (RR (95% CI) 0.82 (0.43, 1.57)) [90], iodine supplementation (RR (95% CI) 1.09 (0.96, 1.24)) [106], and inositol supplementation (RR (95% CI) 1.33 (1.00, 1.75)) [40].

Possible ineffective interventions and no conclusions possible

Many interventions where the evidence certainty was moderate-quality with lack of effectiveness (or harm) and where the evidence certainty was low-to very low-quality were categorized in these groups as listed in Table 2.

Discussion

Summary of main results

This overview included 101 high-quality Cochrane reviews involving 612 RCTs and 193,713 neonates that evaluated 141 interventions.

Overall completeness and applicability of evidence

Only 101 reviews (around 20% of 496 reviews in the Cochrane Neonatal) were eligible for inclusion in the overview. Although there were 101 reviews involving 612 RCTs and 193,713 neonates, the body of evidence was reduced as not all the included reviews reported the primary outcome of interest of the overview. Further, the data on secondary outcomes was limited as only one-third of reviews reported bacterial sepsis, and 10% reported fungal sepsis. All reviews explicitly defined various types of LOS; however, there was some variation in the definition between and within the trials included in the reviews.

Table 2: Summary of effectiveness of interventions on late-onset neonatal sepsis.

	LOS, any (suspected or confirmed)	LOS, culture-proven	LOS, bacterial	LOS, fungal
Effective interventions	– Antibiotic lock for CVC	– Antibiotic lock for CVC	– None	– None
Possible effective interventions	– Kangaroo care for LBW babies – Vancomycin prophylaxis for VLBW babies requiring PN or babies with CVC requiring PN – Antibiotic prophylaxis for neonates with CVC – Chlorhexidine for skin or cord care (in community setting)a	– IVIG prophylaxis (<37 w or LBW) – Probiotics supplementation (<32 w)	– Antibiotic prophylaxis for neonates with CVC	– Systemic antifungal prophylaxis
Ineffective interventions	– Late postnatal corticosteroids for BPD prevention – Heparin infusion for CVC – Iodine supplementation (<37 w)	– None	– Inositol supplementation (>1 dose) (<37 w)	– None
Possible ineffective interventions	– Vitamin E supplementation – Supplemental feeds with bottle vs. not (<37 w) – Early postnatal corticosteroids for BPD prevention – Chlorhexidine vs. Polyurethane dressing for CVC – Maternal education bundle – NIPPV vs. NCPAP for RDS (<37 w) – Thyroid hormone prophylaxis – Animal-derived surfactant for RDS (<37 w) – Anti-staphylococcal immunoglobulin prophylaxis – Chlorhexidine for skin or cord care (in hospital setting)[a] – Prophylactic NCPAP (<32 w)	– PCVC vs. PVC for parenteral nutrition – Glutamine supplementation for severe GI disease or preterm infants – Intravenous inline filter – Therapeutic hypothermia for HIE – Chlorhexidine vs. Polyurethane dressing for CVC – Early erythropoietin prophylaxis (<37 w) – Protein vs. Protein-free surfactant – Formula vs. donor human milk (<37 w) – Early inhaled steroids for CLD prevention	– Animal-derived surfactant vs. protein-free synthetic surfactant – Topical ointment/cream – Inositol supplementation (1 dose) (<37 w) – Steroid as primary treatment for hypotension (<37 w) – Early vs. expectant ibuprofen for PDA (<37 w) – Paracetamol prophylaxis for PDA (<37 w) – Anti-staphylococcal immunoglobulin prophylaxis – Bovine lung lavage vs. modified bovine minced surfactant for RDS (rescue or prophylaxis) – Multiple vs. single dose surfactant (<30 w)	– Topical ointment/cream
No conclusions possible	– Prophylactic intravenous vs. intramuscular vitamin K – Aqueous vs. oil-based vitamin E – G-CSF or GM-CSF prophylaxis – Early discharge on gavage feeds – Early vs. Late kangaroo care – Vitamin a (any dose, high dose) supplementation (<32 w)	– Routine monitoring of gastric residuals – Criterion-based monitoring of gastric residuals – Late ESAs – Antimicrobial-impregnated CVC – G-CSF or GM-CSF prophylaxis – Topical ointment/cream or oil	– Early vs. delayed animal-derived surfactant – Insulin infusion for hyperglycemia – Topical oil – Vancomycin prophylaxis for VLBW babies requiring PN via CVC – Ibuprofen prophylaxis for PDA – Selenium supplementation (<37 w)	– Prophylactic oral/topical antifungal – Prophylactic vs. systemic antifungal – Insulin infusion for hyperglycemia – Topical oil – Early vs. late UVC removal

Table 2: (continued)

LOS, any (suspected or confirmed)	LOS, culture-proven	LOS, bacterial	LOS, fungal
– Radiant warmer vs. incubator care – Routine oro-or-nasopharyngeal suction at birth – Cot-nursing vs. incubator care – Cord antisepsis care (chlorhexidine vs. salicylic acid) – Antibiotics prophylaxis for UAC/UVC/ Ventilated neonates – ML-UVCs vs. SL-UVCs – Fish- vs. non-fish-oil LE (<37 w with surgical problems or cholestasis) – Antibiotics for asymptomatic babies born through MSAF – Co-bedding preterm twin babies – Surgical ligation vs. medical treatment for PDA (<37 w) – Cephazolin for CVC removal – Early vs. Late PN (>34 w) – Cromolyn sodium nebulization (<37 w, CLD) – Late inhaled corticosteroids (<37 w, BPD) – High vs. low dexamethasone (<37 w, BPD) – Lactoferrin or lactoferrin with probiotics supplementation (<37 w) – Short binasal prongs vs. single nasal prongs for NCPAP support – Inhaled vs. systemic steroids for CLD prevention – Short vs. long RBC transfusion – Nasal vs. Oral intubation – Prophylactic NCPAP vs. Assisted ventilation (<32 w) – NIDCAP (<37 w) – Gowns for attendants of the neonates – Acetazolamide and frusemide for babies with severe IVH	– High vs. low protein intake – Radiant warmer vs. incubator care – Early vs. late UVC removal – Fish- vs. non-fish-oil LE (<37 w, <37 w with surgical problems) – Antibiotics for babies born through MSAF – Co-bedding preterm twin babies – Cephazolin for CVC removal – Respiratory support before cord clamping – Early vs. Late PN (>34 w) – Trophic feeds (<32 w) – Delayed feeding (4/> days after birth) in <32 w – Smell and taste of milk (<37 w) – Oropharyngeal colostrum (<37 w) – Salbutamol (<37 w, CLD) – Hydrolyzed formula feeding (<37 w) – Slow vs. faster feed advancement (<32 w) – Darbepoetin prophylaxis (<37 w) – High vs. low dexamethasone (<37 w, BPD) – Lactoferrin supplementation (<37 w) – Human milk vs. bovine milk fortifier (<37 w) – Short binasal prongs vs. single nasal prongs for NCPAP support – Nebulized pentoxifylline for CLD (<32 w) – Physical activity for bone mineralization (<37 w) – Inhaled vs. systemic steroids for CLD prevention or treatment – Early vs. late parenteral lipids (<32 w) – Insulin infusion for hyperglycemia (<32w)	– Early vs. late UVC removal – Steroid vs. inotrope primary treatment for hypotension (<37 w) – Steroid for refractory hypotension (<37 w) – Plastic wrap or thermal mattress during delivery (<37 w) – Ibuprofen vs. Indomethacin for PDA treatment (<37 w) – Ibuprofen: PO vs. IV and high dose vs. standard dose (<37 w) – Paracetamol vs. Ibuprofen or indomethacin for PDA (<37 w) – High vs. low amino acid PN (overall, at initiation, and at maximum dose) – Lactoferrin or lactoferrin with probiotics supplementation (<37 w) – Prophylactic vs. rescue surfactant (<32 w) – Bovine vs. porcine surfactant for RDS (rescue) (<37 w)	– Lactoferrin or lactoferrin with probiotics supplementation (<37 w)

Table 2: (continued)

LOS, any (suspected or confirmed)	LOS, culture-proven	LOS, bacterial	LOS, fungal
– Repeated lumbar/Ventricular tapping for infants with IVH – Alcohol vs. chlorhexidine for hand hygiene	– Animal-derived surfactant for all <30 w preterm infants – Nasal vs. Oral intubation – Less frequent vs. frequent intravenous administration set replacement – Antibiotic prophylaxis for neonates with risk factors – HFNC vs. CPAP (primary support or post-extubation) OR NIPPV (primary support) – Alcohol vs. chlorhexidine for hand hygiene		

[a]Mothers of infants were also participants and received vaginal chlorhexidine washes. The interventions are categorized into 5 categories based on the effectiveness of the intervention and the certainty of the evidence as (1) effective interventions (high certainty in the evidence of effectiveness) (2) possible effective interventions (moderate certainty in the evidence of effectiveness) (3) ineffective interventions (high certainty in the evidence of lack of effectiveness (or harm)) (4) possible ineffective interventions (moderate certainty in the evidence of lack of effectiveness (or harm)), and (5) no conclusions possible (low or very low certainty in evidence). CLD, chronic lung disease; CVC, central venous catheter; ESA, erythropoietin stimulating agents; G-CSF, granulocyte colony-stimulating factor; GI: gastrointestinal; GM-CSF, granulocyte monocyte colony-stimulating factor; HIE: hypoxic-ischemic encephalopathy; HFNC, high flow nasal cannula; IV, intravenous; IVH, intraventricular hemorrhage; LBW, low birth weight; LE, lipid emulsion; LOS, late-onset sepsis; ML-UVCs, multiple lumen umbilical venous catheters; MSAF, meconium-stained amniotic fluid; NCPAP, nasal continuous positive airway pressure; NIDCAP, neonates individualized developmental care and assessment program; NIPPV, nasal intermittent positive pressure ventilation; PCVC, percutaneous central venous catheter; PDA, patent ductus arteriosus; PN, parenteral nutrition; PO, per oral; PVC, peripheral venous cannula; RDS, respiratory distress syndrome; SL-UVCs, single lumen umbilical venous catheters; UAC, umbilical artery catheters; UVC, umbilical venous catheters.

The overview's scope was limited to studying the effectiveness of interventions on LOS; hence, we did not examine the effects of interventions on other outcomes. This is important as some interventions found ineffective in reducing sepsis may have considerable influence on other important outcomes. For example, in this overview, we found high-quality evidence that late postnatal corticosteroids for preventing bronchopulmonary dysplasia [32] are ineffective in reducing sepsis; however, they are beneficial in lowering extubation failure, death, or bronchopulmonary dysplasia, which are other important outcomes that were not studied [32]. Furthermore, clinicians must consider many other factors, such as effect size, harms, cost-effectiveness, and generalizability, by referring to the original studies or individual Cochrane reviews for considering any therapy in neonatal practice [112–114]. For example, though the overview found moderate-quality evidence of effectiveness that probiotics supplementation reduces LOS in very preterm infants, clinicians must consider other factors, such as harms, including probiotics-associated sepsis, anticipated benefit, quality assurance, cost-effectiveness, and so on [112–115].

Quality of evidence

All the 101 included Cochrane reviews were high-quality and rated a low risk of bias based on the AMSTAR 2 tool [9]. The risk of bias of included RCTs in those reviews, assessed using the approach outlined in the Cochrane Handbook for Systematic Reviews of Interventions, was variable; however, it was incorporated in the GRADE approach for evaluating the certainty of the evidence. The most common reason for downgrading the quality was study limitations, followed by imprecision and heterogeneity.

Strengths and limitations

This is a first overview providing a comprehensive summary of Cochrane reviews evaluating interventions to reduce LOS and shall be helpful for clinicians and researchers to aid in choosing interventions for reducing LOS. Also, the overview examines the certainty of the evidence for sepsis-related outcomes that were not evaluated in nearly three-fourths of the Cochrane reviews. Further, the overview provides a rigorous assessment of the evidence depending on the effectiveness of interventions and the certainty of the evidence. The search was comprehensive, and the reporting was transparent, based on the PRIO-harms guideline.

The overview focuses on interventions to reduce LOS and only evaluates sepsis-related outcomes. It did not assess other important outcomes, so clinicians should be careful while inferring this data and consider various other factors, as mentioned above, while applying the evidence to their clinical practice. In addition, the overview did not assess early-onset sepsis as the overview focuses on neonatal interventions and not childbirth or pregnancy interventions. Finally, the overview included only Cochrane reviews, but we realize that most interventions were likely assessed in the Cochrane reviews.

To conclude, the overview summarizes the evidence from the Cochrane reviews assessing interventions in the neonatal period for reducing LOS. Clinicians, researchers, policymakers, and consumers can utilize it for evidence translation and decision-making. Clinicians, however, are recommended to assess the effects of the interventions on other outcomes, including harms, and consider other aspects, such as feasibility, generalizability, anticipated benefit based on the effect size, and others, while translating evidence into clinical practice.

Acknowledgments: Authors would like to acknowledge Ahmed Hamed for initial screening of the articles for the systematic review.
Research funding: No specific funding was sought for this project. Dr. Razak's research is supported by Monash University, Australia.
Author contributions: Abdul Razak conceptualized and designed the study, oversaw the conduct of the review, assessed the quality of systematic reviews, provided intellectual content, drafted the manuscript and approved the final version. Javed Ahmed co-conceptualized and designed the study, performed the initial screening of the articles, abstracted the data, assessed the quality of systematic reviews, revised the manuscript and approved the final version. Omar Ibrahim Alhaidari co-conceptualized and designed the study, performed the screening of the articles, abstracted the data, revised the manuscript and approved the final version. All authors have accepted responsibility for the entire content of this manuscript and approved its submission.
Conflict of interest: The authors have indicated they have no potential conflict of interest to disclose.
Informed consent: Not applicable.
Ethical approval: Not applicable.
Protocol registration: The protocol for the systematic review was registered with PROSPERO (registration number CRD42020192513), the international prospective register for systematic reviews.

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Supplementary Material: The online version of this article offers supplementary material (https://doi.org/10.1515/jpm-2022-0131).