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Pentoxifylline for treatment of sepsis and necrotising enterocolitis in neonates (Review)

Pammi M, Haque KN

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TABLE OF CONTENTS

[Intervention Review]

Pentoxifylline for treatment of sepsis and necrotising enterocolitis in neonates

Mohan Pammi[1], Khalid N Haque[2]

[1]Section of Neonatology, Department of Pediatrics, Baylor College of Medicine, Houston, Texas, USA. [2](Formerly) Division of Neonatology, Department of Child Health, Queen Mary's Hospital for Children, Wrythe Lane, Carshalton, UK

Contact: Mohan Pammi, mohanv@bcm.edu.

A B S T R A C T

Background

Mortality and morbidity due to neonatal sepsis and necrotising enterocolitis (NEC) remain high despite the use of potent antimicrobial agents. Agents that modulate inflammation may improve outcomes. Pentoxifylline (PTX), a phosphodiesterase inhibitor, is one such agent. This is an update of a review first published in 2003 and updated in 2011 and 2015.

Objectives

To assess the effectiveness and safety of intravenous PTX as an adjunct to antibiotic therapy on mortality and morbidity in neonates with suspected or confirmed sepsis and neonates with NEC.

Search methods

We searched CENTRAL, MEDLINE, Embase, CINAHL, and trial registries in July 2022. We also searched the reference lists of identified clinical trials and handsearched conference abstracts.

Selection criteria

We included randomised controlled trials (RCTs) or quasi-RCTs assessing the efficacy of PTX with antibiotics (any dose or duration) for treatment of suspected or confirmed sepsis or NEC in neonates. We included three comparisons: (1) PTX with antibiotics compared to placebo or no intervention with antibiotics; (2) PTX with antibiotics compared to PTX with antibiotics and adjunct treatments such as immunoglobulin M-enriched intravenous immunoglobulin (IgM-enriched IVIG); (3) PTX with antibiotics compared to adjunct treatments such as IgM-enriched IVIG with antibiotics.

Data collection and analysis

We reported typical risk ratio (RR) and risk difference (RD) with 95% confidence intervals (CI) for dichotomous outcomes, and mean difference (MD) for continuous outcomes derived from a fixed-effect model of meta-analysis. We calculated the number needed to treat for an additional beneficial outcome (NNTB) if there was a statistically significant reduction in RD.

Main results

We identified no new studies for this update. We included six RCTs (416 neonates). All of the included studies examined neonates with sepsis; we identified no studies on neonates with NEC. Four of the six trials had high risk of bias for at least one risk of bias domain.

Comparison 1: PTX with antibiotics compared to placebo with antibiotics, or antibiotics alone, in neonates with sepsis may reduce all-cause mortality during hospital stay (typical RR 0.57, 95% CI 0.35 to 0.93; typical RD −0.08, 95% CI −0.14 to −0.01; NNTB 13, 95% CI 7 to

100; 6 studies, 416 participants, low-certainty evidence) and may decrease length of hospital stay (LOS) (MD −7.74, 95% CI −11.72 to −3.76; 2 studies, 157 participants, low-certainty evidence). The evidence is very uncertain that PTX with antibiotics compared to placebo or no intervention results in any change in chronic lung disease (CLD) (RR 1.50, 95% CI 0.45 to 5.05; 1 study, 120 participants, very low-certainty evidence), severe intraventricular haemorrhage (sIVH) (RR 0.75, 95% CI 0.28 to 2.03; 1 study, 120 participants, very low-certainty evidence), periventricular leukomalacia (PVL) (RR 0.50, 95% CI 0.10 to 2.63; 1 study, 120 participants, very low-certainty evidence), NEC (RR 0.56, 95% CI 0.29 to 1.06; 6 studies, 405 participants, very low-certainty evidence), or retinopathy of prematurity (ROP) (RR 0.40, 95% CI 0.08 to 1.98; 1 study, 120 participants, very low-certainty evidence) in neonates with sepsis.

Comparison 2: the evidence is very uncertain that PTX with antibiotics compared to PTX with antibiotics and IgM-enriched IVIG has any effect on mortality (RR 0.71, 95% CI 0.24 to 2.10; 102 participants, 1 study, very low-certainty evidence) or development of NEC in neonates with sepsis (RR 1.33, 95% CI 0.31 to 5.66; 1 study, 102 participants, very low-certainty evidence). The outcomes of CLD, sIVH, PVL, LOS, and ROP were not reported.

Comparison 3: the evidence is very uncertain that PTX with antibiotics compared to IgM-enriched IVIG with antibiotics has any effect on mortality (RR 1.25, 95% CI 0.36 to 4.39; 102 participants, 1 study, very low-certainty evidence) or development of NEC (RR 1.33, 95% CI 0.31 to 5.66; 102 participants, 1 study, very low-certainty evidence) in neonates with sepsis. The outcomes of CLD, sIVH, PVL, LOS, and ROP were not reported.

All of the included studies evaluated adverse effects due to PTX, but none were reported in the intervention group in any of the comparisons.

Authors' conclusions

Low-certainty evidence suggests that adjunct PTX therapy in neonatal sepsis may decrease mortality and length of hospital stay without any adverse effects. The evidence is very uncertain if PTX with antibiotics compared to PTX with antibiotics and IgM-enriched IVIG, or PTX with antibiotics compared to IgM-enriched IVIG with antibiotics, has any effect on mortality or development of NEC. We encourage researchers to undertake well-designed multicentre trials to confirm or refute the effectiveness and safety of pentoxifylline in reducing mortality and morbidity in neonates with sepsis or NEC.

P L A I N   L A N G U A G E   S U M M A R Y

Pentoxifylline for treatment of sepsis and necrotising enterocolitis in neonates

Review question

What are the benefits and risks of pentoxifylline (PTX) for treating infection and a gut condition (necrotising enterocolitis, NEC) in newborns up to 28 days of age?

Key messages

• For treating infection in the newborn, PTX with antibiotics was effective in decreasing death and duration of hospital stay without adverse effects. However, our confidence in this finding is low due to the small number of studies, all of which were of low quality.

• We did not find any studies for the use of PTX in treating severe bowel disorder (NEC)

• We need better and larger studies to fully understand if PTX is beneficial without risks for treatment of infection and NEC in newborns.

What is the problem?

Bacterial or fungal infection of the blood and NEC is a condition with digestive tract injury and infection seen in premature babies. Infection and NEC are treated with antibiotics, but still some babies die and suffer from complications.

How can we improve the treatment for infection or NEC in the newborn?

In addition to antibiotics, changing the body's response to infection (inflammation) may decrease deaths and complications. Pentoxifylline alters the body's response to infection or NEC and may have beneficial effects.

What did we want to find out?

We wanted to know if the use of PTX in addition to antibiotics can decrease deaths and complications such as lung disease, eye disease, duration of stay in the hospital, and time on the breathing machine. We also wanted to know if the use of PTX is safe without adverse effects.

What did we do?

We searched for studies that investigated whether:

• PTX with antibiotics compared to placebo (dummy treatment) with antibiotics or antibiotics alone;

• PTX with antibiotics compared to PTX with antibiotics and other drugs such as immunoglobulin; or

• PTX with antibiotics compared to other drugs such as immunoglobulin with antibiotics

was effective in decreasing deaths or other complications without adverse effects in newborns with infection or NEC. We compared and summarised the results of the studies and rated our confidence in the evidence, based on factors such as study methods and sizes.

What did we find?

We found six eligible studies (416 newborn participants) that evaluated PTX with antibiotics in newborns with infection.

Main results

1. We found that PTX in combination with antibiotics may decrease deaths and duration of hospital stay in newborns with infection.

It is unclear if pentoxifylline treatment has any effect on lung disease, eye disease, gut injury, or brain injury as a result of infection.

The identified studies did not report any adverse effects due to PTX.

No completed studies looked at PTX treatment in newborns with NEC.

2. When PTX was compared to other drugs such as immunoglobulin in addition to PTX, it was unclear if treatment affected deaths or gut injury. Effects of treatment on lung, eye, or brain injury were not studied.

3. When PTX was compared to other drugs such as immunoglobulin, it was unclear if treatment affected deaths or gut injury. Effects of treatment on lung, eye, gut, or brain injury were not studied.

What are the limitations of the evidence?

We have low confidence in our finding that PTX in addition to antibiotics decreases death and duration of hospital stay in newborns with infection.

Three main factors reduced our confidence in the evidence. Firstly, the six identified studies were small with few participants. Secondly, four of the six studies were poorly conducted. Consequently, the results of further research could differ from the results of this review.

We have very low confidence in the effects of:

• PTX compared to other drugs such as immunoglobulin in addition to PTX; or

• PTX compared to other drugs such as immunoglobulin

on deaths and gut injury because only two studies were available with few participants, and the studies were poorly conducted. The effects of these treatments on lung disease, eye disease, or brain injury as a result of infection were not studied.

How up-to-date is this evidence?

The evidence is current to July 2022.

SUMMARY OF FINDINGS

Summary of findings 1.   Pentoxifylline with antibiotics (any dose or duration) compared to placebo or no intervention for neonatal sepsis

Pentoxifylline with antibiotics (any dose or duration) compared to placebo with antibiotics or antibiotics alone for neonatal sepsis

Patient or population: neonates with sepsis

Settings: neonatal intensive care unit

Intervention: PTX

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Placebo	PTX			
All-cause mortality during hospital stay	36/207	20/209	**RR** 0.57 (0.35, 0.93)	416 participants (6 studies)	⊕⊕⊝⊝ Low[a]
Chronic lung disease	4/60	6/60	**RR** 1.50 (0.45, 5.05)	120 participants (1 study)	⊕⊝⊝⊝ Very low[b]
Severe intraventricular haemorrhage	8/60	6/60	**RR** 0.75 (0.28, 2.03)	120 participants (1 study)	⊕⊝⊝⊝ Very low[b]
Periventricular leukomalacia	4/60	2/60	**RR** 0.50 (0.10, 2.63)	120 participants (1 study)	⊕⊝⊝⊝ Very low[b]
Length of hospital stay (LOS) in days	The mean LOS ranged across control groups from 33.8 to 38.3 days.	The mean LOS in the intervention groups was 22.6 to 31.3 days.	Mean difference −7.74, 95% CI −11.72, −3.76	157 participants (2 studies)	⊕⊕⊝⊝ Low[c]

Necrotising enterocolitis, any Bell stage	13/203	23/202	**RR** 0.56 (0.29, 1.06)	405 participants (6 studies)	⊕⊖⊖⊖ **Very low**[d]
Retinopathy of prematurity, any stage	5/60	2/60	**RR** 0.40 (0.08, 1.98)	120 participants (1 study)	⊕⊖⊖⊖ **Very low**[b]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **PTX:** pentoxifylline; **RR:** risk ratio

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded to low because four studies had a high risk of bias, and the summary estimate was imprecise with wide CIs.
[b]Downgraded to very low because there was only one included study and due to imprecision of the summary estimate.
[c]Downgraded to low because there were only two included studies, one of which had a high risk of bias.
[d]Downgraded to very low because three studies had a high risk of bias, and the summary estimate was imprecise with wide CIs.

Summary of findings 2.   Pentoxifylline with antibiotics (any dose or duration) compared to pentoxifylline with antibiotics and immunoglobulin M-enriched intravenous immunoglobulin for neonatal sepsis

Pentoxifylline with antibiotics (any dose or duration) compared to pentoxifylline with antibiotics and immunoglobulin M-enriched intravenous immunoglobulin for neonatal sepsis

Patient or population: neonates with sepsis

Settings: neonatal intensive care unit

Intervention: PTX

Comparison: PTX with IgM-enriched IVIG

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants	Certainty of the evidence	Comments

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6

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	Assumed risk	Corresponding risk		(studies)	(GRADE)	
	PTX with IgM-enriched IVIG	PTX				
All-cause mortality during hospital stay	7/51	5/51	**RR** 0.71 (0.24, 2.10)	102 participants (1 study)	⊕⊖⊖⊖ **Very low**[a]	
Chronic lung disease in survivors	-	-	-	-	-	None reported.
Severe intraventricular haemorrhage	-	-	-	-	-	None reported.
Periventricular leukomalacia	-	-	-	-	-	None reported.
Length of hospital stay in days for survivors to discharge	-	-	-	-	-	None reported.
Necrotising enterocolitis, any Bell stage	3/51	4/51	**RR** 1.33 (0.31, 5.66)	102 participants (1 study)	⊕⊖⊖⊖ **Very low**[a]	
Retinopathy of prematurity, any stage	-	-	-	-	-	None reported.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **IgM:** immunoglobulin M; **IVIG:** intravenous immunoglobulin; **PTX:** pentoxifylline; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded to very low because there was only one included study and due to imprecision of the summary estimate.

Summary of findings 3.   Pentoxifylline with antibiotics (any dose or duration) compared to immunoglobulin M-enriched intravenous immunoglobulin with antibiotics for neonatal sepsis

Pentoxifylline with antibiotics (any dose or duration) compared to immunoglobulin M-enriched intravenous immunoglobulin with antibiotics for neonatal sepsis						
Patient or population: neonates with sepsis						
Settings: neonatal intensive care unit						
Intervention: PTX						
Comparison: IgM-enriched IVIG						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	IgM-enriched IVIG	**PTX**				
All-cause mortality during hospital stay	4/51	5/51	**RR** 1.25 (0.36, 4.39)	102 participants (1 study)	⊕⊖⊖⊖ **Very low**[a]	
Chronic lung diseasein survivors	-	-	-	-	-	None reported.
Severe intraventricular haemorrhage	-	-	-	-	-	None reported.
Periventricular leukomalacia	-	-	-	-	-	None reported.
Length of hospital stay in days for survivors to discharge	-	-	-	-	-	None reported.
Necrotising enterocolitis, any Bell stage	3/51	4/51	**RR** 1.33 (0.31, 5.66)	102 participants (1 study)	⊕⊖⊖⊖ **Very low**[a]	
Retinopathy of prematurity, any stage	-	-	-	-	-	None reported.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **IgM:** immunoglobulin M; **IVIG:** intravenous immunoglobulin; **PTX:** pentoxifylline; **RR:** risk ratio

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GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

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[a]Downgraded to very low because there was only one included study and due to imprecision of the summary estimate.

BACKGROUND

Description of the condition

Neonatal sepsis is the most common cause of neonatal deaths worldwide (Lawn 2006). The incidence of neonatal sepsis in high-income countries is reported to be between 1 and 4 cases per 1000 live births (Stoll 2004a), but in low- and middle-income countries, it is significantly higher (6.5 to 38 per 1000 live births) (Zaidi 2005). The incidence of neonatal sepsis is inversely proportional to gestational age and birthweight (Kaufman 2004). Early-onset sepsis (sepsis in infants less than 72 hours of life) occurs in 1.5% to 1.9% of very low-birthweight (VLBW) infants (birthweight 401 g to 1500 g) (Stoll 2005). In a cohort of 6956 VLBW infants admitted to National Institute of Child Health and Human Development Neonatal Research Network hospitals during 1998 to 2000, 21% had one or more blood culture-proven late-onset sepsis (onset after 72 hours of life) (Stoll 2002). Mortality of infants with late-onset sepsis was 18% (36% for those infected with gram-negative organisms), and morbidities (including patent ductus arteriosus, prolonged ventilation, prolonged need for intravascular access, bronchopulmonary dysplasia, necrotising enterocolitis (NEC), and length of hospital stay) were significantly higher in infected infants. Sepsis significantly affects long-term neurodevelopmental outcomes, either by direct infection of the central nervous system or as a result of inflammatory injury. In a large cohort study of 6093 extremely low-birthweight (ELBW) infants (birthweight less than 1000 g), infected infants had a significantly higher incidence of adverse neurodevelopmental outcomes at follow-up, characterised by cerebral palsy, low scores on Bayley Scales of Infant Development, and vision impairment when compared with uninfected infants (Stoll 2004b).

NEC occurs in about 1% to 5% of infants admitted to the neonatal intensive care unit. The most consistent risk factors are prematurity and low birthweight (Lin 2006). The pathogenesis of NEC is not entirely clear. Gastrointestinal immaturity, enteral feeding (especially formula feeding), presence of bacteria, and inflammation all play a part in the development of NEC (Lin 2006). Tumour necrosis factor alpha (TNF-α) and platelet-activating factor are the most important among pro-inflammatory cytokines to have been implicated in the development of NEC (Caplan 1990a; Caplan 1990b). The pivotal role of TNF-α in NEC is supported by the fact that, in an animal model, monoclonal antibody to TNF-α reduced incidence of NEC from 80% to 17% (Halpern 2006). Mortality from NEC is high (15% to 30%), and 20% to 40% of infants with NEC undergo surgery. Infants who had NEC have delayed neurodevelopmental outcomes at 18 to 22 months corrected age (Lin 2006; Stoll 2004b).

Mortality and morbidity due to sepsis and NEC remain high despite the use of potent antimicrobial agents (Stoll 2002; Stoll 2005). Increased use of antimicrobials has led to a global emergence of antibiotic resistance (Levy 1998). Adjunct therapies may be important in increasing the efficacy of antimicrobial agents. Excessive or uncontrolled inflammatory response may be responsible for the multi-organ dysfunction and systemic inflammatory response seen in sepsis. The balance of pro- and anti-inflammatory cytokines may determine the severity and ultimate outcome in sepsis syndromes and NEC (Edelson 1999; Harris 2005; Ng 2003). Evidence has also shown that inflammation plays an important role in cerebral and pulmonary injury (Adams-Chapman 2006; Speer 1999), especially in the preterm neonate. When used in conjunction with antibiotics, immunomodulating agents may help to re-establish the balance between pro- and anti-inflammatory responses and may influence clinical outcome in neonatal sepsis and NEC.

Description of the intervention

Pentoxifylline, a xanthine derivative, is a phosphodiesterase inhibitor that suppresses TNF-α production by adenyl cyclase activation and increased cellular cyclic adenosine 3',5'-monophosphate concentration. Pentoxifylline has attracted increased interest since the discovery that inhibition of tumour necrosis factor gene transcription reduces mortality from sepsis. TNF-α increases peroxidation of arachidonic acid, activates polymorphonuclear leukocytes, increases eicosanoids, and increases its own production, thereby amplifying the inflammatory response (Vilcek 1991). Inhibition of TNF-α production by pentoxifylline negates this response and thereby may improve outcome. Pentoxifylline also has beneficial effects on endothelial cell function and coagulation in sepsis (Boldt 1996; Wang 1996).

How the intervention might work

Pentoxifylline has been shown to have beneficial effects in humans and animal models of sepsis and NEC. In sepsis, pentoxifylline has been shown to improve haemodynamics (including renal blood flow) and to prevent transition from a hyperdynamic to a hypodynamic response (Bacher 1997; Krysztopik 1996; Yang 1999; Zeni 1996). Pentoxifylline also ameliorates inflammatory lung injury after endotoxaemia (Michetti 2003). In adults and neonates, pentoxifylline has been shown to decrease serum levels TNF-α, interleukin-1, and interleukin-10, but not interleukin-6 or interleukin-8 (Bienvenu 1995; Zeni 1996). In a rat model of NEC, pentoxifylline reduced the incidence and severity of NEC (Travadi 2006). To date, no significant adverse effects have been reported in either animal or human studies.

Why it is important to do this review

The potential beneficial effects of pentoxifylline make it a promising agent for the treatment of sepsis and NEC in neonates. We performed this systematic review to determine the efficacy and safety of pentoxifylline as an adjunct to antibiotics in the treatment of sepsis or NEC in neonates.

OBJECTIVES

To assess the effectiveness and safety of intravenous pentoxifylline as an adjunct to antibiotic therapy on mortality and morbidity in neonates with suspected or confirmed sepsis and neonates with necrotising enterocolitis.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised or quasi-randomised controlled trials.

Types of participants

We included neonates (less than 28 days old, at any gestational age or birthweight) with confirmed or suspected sepsis or neonates with NEC (Bell's stage 2 or 3) on antibiotics (Bell 1978).

We defined confirmed sepsis as clinical signs and symptoms consistent with infection and microbiologically proven with a positive blood culture, cerebrospinal fluid culture, urine culture (obtained by a suprapubic tap), or culture from a normally sterile site (e.g. pleural fluid, peritoneal fluid, or autopsy specimens) for bacteria or fungi.

We defined suspected sepsis as clinical signs and symptoms consistent with sepsis without isolation of a causative organism.

We defined NEC as an acute gastrointestinal disorder that manifests clinically with systemic signs (temperature instability, apnoea, bradycardia, lethargy, hypotension, metabolic acidosis, hyponatraemia, thrombocytopenia, disseminated intravascular coagulation), intestinal signs (feed intolerance, gastrointestinal bleeding, abdominal tenderness, abdominal wall cellulitis, abdominal distension), radiological features (non-specific intestinal dilation and ileus in stage I, by pneumatosis intestinalis and air in the portal tree in stage II, or pneumoperitoneum in stage III), and pathologically by intestinal necrosis (Bell 1978; Walsh 1986).

Types of interventions

The intervention was intravenous pentoxifylline at any dosage or duration used as adjunct to antibiotics to treat suspected or confirmed neonatal sepsis or NEC.

We included the following comparisons.

1. Pentoxifylline with antibiotics (any dose or duration) compared to placebo with antibiotics or antibiotics alone.
2. Pentoxifylline with antibiotics (any dose or duration) compared to pentoxifylline with antibiotics and adjunct treatments such as immunoglobulin M-enriched intravenous immunoglobulin (IgM-enriched IVIG).
3. Pentoxifylline with antibiotics (any dose or duration) compared to adjunct treatments such as IgM-enriched IVIG with antibiotics.

Types of outcome measures

Primary outcomes

1. All-cause mortality during hospital stay.

Secondary outcomes

1. Neurological outcome at two years of age or more (neurodevelopmental outcome assessed by a validated test) (Bayley 2005; Jacobs 2013).
2. Chronic lung disease in survivors (chronic lung disease defined as oxygen requirement at 36 weeks' postmenstrual age) (Jobe 2001; NIH 1979).
3. Adverse outcomes directly attributable to pentoxifylline: thrombocytopenia (platelet count less than 100 x 10^9/L), increased gastric residue (gastric aspirate greater than 10% of oral feed), vomiting, cholestatic jaundice requiring therapy.
4. Severe intraventricular haemorrhage, grades III and IV (Papile 1978).
5. Periventricular leukomalacia (defined as necrosis of white matter in a characteristic distribution, i.e. in the white matter dorsal and lateral to the external angles of lateral ventricles involving particularly the centrum semiovale and optic and

acoustic radiations and diagnosed by neuroimaging) (Volpe 1995).
6. Duration of assisted ventilation through an endotracheal tube (days).
7. Length of hospital stay in days for survivors to discharge.
8. Necrotising enterocolitis (infants with sepsis only): a) NEC any Bell stage and b) NEC (definite NEC and perforated NEC, Bell's stage 2 or 3) (Bell 1978; Walsh 1986).
9. Retinopathy of prematurity (post hoc analysis): a) ROP any stage, b) ROP stages III and IV (ICROP 1984).

Search methods for identification of studies

Cochrane Neonatal Information Specialist M Fiander wrote new search strategies to increase sensitivity. Given these changes, no date limits were applied to the searches.

Electronic searches

We searched the following databases in July 2022. We conducted searches without language or publication type limits. We applied no date limit to searches for trials, but limited searches for systematic reviews from 2020 forward.

1. Cochrane Central Register of Controlled Trials (CENTRAL) via Cochrane Register of Studies (CRS) (Issue 7, 2022)
2. Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions (1946 to 29 July 2022)
3. Embase via Ovid (1974 to 29 July 2022)
4. CINAHL (EBSCOhost) (Cumulative Index to Nursing and Allied Health Literature) (1985 to 31 July 2022)

Search strategies are shown in Appendix 1; Appendix 2; Appendix 3; Appendix 4.

Searching other resources

We searched the following trial registries on 29 July 2022.

1. ISRCTN registry (www.isrctn.com) (formerly controlledtrials.com)
2. World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (www.who.int/clinical-trials-registry-platform/the-ictrp-search-portal)
3. US National Library of Medicine ClinicalTrials.gov (www.clinicaltrials.gov)
4. Australian New Zealand Clinical Trials Registry (ANZCTR) (anzctr.org.au/)

Search strategies are shown in Appendix 5.

We searched the following conferences or conference sources up to 2020 or 2022, depending upon availability.

1. Pediatric Academic Societies (PAS) conference up to 2022
2. European Academy of Paediatric Societies (EAPS) up to 2020
3. BIOSIS from January 1992 to July 2021 (we did not have access after July 2021)

Note: for the previous version of this review (Pammi 2015), Abstracts2View was searched; however, this site has not been available since 2014.

We contacted authors who published in the field for possible unpublished studies and identified one ongoing study (ACTRN12606000257561). We additionally searched the reference lists of identified clinical trials and review authors' personal files up to July 2022

Data collection and analysis

We employed the standard methods of Cochrane Neonatal Review Group guidelines in creating this update.

Selection of studies

We managed search results in EndNote (EndNote). We used Covidence for screening (Covidence), and recorded results in sufficient detail to create a PRISMA flow diagram (Liberati 2009). We conducted title/abstract review independently. We independently assessed the full-text versions of potentially relevant studies identified during title/abstract screening. At both stages, we resolved any disagreements by discussion. We documented the reasons for exclusion or any studies excluded at the full-text stage; for details see Characteristics of excluded studies.

Data extraction and management

We designed forms for trial inclusion/exclusion, data extraction, and for requesting additional information from authors of the original reports. We performed data extraction independently using specifically designed paper forms and compared for any differences, which we then resolved by discussion.

Assessment of risk of bias in included studies

We independently assessed the risk of bias (low, high, or unclear) of all included trials using the Cochrane risk of bias tool for the following domains (Higgins 2011).

1. Sequence generation (selection bias)
2. Allocation concealment (selection bias)
3. Blinding of participants and personnel (performance bias)
4. Blinding of outcome assessment (detection bias)
5. Incomplete outcome data (attrition bias)
6. Selective reporting (reporting bias)
7. Any other bias

Any disagreements were resolved by discussion. See Appendix 6 for a more detailed description of risk of bias for each domain.

Measures of treatment effect

We used the standard methods of Cochrane Neonatal. We performed statistical analyses using Cochrane Review Manager 5 software (Review Manager 2020). We analysed categorical data using risk ratio (RR), risk difference (RD), and the number needed to treat for an additional beneficial outcome (NNTB). We analysed continuous data using mean difference (MD). We reported the 95% confidence interval (CI) on all estimates.

Unit of analysis issues

The unit of analysis was the participating infant in individually randomised trials, and an infant was considered only once in the analysis. If in future updates we find cluster-randomised trials, the participating neonatal unit or section of a neonatal unit or hospital will be the unit of analysis. We will analyse any cluster-randomised trials using an estimate of the intracluster correlation coefficient (ICC) derived from the trial (if possible), or from a similar trial or from a study with a similar population, as described in Section 16.3.6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019). If we use ICCs from a similar trial or from a study with a similar population, we will report this and conduct a sensitivity analysis to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually randomised trials, we will only combine the results from both if there is little heterogeneity between the study designs, and interaction between the effect of the intervention and the choice of randomisation unit is considered to be unlikely. We will acknowledge any possible heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate possible effects of the randomisation unit.

Dealing with missing data

Where feasible, we performed analysis on an intention-to-treat basis for all outcomes. Whenever possible, we analysed all participants in the treatment group to which they had been randomised, regardless of the actual treatment received. When we identified important missing data (in the outcomes) or unclear data, we contacted the original investigators to request the missing data.

Assessment of heterogeneity

We assessed heterogeneity of treatment effects between trials using the I^2 statistic to determine the appropriateness of pooling data and performing meta-analysis. We deferred meta-analysis if heterogeneity was high (greater than 75%). We used the following cut-offs to report on the degree of heterogeneity:

1. less than 25%: no heterogeneity;
2. 25% to 49%: low heterogeneity;
3. 50% to 74%: moderate heterogeneity; and
4. greater than 75%: high heterogeneity.

If we detected statistical heterogeneity, we explored the possible causes (e.g. differences in study quality, participants, intervention regimens, or outcome assessments) using post hoc subgroup analyses. We used a fixed-effect model for meta-analysis.

Assessment of reporting biases

We assessed reporting bias by comparing the stated primary outcomes and secondary outcomes against the reported outcomes. Where study protocols were available, we compared these to the full publications to determine the likelihood of reporting bias. We planned to document studies using the interventions in a potentially eligible infant population but not reporting on any of the primary and secondary outcomes in the 'Characteristics of included studies' tables. We planned to use funnel plots to screen for publication bias if there were a sufficient number of studies (> 10) reporting the same outcome. If publication bias was suggested by a significant asymmetry of the funnel plot on visual assessment, we would incorporate this in our assessment of the certainty of the evidence.

Data synthesis

We performed the meta-analysis using Review Manager 5 software (Review Manager 2020). For estimates of typical RR and RD, we used

the Mantel-Haenszel method. For measured quantities, we used the inverse variance method. We performed all meta-analyses using the fixed-effect model.

We analysed all neonates including subgroups defined in Criteria for considering studies for this review on an intention-to-treat basis, irrespective of whether they survived to complete their allocated treatment.

Subgroup analysis and investigation of heterogeneity

We planned the following subgroup analyses.

1. Gestational age:
   a. preterm neonates (born before 37 completed weeks' gestation);
   b. term neonates (born at or after 37 completed weeks of gestation).
2. Time of onset of sepsis:
   a. early-onset sepsis (sepsis in the first 72 hours of life);
   b. late-onset sepsis (sepsis after the first 72 hours of life).
3. Suspected or confirmed sepsis:
   a. neonates with suspected sepsis (clinical signs and symptoms consistent with sepsis without isolation of causative organism treated with antibiotics);
   b. neonates with confirmed sepsis;
   c. neonates with confirmed gram-negative sepsis;
   d. neonates with confirmed fungal sepsis.

Sensitivity analysis

If we identified substantial heterogeneity, we would conduct sensitivity analysis to determine if the findings were affected by inclusion of only those trials considered to have used adequate methodology with a low risk of bias (selection and performance bias). We planned to report results of sensitivity analyses for our primary outcomes only.

Summary of findings and assessment of the certainty of the evidence

We used the GRADE approach, as outlined in the GRADE Handbook (Schünemann 2013), to assess the certainty of evidence of the following (clinically relevant) outcomes.

1. All-cause mortality before hospital discharge
2. Chronic lung disease
3. Severe intraventricular haemorrhage
4. Periventricular leukomalacia
5. Length of hospital stay
6. Necrotising enterocolitis, any Bell stage

7. Retinopathy of prematurity, any stage

We used GRADEpro GDT software to create three summary of findings tables to report the certainty of the evidence for the following three comparisons (GRADEpro GDT).

1. Comparison 1: pentoxifylline with antibiotics (any dose or duration) compared to placebo or no intervention with antibiotics (Summary of findings 1).
2. Comparison 2: pentoxifylline with antibiotics (any dose or duration) compared to pentoxifylline with antibiotics and adjunct treatments such as IgM-enriched IVIG (Summary of findings 2).
3. Comparison 3: pentoxifylline with antibiotics (any dose or duration) compared to adjunct treatments such as IgM-enriched IVIG with antibiotics (Summary of findings 3).

The GRADE approach results in an assessment of the certainty of a body of evidence as one of four grades.

1. High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
2. Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
3. Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
4. Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

R E S U L T S

Description of studies

For details of studies, see Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies.

Results of the search

The search identified 565 references (499 from databases and 66 from trial registries). After removal of 136 duplicates, 429 references were available for title/abstract screening. We reviewed 13 full texts, of which we excluded 4 studies, assessed 1 study as awaiting classification; and identified 2 ongoing studies (Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies). We included six studies in the review (Adel 2010; Akdag 2014; Ali 2006; Lauterbach 1996; Lauterbach 1999; Shabaan 2015). For details of the study selection process, see Figure 1.

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Figure 1. PRISMA flow diagram illustrating study selection process.
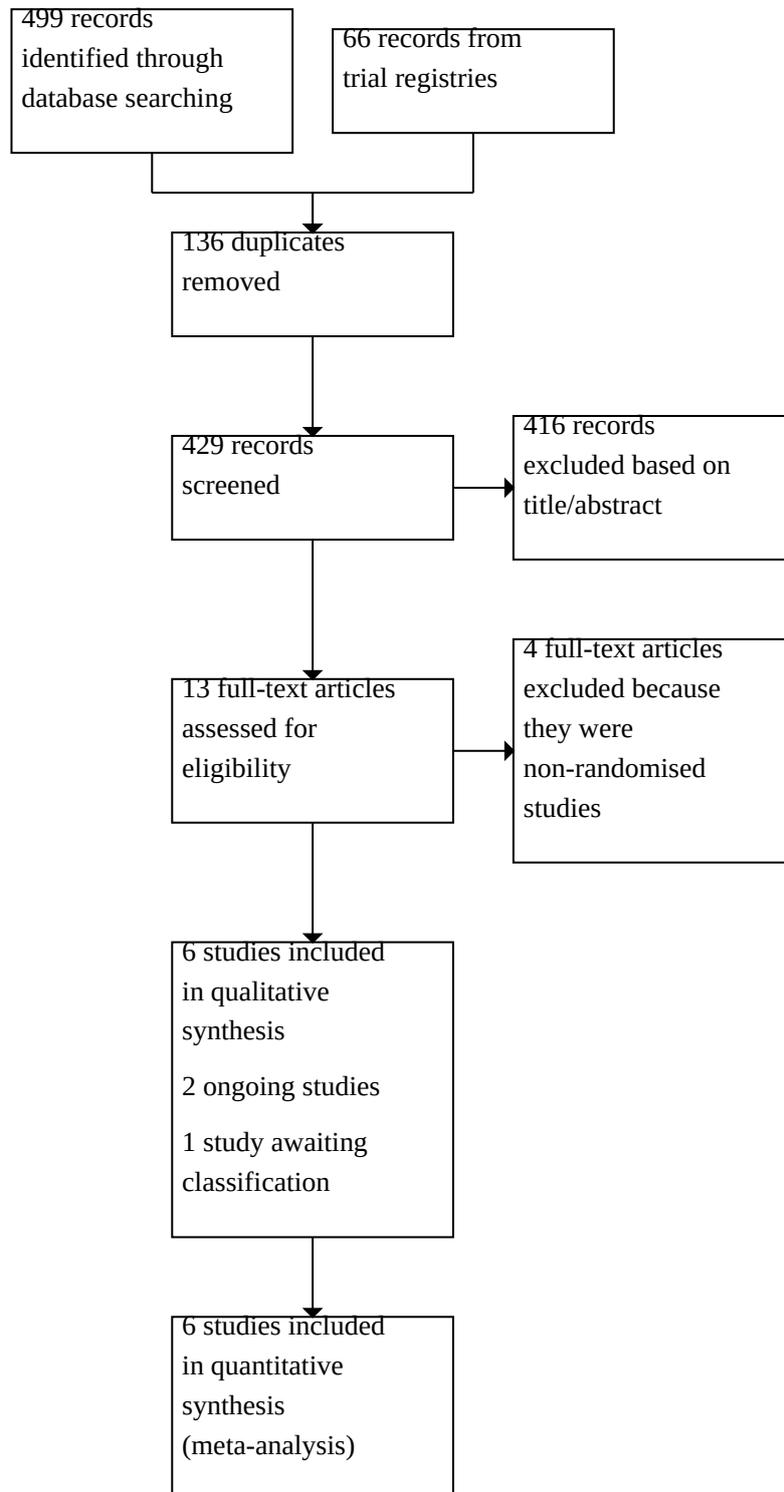
Included studies

Adel 2010 quasi-randomised 37 neonates with sepsis based on the day of admission to the neonatal unit to intravenous (IV) pentoxifylline (5 mg/kg/h for 6 hours for 6 consecutive days) or placebo (equal volume of normal saline for 6 consecutive days) as adjuncts to antibiotics. Seventeen out of 37 received pentoxifylline, and 20 out of 37 received placebo. The study reported the outcomes of mortality, length of hospital stay, multi-organ dysfunction, coagulation profiles including platelet count and C-reactive protein, shock, and NEC. Of the 37 neonates with suspected sepsis, 6 infants were culture-negative but included in the analysis.

Akdag 2014 randomised 204 neonates with sepsis to 4 groups: pentoxifylline (6 mg/kg IV over 4 hours for 3 consecutive days), pentoxifylline and IgM-enriched IVIG (pentaglobin, 250 mg/kg over 4 hours for 3 consecutive days), IgM-enriched IVIG (pentaglobin), or placebo (normal saline). The study reported the outcomes of mortality, NEC, oliguria/anuria, hepatic failure, disseminated intravascular coagulation, pulmonary haemorrhage, and laboratory parameters of inflammation (white blood cell count, C-reactive protein, interleukin-6, TNF-α, and neutrophil CD64). Length of hospital stay was reported in days (mean) but did not have standard deviations to use in meta-analysis.

Ali 2006 randomised 50 preterm neonates with culture-proven sepsis (less than 37 weeks' gestational age) to pentoxifylline intravenously (5 mg/kg/h for 6 hours for 3 consecutive days, n = 25) as an adjunct to antibiotics, or to a control group that received antibiotics alone (n = 25). The study reported the outcomes of mortality, development of NEC, length of hospital stay, duration of ventilation, and adverse effects. Duration of ventilation and length of hospital stay were reported in days (mean) but did not have standard deviations to use in meta-analysis.

Lauterbach 1996 randomised 40 preterm neonates (less than 36 weeks' gestation) with suspected late-onset sepsis to receive either pentoxifylline or placebo as adjunct to antibiotics. In 4 out of 20 neonates in the treatment group and 7 out of 20 neonates in the placebo group sepsis was not confirmed, and these neonates were excluded from analysis. Outcomes were thus reported in only the 29 neonates with confirmed sepsis (16 in treatment and 13 in placebo group). Of these neonates, confirmed gram-negative sepsis occurred in 10 in the pentoxifylline group and 10 in the placebo group. The following outcomes were reported: i) plasma TNF-α levels, ii) mortality during hospital stay, iii) NEC, and iv) adverse effects (adverse effects due to pentoxifylline were not reported specifically).

Lauterbach 1999 randomised 100 preterm neonates (less than 36 weeks' gestation) with suspected late-onset sepsis to receive either pentoxifylline or placebo as adjunct to antibiotics. In 10 out of 50 neonates in the treatment group and 12 out of 50 neonates in the placebo group sepsis was not confirmed, and these neonates were excluded from analysis. Outcomes were thus reported for only the 78 neonates with confirmed sepsis (40 in the pentoxifylline and 38 in the placebo group). Of these neonates, confirmed gram-negative sepsis occurred in 15 in the pentoxifylline group and 14 in the placebo group. The following outcomes were reported: i) plasma levels of TNF-α, interleukin-6, and interleukin-1, ii) mortality during hospital stay, iii) NEC, and iv) adverse effects (adverse effects due to pentoxifylline were not reported specifically).

Shabaan 2015 randomised 120 preterm neonates to intravenous pentoxifylline at 5 mg/kg/h for 6 hours on 6 successive days or normal saline (placebo). Of these neonates, 78 had confirmed sepsis and 52 had confirmed gram-negative sepsis. The primary outcome was death before hospital discharge; secondary outcomes were length of hospital stay, duration of respiratory support, duration of antibiotic use, short-term morbidity (chronic lung disease, NEC, intraventricular haemorrhage, periventricular leukomalacia, and retinopathy of prematurity), TNF-α concentrations, C-reactive protein concentrations, and adverse effects of pentoxifylline.

For further details, see Characteristics of included studies.

Excluded studies

We excluded four studies at the full-text stage.

1. Non-randomised study from Turkey evaluating intravenous pentoxifylline as an adjunct to antibiotic therapy on mortality and morbidity in VLBW preterm neonates with nosocomial sepsis (n = 18) (Hamilcikan 2017a).
2. Non-randomised study from Turkey comparing pentoxifylline and pentaglobin used as adjuncts to antibiotics in VLBW preterm neonates with nosocomial sepsis (Hamilcikan 2017b). This study may have included the same participants as Hamilcikan 2017a.
3. Seventeen preterm infants with sepsis were given pentoxifylline and compared with a historical control group of 13 septic infants who did not receive pentoxifylline. The study reported mortality and adverse effects. We excluded the study as it was neither randomised nor quasi-randomised (Lauterbach 1994).
4. Non-randomised study including 20 neonates with sepsis; the first 13 infants received pentoxifylline, and the next 7 participants constituted the control group. The study reported outcomes of mortality, leukocyte count, serum C-reactive protein level, TNF-α, and interleukin-6 levels (Selim 2004).

For further details, see Characteristics of excluded studies.

Studies awaiting classification

Sareno 2013 reported a randomised controlled trial where preterm infants ≤ 1500 g with suspected infection admitted to the neonatal intensive care unit were randomised to receive either pentoxifylline at a dose of 6 mg/kg/h or placebo. The primary outcome measured was occurrence of all-cause mortality between groups; this was analysed on an intention-to-treat basis. Secondary outcomes measured included mortality from sepsis, adverse drug reactions, and length of hospital stay. The report is published as a conference abstract, and we are awaiting missing data from authors.

For further details, see Characteristics of studies awaiting classification.

Ongoing studies

ACTRN12606000257561 is a pilot study to randomise 80 preterm (less than 32 weeks' gestation) neonates with stage 2 or 3 NEC to intravenous pentoxifylline or an equal volume of placebo at 5 mg/kg/h for 12 hours a day (60 mg/kg/day) for 2 consecutive days, followed by infusion for 6 hours a day (30 mg/kg/day) for the next 4 consecutive days. The primary outcome is to assess the efficacy and safety of pentoxifylline in preventing the progression of NEC or death, or both. Secondary outcomes are reduction in plasma

TNF-α levels, duration of hospital stay, duration of total parenteral nutrition support, and time to full enteral feeds. This study did not enrol patients, but has metamorphosed into the PROTECT trial (ACTRN12616000405415), with changes to study participants and objectives; we are awaiting communication with the principal investigator.

ACTRN12616000405415 is an international multicentre trial that plans to enrol approximately 1800 preterm neonates (born < 29 weeks' gestational age). The primary aim is to evaluate the effect of treatment with intravenous pentoxifylline compared to placebo, starting within six hours from blood culture taken for suspected late-onset sepsis or NEC. After 48 hours, treatment will cease if diagnosis is refuted, or will continue for 4 days if diagnosis is proven. The primary outcome to measure effectiveness is survival without disability at 18 to 24 months of age (corrected for gestation).

For further details, see Characteristics of ongoing studies.

Risk of bias in included studies

See: Characteristics of included studies (Figure 2; Figure 3)

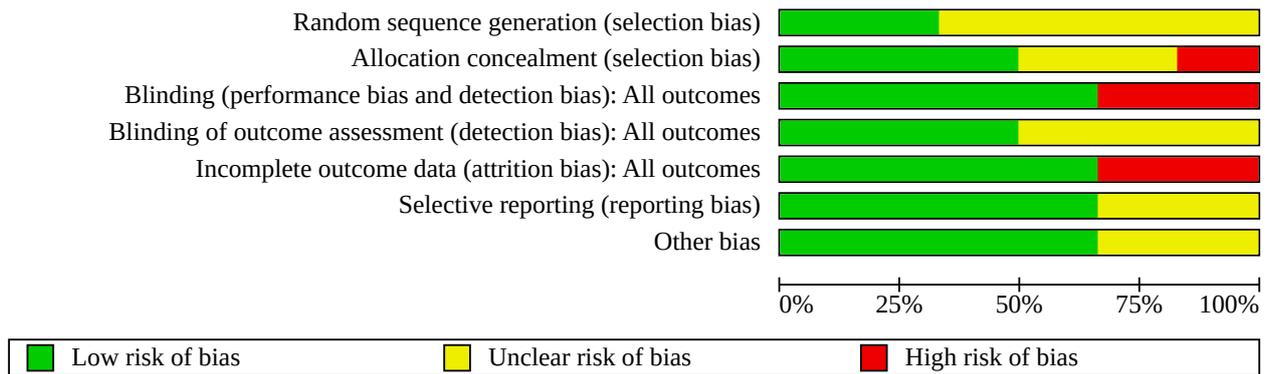**Figure 2. Risk of bias summary of the included studies in seven domains.**

Figure 3.   Risk of bias of the included studies in seven domains.

Allocation

Three trials had high risk of selection bias due to either lack of randomisation details or absence of concealment of allocation (Adel 2010; Ali 2006; Lauterbach 1996).

Blinding

All included trials except two, Adel 2010; Ali 2006, reported blinding of the intervention. None of the included trials reported clearly on blinding of outcome assessment, hence detection bias could be an issue.

Incomplete outcome data

Two trials had high risk of attrition bias, as participants were excluded from the final analysis (Lauterbach 1996; Lauterbach 1999).

Selective reporting

Two trials reported outcomes only in neonates with culture-proven sepsis (Lauterbach 1996; Lauterbach 1999).

Other potential sources of bias

Two trials had unclear risk for other bias due to lack of methodological details of the study (Lauterbach 1996; Lauterbach 1999).

The number of risk of bias domains increased to seven compared to the previous version of the review (Pammi 2015); this has not impacted our conclusions regarding risk of bias in the included studies.

Effects of interventions

See: **Summary of findings 1** Pentoxifylline with antibiotics (any dose or duration) compared to placebo or no intervention for neonatal sepsis; **Summary of findings 2** Pentoxifylline with antibiotics (any dose or duration) compared to pentoxifylline with antibiotics and immunoglobulin M-enriched intravenous immunoglobulin for neonatal sepsis; **Summary of findings 3** Pentoxifylline with antibiotics (any dose or duration) compared to immunoglobulin M-enriched intravenous immunoglobulin with antibiotics for neonatal sepsis

Comparison 1: Pentoxifylline with antibiotics (any dose or duration) compared to placebo with antibiotics or antibiotics alone

Six randomised controlled trials where pentoxifylline was used for the treatment of neonatal sepsis were eligible for inclusion in the review (Adel 2010; Akdag 2014; Ali 2006; Lauterbach 1996; Lauterbach 1999; Shabaan 2015), and reported the following outcomes.

Primary outcome

All-cause mortality during hospital stay

All six studies reported on all-cause mortality in infants with sepsis (Adel 2010; Akdag 2014; Ali 2006; Lauterbach 1996; Lauterbach 1999; Shabaan 2015). Pentoxifylline used as an adjunct to antibiotics in neonates with sepsis may reduce all-cause mortality during hospital stay compared to placebo or no intervention (typical risk ratio (RR) 0.57, 95% confidence interval (CI) 0.35 to 0.93; typical risk difference (RD) −0.08, 95% CI −0.14 to −0.01;

number needed to treat for an additional beneficial outcome (NNTB) 13, 95% CI 7 to 100; 6 studies, 416 participants, low-certainty evidence, Analysis 1.1). There was mild heterogeneity (I^2 = 30% for RR) among the six trials for this outcome.

Subgroup analyses

1. Gestational age

a. Preterm neonates (born before 37 completed weeks' gestation)

Four trials reported outcomes for the subgroup of preterm infants (Ali 2006; Lauterbach 1996; Lauterbach 1999; Shabaan 2015). Pentoxifylline used as an adjunct to antibiotics in preterm neonates with sepsis may reduce all-cause mortality during hospital stay (typical RR 0.38, 95% CI 0.20 to 0.71; typical RD −0.13, 95% CI −0.21 to −0.05; NNTB 8, 95% CI 5 to 20; 4 studies, 277 participants, low-certainty evidence, Analysis 1.1). There was no heterogeneity (I^2 = 0) among the four trials for this outcome.

b. Term neonates (born at or after 37 completed weeks of gestation). No data were available for subgroup analysis.

2. Time of onset of sepsis

a. Early-onset sepsis (sepsis in the first 72 hours of life). No data were available for subgroup analysis.

b. Late-onset sepsis (sepsis after the first 72 hours of life)

Three studies reported on all-cause mortality in infants with late-onset sepsis (Lauterbach 1996; Lauterbach 1999; Shabaan 2015). Pentoxifylline used as an adjunct to antibiotics in neonates with sepsis may reduce all-cause mortality during hospital stay in neonates with late-onset sepsis (typical RR 0.42, 95% CI 0.19 to 0.95; typical RD −0.12, 95% CI −0.23 to −0.02; NNTB 8, 95% CI 4 to 50; 3 studies, 169 participants, low-certainty evidence, Analysis 1.1). There was no heterogeneity (I^2 = 0 for RR) among the three trials for this outcome.

3. Suspected or confirmed sepsis

a. Neonates with suspected sepsis (clinical signs and symptoms consistent with sepsis without isolation of causative organism treated with antibiotics). No data were available for subgroup analysis.

b. Neonates with confirmed sepsis

Four studies reported on all-cause mortality in infants with confirmed sepsis (Ali 2006; Lauterbach 1996; Lauterbach 1999; Shabaan 2015). Pentoxifylline used as an adjunct to antibiotics in neonates with confirmed sepsis may reduce all-cause mortality during hospital stay (typical RR 0.37, 95% CI 0.19 to 0.73; typical RD −0.14, 95% CI −0.23 to −0.05; NNTB 7, 95% CI 4 to 20; 4 studies, 235 participants, low-certainty evidence, Analysis 1.1). There was no heterogeneity (I^2 = 0% for RR) among the four trials for this outcome.

c. Neonates with confirmed gram-negative sepsis

Four studies reported on all-cause mortality in infants with confirmed sepsis (Ali 2006; Lauterbach 1996; Lauterbach 1999; Shabaan 2015). Pentoxifylline used as an adjunct to antibiotics in neonates with confirmed gram-negative sepsis may decrease all-cause mortality during hospital stay (typical RR 0.33, 95% CI 0.16 to

0.72; typical RD −0.19, 95% CI −0.31 to −0.07; NNTB 5, 95% CI 3 to 14; 4 studies, 143 participants, low-certainty evidence, Analysis 1.1). There was no heterogeneity (I^2 = 0% for RR) among the four studies for this outcome.

d. Neonates with confirmed fungal sepsis. No data were available for subgroup analysis.

Secondary outcomes

1. Neurological outcome at two years of age or more

No study reported this outcome.

2. Chronic lung disease

One study reported this outcome (Shabaan 2015). The evidence is very uncertain whether pentoxifylline used as an adjunct to antibiotics in neonates with sepsis affects risk of chronic lung disease compared to antibiotics alone (RR 1.50, 95% CI 0.45 to 5.05; RD 0.03, 95% CI −0.07 to 0.13; 1 study, 120 participants, very low-certainty evidence, Analysis 1.2).

3. Adverse outcomes

No study reported this outcome.

4. Severe intraventricular haemorrhage

One study reported this outcome (Shabaan 2015). The evidence is very uncertain whether pentoxifylline used as an adjunct to antibiotics in neonates with sepsis affects risk of severe intraventricular haemorrhage compared to antibiotics alone (RR 0.75, 95% CI 0.28 to 2.03; RD −0.03, 95% CI −0.15 to 0.08; 1 study, 120 participants, very low-certainty evidence, Analysis 1.3).

5. Periventricular leukomalacia

One study reported this outcome (Shabaan 2015). The evidence is very uncertain whether pentoxifylline used as an adjunct to antibiotics in neonates with sepsis affects risk of periventricular leukomalacia compared to antibiotics alone (RR 0.50, 95% CI 0.10 to 2.63; RD −0.03, 95% CI −0.11 to 0.04; 1 study, 120 participants, very low-certainty evidence, Analysis 1.4).

6. Duration of assisted ventilation through an endotracheal tube (days)

No study reported this outcome.

7. Length of hospital stay

Two studies reported this outcome (Adel 2010; Shabaan 2015). The evidence suggests that pentoxifylline used as an adjunct to antibiotics in neonates with sepsis may decrease length of hospital stay (the estimated mean difference for the outcome was MD −7.74, 95% CI −11.72 to −3.76; 2 studies, 157 participants, low-certainty evidence, Analysis 1.5). There was no heterogeneity (I^2 = 0 for RR) between the two trials for this outcome.

8. Outcome for neonates with sepsis only: NEC, any Bell stage

Six studies reported this outcome (Adel 2010; Akdag 2014; Ali 2006; Lauterbach 1996; Lauterbach 1999; Shabaan 2015). The evidence is very uncertain whether pentoxifylline used as an adjunct to antibiotics in neonates with sepsis has any effect on the risk of developing NEC compared to antibiotics alone (typical RR 0.56, 95% CI 0.29 to 1.06; typical RD −0.05, 95% CI −0.11 to 0.00; 6 studies, 405 participants, very low-certainty evidence, Analysis 1.6). There was

mild heterogeneity (I^2 = 21% for RR) among the three trials for this outcome.

9. Retinopathy of prematurity, any stage

One study reported this outcome (Shabaan 2015). The evidence is very uncertain whether pentoxifylline used as an adjunct to antibiotics in neonates with sepsis affects retinopathy of prematurity compared to antibiotics alone (RR 0.40, 95% CI 0.08 to 1.98; RD −0.05, 95% CI −0.13 to 0.03; 1 study, 120 participants, very low-certainty evidence, Analysis 1.7).

Comparison 2. Pentoxifylline with antibiotics (any dose or duration) compared to pentoxifylline with antibiotics and adjunct treatments such as IgM-enriched IVIG

One study was eligible for inclusion in this comparison (Akdag 2014).

Primary outcome

All-cause mortality during hospital stay

One study reported this outcome (Akdag 2014). The evidence is very uncertain whether pentoxifylline used as an adjunct to antibiotics compared to pentoxifylline plus IgM-enriched IVIG in neonates with sepsis affects all-cause mortality during hospital stay (RR 0.71, 95% CI 0.24 to 2.10; RD −0.04, 95% CI −0.16 to 0.09; 1 study, 102 participants, very low-certainty evidence, Analysis 2.1).

Secondary outcomes

The following outcomes were not reported on in the included study (Akdag 2014).

1. Neurological outcome at two years of age or more
2. Chronic lung disease in survivors (chronic lung disease defined as oxygen requirement at 36 weeks' postmenstrual age)
3. Adverse outcomes
4. Severe intraventricular haemorrhage
5. Periventricular leukomalacia
6. Duration of assisted ventilation through an endotracheal tube (days)
7. Length of hospital stay in days for survivors to discharge

8. Necrotising enterocolitis, any Bell stage

One study reported this outcome (Akdag 2014). The evidence is very uncertain whether pentoxifylline used as an adjunct to antibiotics compared to pentoxifylline plus IgM-enriched IVIG in neonates with sepsis affects risk of NEC (RR 1.33, 95% CI 0.31 to 5.66; RD 0.02, 95% CI −0.08 to 0.12; 1 study, 102 participants, very low-certainty evidence, Analysis 2.2).

9. Retinopathy of prematurity, any stage

No study reported this outcome.

Comparison 3. Pentoxifylline with antibiotics (any dose or duration) compared to adjunct treatments such as IgM-enriched IVIG with antibiotics

One study was eligible for inclusion in this comparison (Akdag 2014).

Primary outcome

All-cause mortality during hospital stay

One study reported this outcome (Akdag 2014). The evidence is very uncertain whether pentoxifylline used as an adjunct to antibiotics compared to IgM-enriched IVIG in neonates with sepsis affects all-cause mortality during hospital stay (RR 1.25, 95% CI 0.36 to 4.39; RD 0.02, 95% CI −0.09 to 0.13; 1 study, 102 participants, very low-certainty evidence, Analysis 3.1).

Secondary outcomes

The following outcomes were not reported on in the included study (Akdag 2014).

1. Neurological outcome at two years of age or more
2. Chronic lung disease in survivors (chronic lung disease defined as oxygen requirement at 36 weeks' postmenstrual age)
3. Adverse outcomes
4. Severe intraventricular haemorrhage
5. Periventricular leukomalacia
6. Duration of assisted ventilation through an endotracheal tube (days)
7. Length of hospital stay in days for survivors to discharge

8. Necrotising enterocolitis, any Bell stage

One study reported this outcome (Akdag 2014). The evidence is very uncertain whether pentoxifylline used as an adjunct to antibiotics compared to IgM-enriched IVIG in neonates with sepsis affects risk of NEC (RR 1.33, 95% CI 0.31 to 5.66; RD 0.02, 95% CI −0.08 to 0.12; 1 study, 102 participants, very low-certainty evidence, Analysis 3.2).

9. Retinopathy of prematurity, any stage

No study reported this outcome.

II. Pentoxifylline for neonates with NEC

Lack of eligible randomised or quasi-randomised trials precluded comparisons of pentoxifylline for the treatment of NEC.

DISCUSSION

Summary of main results

We identified six randomised controlled trials that reported our prespecified neonatal outcomes. The included trials randomised 416 newborn infants with sepsis to pentoxifylline, placebo, or IVIG. Pentoxifylline used as an adjunct to antibiotics in neonates with sepsis may reduce all-cause mortality during hospital stay compared to placebo or no intervention (typical RR 0.57, 95% CI 0.35 to 0.93; typical RD −0.08, 95% CI −0.14 to −0.01; NNTB 13, 95% CI 7 to 100; 6 studies, 416 participants, low-certainty evidence). In subgroup analyses of all-cause mortality during hospital stay, low-certainty evidence suggests that pentoxifylline therapy may decrease neonatal deaths due to confirmed sepsis, confirmed gram-negative sepsis, in late-onset sepsis, and in preterm infants. The evidence suggests that pentoxifylline used as an adjunct to antibiotics in neonates with sepsis may decrease length of hospital stay (the estimated mean difference for the outcome was −7.74 days, 95% CI −11.72 to −3.76; 2 studies, 157 participants, low-certainty evidence). Based on one to three trials with high risk of bias, the evidence is very uncertain that pentoxifylline therapy has any effect on chronic lung disease, severe intraventricular

haemorrhage, periventricular leukomalacia, development of NEC, or retinopathy of prematurity.

The evidence is very uncertain whether pentoxifylline used as an adjunct to antibiotics compared to pentoxifylline plus IgM-enriched IVIG in neonates with sepsis affects all-cause mortality during hospital stay or development of NEC (1 study, 102 participants, very low-certainty evidence).

The evidence is very uncertain whether pentoxifylline used as an adjunct to antibiotics compared to IgM-enriched IVIG in neonates with sepsis affects all-cause mortality during hospital stay or development of NEC (1 study, 102 participants, very low-certainty evidence).

Adverse outcomes directly attributable to pentoxifylline (thrombocytopenia (platelet count less than 100 x 10^9/L), increased gastric residue (gastric aspirate greater than 10% of oral feed), vomiting, cholestatic jaundice requiring therapy) were not reported in the included trials.

Overall completeness and applicability of evidence

The six randomised controlled trials were performed in neonatal intensive care units in Poland, Egypt, Turkey, and India. Four of these studies suffered from high risk of bias, namely selection, detection, and attrition biases. However, all of the included trials evaluated neonates with sepsis, including preterm infants and infants with proven sepsis. The small sample sizes and low certainty of the evidence decrease the generalisability and applicability of the evidence.

Quality of the evidence

We rated four studies as at high risk of bias, and two studies as at low risk of bias. Using the GRADE approach, we downgraded the certainty of the evidence from six studies for the outcome all-cause mortality during hospital stay to low. Reasons for downgrading included high risk of bias in the included studies and the imprecision of the summary estimate. We also downgraded the certainty of the evidence to low for the outcome length of hospital stay, because the evidence came from only two studies, one of which had a high risk of bias. We downgraded the certainty of the evidence for the outcomes of chronic lung disease, severe intraventricular haemorrhage, periventricular leukomalacia, and retinopathy of prematurity to very low because only a few studies reported these data, and the summary estimate was imprecise with large CIs. Only one study reported the comparisons of pentoxifylline with IVIG alone or with pentoxifylline plus IVIG, and the summary estimate was imprecise.

Potential biases in the review process

We strove to decrease biases in the review process by following standard Cochrane methodology, which included a sensitive literature search without date limits; despite this, we did not identify any new studies for inclusion in this update. We did not find trials that evaluated pentoxifylline in neonates with NEC, and it is likely that any such trials were not done rather than missed by our search strategy. The included studies did not report relevant secondary outcomes. Our post hoc analysis of retinopathy of prematurity as an additional outcome did not change our conclusions. We pursued the investigators of published

randomised controlled trials for additional data and missing information with limited success.

Agreements and disagreements with other studies or reviews

Harris and colleagues reviewed the use of pentoxifylline in preterm neonates who had sepsis (two randomised controlled trials (included in this review), one quasi-randomised study (included in this review), and two observational studies) or NEC (one case series) (Harris 2010). The review authors also included cohort and observational studies and did not synthesise data into a meta-analysis. Harris and colleagues discuss a decrease in mortality similar to this review and improvement in other neonatal outcomes including lung disease and inflammatory markers. The review authors acknowledged that the included studies were small with significant methodological limitations, hence better-quality evidence is needed.

Peng 2022 conducted a meta-analysis using a random-effects model of seven studies (one observational study (Selim 2004), and the six randomised controlled trials included in our review). Peng and colleagues reported that pentoxifylline decreased length of hospital stay and metabolic acidosis but not mortality (Peng 2022).

AUTHORS' CONCLUSIONS

Implications for practice

Evidence from six small studies suggests that pentoxifylline therapy as an adjunct to antibiotics compared to placebo or no intervention in neonatal sepsis may decrease mortality (low-certainty evidence) and length of hospital stay (low-certainty evidence) without any adverse effects, but evidence is very uncertain on the development of necrotising enterocolitis (very low-certainty evidence). The evidence is very uncertain if pentoxifylline with antibiotics compared to pentoxifylline with antibiotics and immunoglobulin M-enriched intravenous immunoglobulin (IgM-enriched IVIG) or pentoxifylline with antibiotics compared to IgM-enriched IVIG with antibiotics affects mortality or development of necrotising enterocolitis (very low-certainty evidence). We encourage researchers to undertake large, well-designed multicentre trials to confirm or refute the effectiveness and safety of pentoxifylline in reducing mortality and morbidity in neonates with sepsis or necrotising enterocolitis.

Implications for research

Researchers should be encouraged to undertake adequately powered, well-designed, multicentre randomised controlled trials to confirm or refute the role of pentoxifylline in the treatment of neonatal sepsis and necrotising enterocolitis. Trials should report on clinically important comorbidities of sepsis (e.g. chronic lung disease, periventricular leukomalacia, and duration of assisted ventilation, among others) and long-term neurological outcomes. Researchers may consider comparing pentoxifylline with other adjunctive modalities that decrease inflammatory injury in the treatment of neonatal sepsis and necrotising enterocolitis.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Adel 2010

Study characteristics	
Methods	Single-centre, quasi-randomised trial where neonates with suspected sepsis were randomised to pentoxifylline if they were admitted on Tuesday or Thursday and to placebo if admitted on Monday or Wednesday
	Period of study: December 2007 and August 2008
	No concealment of allocation
	Blinding of intervention: yes
	Blinding of outcome assessment: unclear
	Completeness of follow-up: yes
Participants	Single centre, at Ain Shams University, Cairo, Egypt
	Total participants: 37
	PTX group: n = 17 (gestational age 35.94 ± 4.04 weeks, bwt 2.47 ± 0.89 kg)
	Control group: n = 20 (gestational age 36.05 ± 3.12 weeks, bwt 2.21 ± 0.59 kg)
	Neonates with suspected sepsis with maternal and clinical risk factors
	Maternal risk factors: fever ≥ 38 °C or premature rupture of membranes > 36 hours, or both
	Neonatal risk factors: elevated C-reactive protein and abnormalities of complete blood count, deterioration of respiratory and cardiac functions, feeding intolerance, abdominal distension, temperature instability, lethargy or irritability, and hepatosplenomegaly
	The intervention and placebo groups did not differ significantly in gestational age, birthweight, or Apgar scores.
Interventions	Pentoxifylline (5 mg/kg/h for 6 hours for 6 consecutive days) or placebo (equal volume of normal saline for 6 consecutive days) as an adjunct to antibiotics
Outcomes	Mortality, length of hospital stay, multi-organ dysfunction, coagulation profiles including platelet count and C-reactive protein, shock, and NEC
Notes	6 of 37 neonates with sepsis were culture-negative, and outcomes were not reported separately for this group.
	Funding sources or declarations of interest were not stated.

Adel 2010 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not clear
Allocation concealment (selection bias)	High risk	No allocation concealment due to quasi-randomisation by day of the week
Blinding (performance bias and detection bias) All outcomes	High risk	Test drug and placebo dispensed in similar syringes, but participants were quasi-randomised based on the day of admission. Hence, the efficacy of the blinding unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes for all infants reported.
Selective reporting (reporting bias)	Low risk	None noted
Other bias	Low risk	None noted

Akdag 2014

Study characteristics

Methods	Prospective, double-blind, controlled study, conducted in the neonatal intensive care unit of Zekai Tahir Burak Maternity Teaching Hospital, Ankara, Turkey
	Period of study: August 2009 to October 2010
	4-arm study comparing pentoxifylline, IgM-enriched IVIG, and both against placebo
Participants	Newborn infants with sepsis
	Exclusion criteria were major congenital abnormalities, intraventricular haemorrhage (grade 3 or 4), symptoms of a congenital infection, and inborn errors of metabolism
	Total number of participants: 204 in 4 groups
	Placebo group: (n = 51, median and range of bwt 1410 g (620 g to 4300 g), gestational age 31 (25 to 40) weeks)
	Pentoxifylline group (n = 51, median and range of bwt 1490 g (620 g to 4580 g), gestational age 31 (24 to 42) weeks)
	Pentaglobin group (n = 51, median and range of bwt 1320 g (620 g to 3860 g), gestational age 30 (24 to 41) weeks)
	Pentoxifylline + pentaglobin group (n = 51, median and range of bwt 1330 g (540 g to 4100 g), gestational age 30 (24 to 40) weeks)
	89/204 had positive blood cultures, and 13 had positive urine cultures.

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Akdag 2014 *(Continued)*

Interventions	Pentoxifylline (6 mg/kg IV over 4 hours for 3 consecutive days), pentoxifylline + IgM-enriched IVIG (pentaglobin, 250 mg/kg over 4 hours for 3 consecutive days), IgM-enriched IVIG (pentaglobin for 3 consecutive days), or placebo (normal saline for 3 consecutive days)
Outcomes	Mortality, NEC, oliguria/anuria, hepatic failure, disseminated intravascular coagulation, pulmonary haemorrhage, and lab parameters (white blood cell count, C-reactive protein, interleukin-6, TNF-α, and neutrophil CD64)
Notes	The authors state that there were no funding or conflicts of interest. Length of hospital stay was reported in days (mean), but did not have standard deviations to use in meta-analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	None reported
Allocation concealment (selection bias)	Low risk	Sealed, opaque envelopes containing the randomisation arm.
Blinding (performance bias and detection bias) All outcomes	Low risk	The infusions were covered with plastic covers, and infusion vials were identical for the different arms.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The infusions were covered with plastic covers, and infusion vials were identical for the different arms.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up reported.
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	None noted

Ali 2006

Study characteristics

Methods	Single-centre trial at Sher-i-Kashmir Institute of Medical Sciences (SKIMS), Srinagar, India
	Period of study: October 2004 to November 2005
	Randomisation details not reported.
	Concealment of allocation: unclear
	Blinding of intervention: no
	Blinding of outcome assessment: unclear
	Completeness of follow-up: yes

Ali 2006 *(Continued)*

Participants	50 premature infants with culture-proven sepsis (< 37 weeks' gestational age); 25 in PTX group and 25 in control group
	Inclusion criteria: culture-proven sepsis, gestation < 37 weeks, clinical signs of sepsis including cardio-vascular and respiratory dysfunction, and written consent
	Exclusion criteria: intraventricular haemorrhage, congenital infection, and culture negativity
	Gestational age in both the treatment and placebo groups ranged from 32 to 37 weeks.
	Birthweight ranged from 950 g to 2580 g in the treatment group, and 1000 g to 2650 g in the control group.
	42/50 of enroled infants had gram-negative sepsis.
Interventions	Pentoxifylline intravenously (5 mg/kg/h for 6 hours for 3 consecutive days) in conjunction with antibiotics or control group who received antibiotics
	First-line antibiotics were amoxicillin + clavulanic acid and amikacin
Outcomes	Mortality, development of NEC, length of hospital stay, duration of ventilation, and adverse effects (hypertension, irritability, deterioration of vital signs) were reported.
Notes	Although mean length of hospital stay and duration of ventilation were reported, standard deviations were not, and so not included in meta-analyses.
	Funding sources and declarations of interest were not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not clear
Allocation concealment (selection bias)	Unclear risk	No details of randomisation reported.
Blinding (performance bias and detection bias) All outcomes	High risk	None reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes for all participants reported.
Selective reporting (reporting bias)	Low risk	None noted
Other bias	Low risk	None noted

Lauterbach 1996

Study characteristics

Methods	Single-centre, randomised, placebo-controlled trial
	No details of randomisation given.
	Blinding of intervention: yes
	Blinding of outcome: yes
	Completeness of follow-up: no
	11/40 participants were excluded from analysis.
Participants	Neonatal Unit, Jagiellonian University Hospital, Poland
	Neonates < 36 weeks' gestation with clinically suspected sepsis after the first week of life
	Criteria for sepsis: at least 2 of the following: feed intolerance, abdominal distention, lethargy, irritability, temperature instability, hyperbilirubinaemia, hepatosplenomegaly
	Exclusions: major congenital malformation, grades III and IV intraventricular haemorrhage, and congenital infections
	Mean gestational age was 31.5 weeks in treatment group and 32.3 weeks in placebo group.
	Mean birthweight was 1.75 kg in treatment group and 1.86 kg in placebo group.
	Period of study: 1 March to 30 July 1994
	Total participants: 40; 20 in each group
	Only infants with positive blood culture were analysed. Treatment group 16/20 (4 negative culture), placebo group 13/20 (7 negative culture).
Interventions	Pentoxifylline (Trental; Boehring-Hoscht) 5 mg/kg/h for 6 hours, repeated on 2nd and 3rd day (n = 20)
	Placebo: equal volume of normal saline for 6 hours, repeated on 2nd and 3rd day (n = 20)
	Amoxicillin + clavulanate (Augmentin) and amikacin were used as first-line antibiotics in both groups. All enroled neonates received a single dose of immunoglobulin intravenously on the first day of therapy.
Outcomes	Reported outcomes were:
	1. mortality;
	2. plasma TNF-α levels before the first infusion and after the third infusion of the drug or placebo;
	3. NEC;
	4. adverse reactions to the drug.
Notes	Funded by the Polish State Committee for Research (grant nos 4 P05E03408 and 0070/S4)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not known
Allocation concealment (selection bias)	Unclear risk	Unclear.

Lauterbach 1996 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding of intervention - yes.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Yes.
Incomplete outcome data (attrition bias) All outcomes	High risk	11/40 participants were excluded from analyses.
Selective reporting (reporting bias)	Unclear risk	Not clear
Other bias	Unclear risk	Not clear

Lauterbach 1999

Study characteristics	
Methods	2-centre study: Neonatal Unit, Medical College Jagiellonian, University of Kraków, Poland and Intensive Therapy Unit at Polish Mother Memorial Hospital, Lodz, Poland
	Randomised, placebo-controlled study
	Concealment of randomisation: yes
	Blinding of intervention: yes
	Blinding of outcome assessment: unclear
	Completeness of follow-up: no
	22/100 were excluded.
Participants	Preterm infants < 36 weeks of gestation, after first week of life with suspected sepsis
	Criteria for sepsis: at least 3 of the following: feeding intolerance, abdominal distention, temperature instability, disordered peripheral circulation (as described by paleness, peripheral cyanosis, mottled skin, and capillary refill time > 3 seconds), lethargy, irritability, and hepatosplenomegaly
	Positive blood culture required for confirmation of sepsis.
	Period of study: 1 January 1995 to 30 July 1996
	Exclusions: congenital malformations, congenital infections, and grades III and IV intraventricular haemorrhage
	Total recruitment: 100
	10/50 from the treatment group and 12/50 from placebo group excluded as sepsis was not confirmed.
Interventions	Pentoxifylline (Pentilin; KRKA Slovenia) 5 mg/kg/h for 6 hours for 6 successive days (n = 50)
	Placebo: equal volume of normal saline for 6 hours for 6 successive days (n = 50)
	First-line antibiotics were amoxicillin + clavulanate (Augmentin) and amikacin and were comparable between groups.

Lauterbach 1999 *(Continued)*

Outcomes	Reported outcomes were: 1. mortality; 2. incidence and mortality of gram-negative sepsis; 3. plasma TNF-α, interleukin-1, and interleukin-6 levels before and after the 1st and 3rd dose and before and after the 6th dose; 4. NEC; 5. adverse effects.
Notes	Funding sources and declarations of interest were not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Adequate.The code was held by the representative of Pharmaceutical Inc.-KR-KA-Slovenia
Blinding (performance bias and detection bias) All outcomes	Low risk	Adequate.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear.
Incomplete outcome data (attrition bias) All outcomes	High risk	22/100 were excluded.
Selective reporting (reporting bias)	Unclear risk	Not clear
Other bias	Unclear risk	Not clear

Shabaan 2015

Study characteristics

Methods	Double-blind randomised controlled trial Neonatal Intensive Care Unit of Mansoura University Children's Hospital, Mansoura, Egypt Period of study: June 2011 to May 2013
Participants	120 preterm infants were enroled in the trial. 60 in the PTX group with a mean ± SD of bwt (grams) 1404 ± 417; gestational age (weeks) 30.2 ± 2.5 60 in the placebo arm with a mean ± SD of bwt (grams) 1370 ± 471; gestational age (weeks) 30.1 ± 2.2 Inclusion criteria: appropriate for gestational age, preterm infants with suspected or confirmed LOS (sepsis recognised after 72 hours from birth)

Shabaan 2015 *(Continued)*

	Exclusion criteria: preterm infants with major congenital malformations, chromosomal anomalies, inborn errors of metabolism, and clinical or laboratory evidence of a congenital infection
Interventions	Intravenous pentoxifylline 5 mg/kg/h for 6 hours on 6 successive days or normal saline (placebo) same volume over 6 hours on 6 successive days
	First-line antibiotics were ampicillin/sulbactam and gentamicin and were comparable between groups.
Outcomes	The primary outcome was death before hospital discharge.
	Secondary outcomes were length of hospital stay, duration of respiratory support, duration of antibiotics use, short-term morbidity (chronic lung disease, NEC, severe intraventricular haemorrhage, periventricular leukomalacia, retinopathy of prematurity), TNF-α concentrations, C-reactive protein levels, and adverse effects of pentoxifylline.
Notes	Published article in 2015. Abstract was in 2014.
	Funding sources and declarations of interest were not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation by computer-generated numbers.
Allocation concealment (selection bias)	Low risk	Randomisation by computer-generated numbers and the randomisation code was held by the representative nurse practitioner assigned for drugs preparation.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind controlled trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind controlled trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up.
Selective reporting (reporting bias)	Low risk	None noted
Other bias	Low risk	None noted

bwt: birthweight; IgM: immunoglobulin M; IV: intravenous; IVIG: intravenous immunoglobulin; LOS: late-onset sepsis; NEC: necrotising enterocolitis; PTX: pentoxifylline; SD: standard deviation; TNF-α: tumour necrosis factor alpha

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Hamilcikan 2017a	Not a randomised or quasi-randomised trial

Study	Reason for exclusion
Hamilcikan 2017b	Not a randomised or quasi-randomised trial
Lauterbach 1994	Not a randomised or quasi-randomised trial
Selim 2004	Not a randomised or quasi-randomised trial

Characteristics of studies awaiting classification [ordered by study ID]

Sareno 2013

Methods	Randomised controlled trial where participants were randomised to receive either pentoxifylline at a dose of 6 mg/kg/h or placebo
Participants	Preterm infants ≤ 1500 g with suspected infection admitted to the neonatal intensive care unit. Infants with major congenital malformations, congenital infections, and severe haemorrhage were excluded from the study.
Interventions	Pentoxifylline at a dose of 6 mg/kg/h or placebo. Pentoxifylline was administered as a 6 mL infusion for 6 hours for 6 days. The control group received normal saline in the same manner as the pentoxifylline infusion. Infants, parents, and physicians (outcome assessors) were blinded to the treatment assignments.
Outcomes	The primary outcome measured in the study was the occurrence of all-cause mortality between groups. Secondary outcomes measured include mortality from sepsis, adverse drug reactions, and length of hospital stay. The primary outcome was analysed on an intention-to-treat basis.
Notes	Published as an abstract. We contacted the author for more details, but as of yet have received no response.

Characteristics of ongoing studies [ordered by study ID]

ACTRN12606000257561

Study name	Safety and efficacy of pentoxifylline as a treatment for preventing the progression of NEC in preterm neonates
Methods	Randomised, placebo-controlled trial
Participants	Premature neonates < 32 weeks' gestation with stage 2 or 3 NEC
Interventions	Pentoxifylline at 5 mg/kg/h for 12 hours for 2 days followed by infusion for 6 hours a day for the next 4 days OR equal volume of placebo in controls
Outcomes	Primary: efficacy and safety of pentoxifylline in preventing the progression of NEC or death, or both Secondary: reduction in plasma tumour necrosis factor alpha levels, extent of bowel resection at surgery, duration of hospital stay and total parenteral nutrition support, and duration to full enteral feeds
Starting date	Late 2014

ACTRN12606000257561 *(Continued)*

Contact information	Sanjay Patole, email: Sanjay.Patole@health.wa.gov.au
Notes	This trial has not recruited any patients till data (as of March 2023).

ACTRN12616000405415

Study name	Can pentoxifylline improve long-term outcomes in preterm infants with late-onset sepsis or necrotising enterocolitis? A pragmatic, randomised, placebo-controlled trial
Methods	Randomised controlled trial
Participants	Preterm infants born at < 29 weeks' gestation
Interventions	Ideally within 6 hours (no later than 12 hours) of onset of suspected LOS or NEC, patient will receive pentoxifylline intravenous infusion 1 mL/kg/h for 12 hours/day (60 mg/kg/day) for 2 days. If the diagnosis of NEC or sepsis diagnosis is confirmed, this will be followed by 1 mL/kg/h for 6 hours/day (30 mg/kg/day) on days 3 to 6. If the diagnosis of NEC or LOS is not confirmed, the intervention will be discontinued at that time. Placebo is normal saline. Within 6 hours of onset of suspected LOS or NEC, patient will receive normal saline (NaCl 0.9%) intravenous infusion 1 mL/kg/h for 12 hours/day for 2 days. If the diagnosis of NEC or sepsis diagnosis is confirmed, this will be followed by 1 mL/kg/h for 6 hours/day (30 mg/kg/day) on days 3 to 6. If the diagnosis of NEC or LOS is not confirmed, the intervention will be discontinued at that time.
Outcomes	The primary outcome is survival without any disability at 24 months (corrected for gestation) in infants treated with intravenous pentoxifylline or placebo for LOS or NEC. Secondary outcomes are survival until discharge home and at 24 months (+/− 6 months), any disability at 24 months (+/− 6 months), disability by different grades and types will be assessed based on the BSID III and/or ASQ score and/or short health questionnaire administered to access cerebral palsy, deafness and blindness, composite secondary outcome looking at i) surgery for proven NEC and ii) progression of NEC stage II to stage IIIA/B as per Modified Bell's Staging Criteria for NEC, duration of parenteral nutrition, brain injury is defined as grade 3 and 4 intraventricular haemorrhage (on either side of the head), duration of mechanical ventilation in days, chronic lung disease, severe retinopathy of prematurity, length of hospital stay, plasma cytokine levels, magnetic resonance imaging at 38 to 42 weeks' corrected gestational age, and time to full enteral feeds.
Starting date	2016
Contact information	Prof Karen Simmer AO, email: karen.simmer@health.wa.gov.au
Notes	Currently recruiting, 597 of 1800 already recruited

ASQ: Ages & Stages Questionnaires; BSID: Bayley Scales of Infant Development; LOS: length of stay; NEC: necrotising enterocolitis

DATA AND ANALYSES

Comparison 1. Pentoxifylline with antibiotics (any dose or duration) compared to placebo or no intervention for the treatment of neonatal sepsis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 All-cause mortality during hospital stay	6	1240	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.32, 0.57]
1.1.1 All neonates	6	416	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.35, 0.93]
1.1.2 Preterm neonates	4	277	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.20, 0.71]
1.1.3 Late-onset sepsis	3	169	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.19, 0.95]
1.1.4 Confirmed sepsis	4	235	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.19, 0.73]
1.1.5 Neonates with confirmed gram negative sepsis	4	143	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.16, 0.72]
1.2 Chronic lung disease	1	120	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [0.45, 5.05]
1.3 Severe intraventricular haemorrhage (grade 3 and 4)	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.28, 2.03]
1.4 Periventricular leukomalacia	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.10, 2.63]
1.5 Length of hospital stay	2	157	Mean Difference (IV, Fixed, 95% CI)	-7.74 [-11.72, -3.76]
1.6 Necrotising enterocolitis, any Bell stage	6	405	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.29, 1.06]
1.7 Retinopathy of prematurity, any stage	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.08, 1.98]

Analysis 1.1. Comparison 1: Pentoxifylline with antibiotics (any dose or duration) compared to placebo or no intervention for the treatment of neonatal sepsis, Outcome 1: All-cause mortality during hospital stay

Study or Subgroup	Pentoxifylline Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
1.1.1 All neonates							
Adel 2010	4	17	5	20	3.5%	0.94 [0.30 , 2.96]	
Akdag 2014	5	51	2	51	1.5%	2.50 [0.51 , 12.30]	
Ali 2006	4	25	10	25	7.6%	0.40 [0.14 , 1.11]	
Lauterbach 1996	0	16	3	13	2.9%	0.12 [0.01 , 2.09]	
Lauterbach 1999	1	40	6	38	4.7%	0.16 [0.02 , 1.25]	
Shabaan 2015	6	60	10	60	7.6%	0.60 [0.23 , 1.55]	
Subtotal (95% CI)		**209**		**207**	**28.0%**	**0.57 [0.35 , 0.93]**	
Total events:	20		36				
Heterogeneity: Chi² = 7.15, df = 5 (P = 0.21); I² = 30%							
Test for overall effect: Z = 2.24 (P = 0.03)							
1.1.2 Preterm neonates							
Ali 2006	4	25	10	25	7.6%	0.40 [0.14 , 1.11]	
Lauterbach 1996	0	16	3	13	2.9%	0.12 [0.01 , 2.09]	
Lauterbach 1999	1	40	6	38	4.7%	0.16 [0.02 , 1.25]	
Shabaan 2015	6	60	10	60	7.6%	0.60 [0.23 , 1.55]	
Subtotal (95% CI)		**141**		**136**	**22.9%**	**0.38 [0.20 , 0.71]**	
Total events:	11		29				
Heterogeneity: Chi² = 2.22, df = 3 (P = 0.53); I² = 0%							
Test for overall effect: Z = 3.01 (P = 0.003)							
1.1.3 Late-onset sepsis							
Lauterbach 1996	0	10	3	10	2.7%	0.14 [0.01 , 2.45]	
Lauterbach 1999	1	15	4	14	3.2%	0.23 [0.03 , 1.84]	
Shabaan 2015	6	60	10	60	7.6%	0.60 [0.23 , 1.55]	
Subtotal (95% CI)		**85**		**84**	**13.5%**	**0.42 [0.19 , 0.95]**	
Total events:	7		17				
Heterogeneity: Chi² = 1.40, df = 2 (P = 0.50); I² = 0%							
Test for overall effect: Z = 2.10 (P = 0.04)							
1.1.4 Confirmed sepsis							
Ali 2006	4	25	10	25	7.6%	0.40 [0.14 , 1.11]	
Lauterbach 1996	0	16	3	13	2.9%	0.12 [0.01 , 2.09]	
Lauterbach 1999	1	40	6	38	4.7%	0.16 [0.02 , 1.25]	
Shabaan 2015	4	38	6	40	4.5%	0.70 [0.21 , 2.29]	
Subtotal (95% CI)		**119**		**116**	**19.8%**	**0.37 [0.19 , 0.73]**	
Total events:	9		25				
Heterogeneity: Chi² = 2.40, df = 3 (P = 0.49); I² = 0%							
Test for overall effect: Z = 2.86 (P = 0.004)							
1.1.5 Neonates with confirmed gram negative sepsis							
Ali 2006	4	23	10	19	8.4%	0.33 [0.12 , 0.89]	
Lauterbach 1996	0	10	3	10	2.7%	0.14 [0.01 , 2.45]	
Lauterbach 1999	1	15	4	14	3.2%	0.23 [0.03 , 1.84]	
Shabaan 2015	2	28	2	24	1.6%	0.86 [0.13 , 5.63]	
Subtotal (95% CI)		**76**		**67**	**15.9%**	**0.33 [0.16 , 0.72]**	
Total events:	7		19				
Heterogeneity: Chi² = 1.42, df = 3 (P = 0.70); I² = 0%							
Test for overall effect: Z = 2.81 (P = 0.005)							

Analysis 1.1. (Continued)

Test for overall effect: Z = 2.81 (P = 0.005)

Total (95% CI)		**630**	**610**	**100.0%**	**0.43 [0.32 , 0.57]**	
Total events:		54	126			

Heterogeneity: Chi² = 16.28, df = 20 (P = 0.70); I² = 0%

Test for overall effect: Z = 5.77 (P < 0.00001)

Test for subgroup differences: Chi² = 1.95, df = 4 (P = 0.74), I² = 0%

```
0.01    0.1      1      10    100
Favours Pentoxifylline   Favours placebo
```

Analysis 1.2. Comparison 1: Pentoxifylline with antibiotics (any dose or duration) compared to placebo or no intervention for the treatment of neonatal sepsis, Outcome 2: Chronic lung disease

Study or Subgroup	Pentoxifylline Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Shabaan 2015	6	60	4	60	100.0%	1.50 [0.45 , 5.05]	
Total (95% CI)		**60**		**60**	**100.0%**	**1.50 [0.45 , 5.05]**	
Total events:	6		4				

Heterogeneity: Not applicable

Test for overall effect: Z = 0.65 (P = 0.51)

Test for subgroup differences: Not applicable

```
0.01    0.1      1      10    100
Favours Pentoxifylline   Favours placebo
```
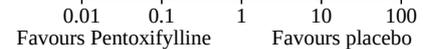
Analysis 1.3. Comparison 1: Pentoxifylline with antibiotics (any dose or duration) compared to placebo or no intervention for the treatment of neonatal sepsis, Outcome 3: Severe intraventricular haemorrhage (grade 3 and 4)

Study or Subgroup	Pentoxifylline Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Shabaan 2015	6	60	8	60	100.0%	0.75 [0.28 , 2.03]	
Total (95% CI)		**60**		**60**	**100.0%**	**0.75 [0.28 , 2.03]**	
Total events:	6		8				

Heterogeneity: Not applicable

Test for overall effect: Z = 0.57 (P = 0.57)

Test for subgroup differences: Not applicable

```
0.01    0.1      1      10    100
Favours Pentoxifylline   Favours placebo
```

Analysis 1.4. Comparison 1: Pentoxifylline with antibiotics (any dose or duration) compared to placebo or no intervention for the treatment of neonatal sepsis, Outcome 4: Periventricular leukomalacia

Study or Subgroup	Pentoxifylline Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Shabaan 2015	2	60	4	60	100.0%	0.50 [0.10 , 2.63]	
Total (95% CI)		**60**		**60**	**100.0%**	**0.50 [0.10 , 2.63]**	
Total events:	2		4				

Heterogeneity: Not applicable

Test for overall effect: Z = 0.82 (P = 0.41)

Test for subgroup differences: Not applicable

```
0.01    0.1      1      10    100
Favours Pentoxifylline   Favours placebo
```

Analysis 1.5. Comparison 1: Pentoxifylline with antibiotics (any dose or duration) compared to placebo or no intervention for the treatment of neonatal sepsis, Outcome 5: Length of hospital stay

Study or Subgroup	Pentoxifylline Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
Adel 2010	22.6	13.2	17	33.8	16.2	20	17.6%	-11.20 [-20.68 , -1.72]	
Shabaan 2015	31.3	12.2	60	38.3	12.3	60	82.4%	-7.00 [-11.38 , -2.62]	
Total (95% CI)			**77**			**80**	**100.0%**	**-7.74 [-11.72 , -3.76]**	

Heterogeneity: Chi² = 0.62, df = 1 (P = 0.43); I² = 0%
Test for overall effect: Z = 3.81 (P = 0.0001)
Test for subgroup differences: Not applicable

-20 -10 0 10 20
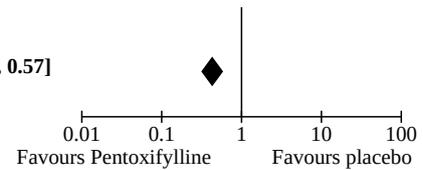Favours Pentoxifylline   Favours placebo

Analysis 1.6. Comparison 1: Pentoxifylline with antibiotics (any dose or duration) compared to placebo or no intervention for the treatment of neonatal sepsis, Outcome 6: Necrotising enterocolitis, any Bell stage

Study or Subgroup	Pentoxifylline Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Adel 2010	2	17	1	20	3.9%	2.35 [0.23 , 23.75]	
Akdag 2014	4	51	2	51	8.5%	2.00 [0.38 , 10.44]	
Ali 2006	2	25	7	25	29.9%	0.29 [0.07 , 1.24]	
Lauterbach 1996	1	16	1	16	4.3%	1.00 [0.07 , 14.64]	
Lauterbach 1999	2	34	8	30	36.3%	0.22 [0.05 , 0.96]	
Shabaan 2015	2	60	4	60	17.1%	0.50 [0.10 , 2.63]	
Total (95% CI)		**203**		**202**	**100.0%**	**0.56 [0.29 , 1.06]**	
Total events:	13		23				

Heterogeneity: Chi² = 6.31, df = 5 (P = 0.28); I² = 21%
Test for overall effect: Z = 1.78 (P = 0.07)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
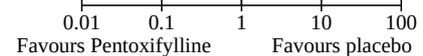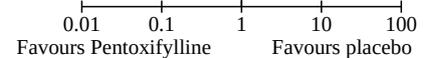Favours Pentoxifylline   Favours placebo

Analysis 1.7. Comparison 1: Pentoxifylline with antibiotics (any dose or duration) compared to placebo or no intervention for the treatment of neonatal sepsis, Outcome 7: Retinopathy of prematurity, any stage

Study or Subgroup	Pentoxifylline Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Shabaan 2015	2	60	5	60	100.0%	0.40 [0.08 , 1.98]	
Total (95% CI)		**60**		**60**	**100.0%**	**0.40 [0.08 , 1.98]**	
Total events:	2		5				

Heterogeneity: Not applicable
Test for overall effect: Z = 1.12 (P = 0.26)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Favours Pentoxifylline   Favours placebo

Comparison 2. Pentoxifylline with antibiotics (any dose or duration) compared to pentoxifylline with antibiotics and adjunct treatments such as IgM-enriched IVIG

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
2.1 All-cause mortality	1	102	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.24, 2.10]
2.2 Necrotising enterocolitis, any Bell stage	1	102	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.31, 5.66]

Analysis 2.1. Comparison 2: Pentoxifylline with antibiotics (any dose or duration) compared to pentoxifylline with antibiotics and adjunct treatments such as IgM-enriched IVIG, Outcome 1: All-cause mortality

Study or Subgroup	Pentoxifylline Events	Pentoxifylline Total	Pentoxifylline + IVIG Events	Pentoxifylline + IVIG Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Akdag 2014	5	51	7	51	100.0%	0.71 [0.24 , 2.10]	
Total (95% CI)		**51**		**51**	**100.0%**	**0.71 [0.24 , 2.10]**	
Total events:	5		7				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.61 (P = 0.54)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
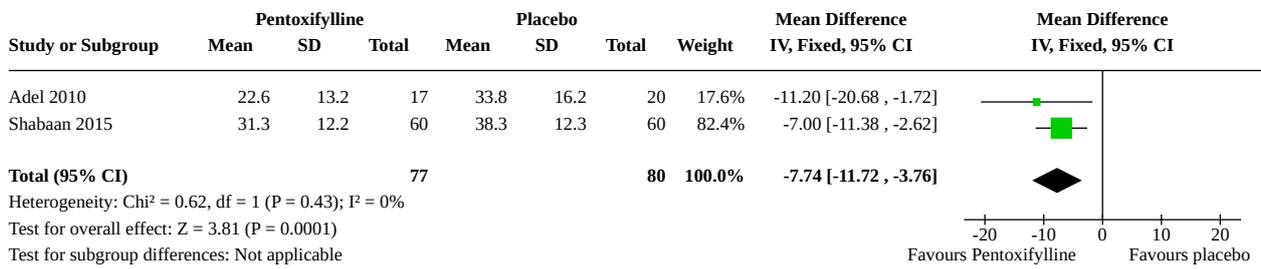Favours Pentoxifylline   Favours Pentoxifylline + IVIG

Analysis 2.2. Comparison 2: Pentoxifylline with antibiotics (any dose or duration) compared to pentoxifylline with antibiotics and adjunct treatments such as IgM-enriched IVIG, Outcome 2: Necrotising enterocolitis, any Bell stage
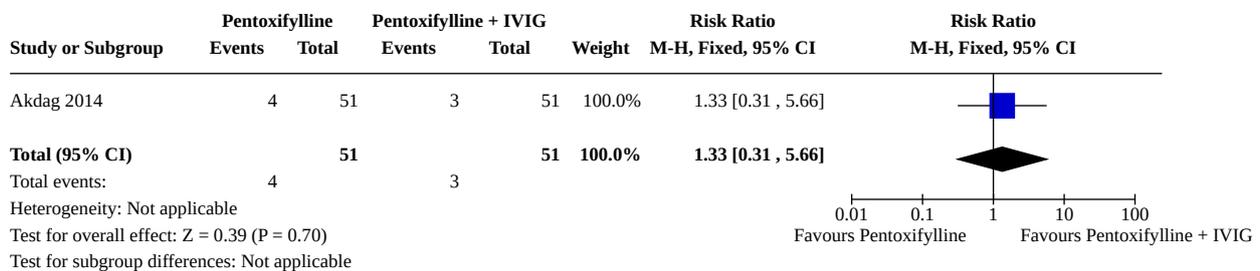
Study or Subgroup	Pentoxifylline Events	Pentoxifylline Total	Pentoxifylline + IVIG Events	Pentoxifylline + IVIG Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Akdag 2014	4	51	3	51	100.0%	1.33 [0.31 , 5.66]	
Total (95% CI)		**51**		**51**	**100.0%**	**1.33 [0.31 , 5.66]**	
Total events:	4		3				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.39 (P = 0.70)
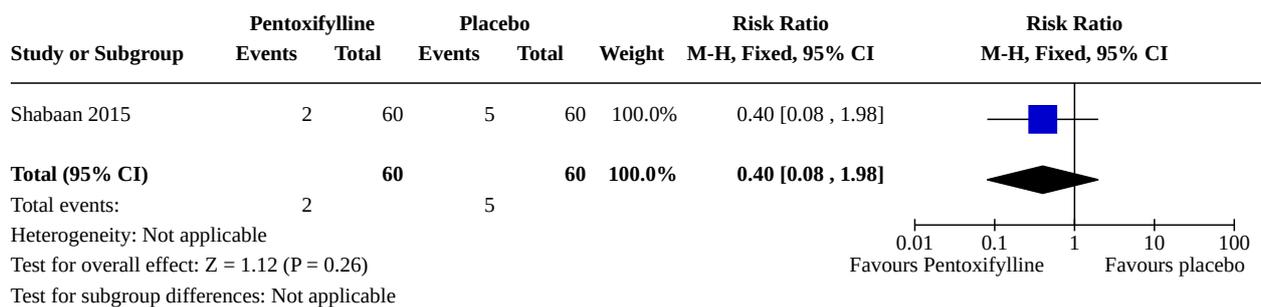Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Favours Pentoxifylline   Favours Pentoxifylline + IVIG

Comparison 3. Pentoxifylline with antibiotics (any dose or duration) compared to adjunct treatments such as IgM-enriched IVIG with antibiotics

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
3.1 All-cause mortality	1	102	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.36, 4.39]
3.2 Necrotising enterocolitis, any Bell stage	1	102	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.31, 5.66]

Analysis 3.1. Comparison 3: Pentoxifylline with antibiotics (any dose or duration) compared to adjunct treatments such as IgM-enriched IVIG with antibiotics, Outcome 1: All-cause mortality

Study or Subgroup	Pentoxifylline Events	Total	IVIG Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Akdag 2014	5	51	4	51	100.0%	1.25 [0.36 , 4.39]	
Total (95% CI)		51		51	100.0%	**1.25 [0.36 , 4.39]**	
Total events:	5		4				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.35 (P = 0.73)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Favours Pentoxifylline   Favours IVIG
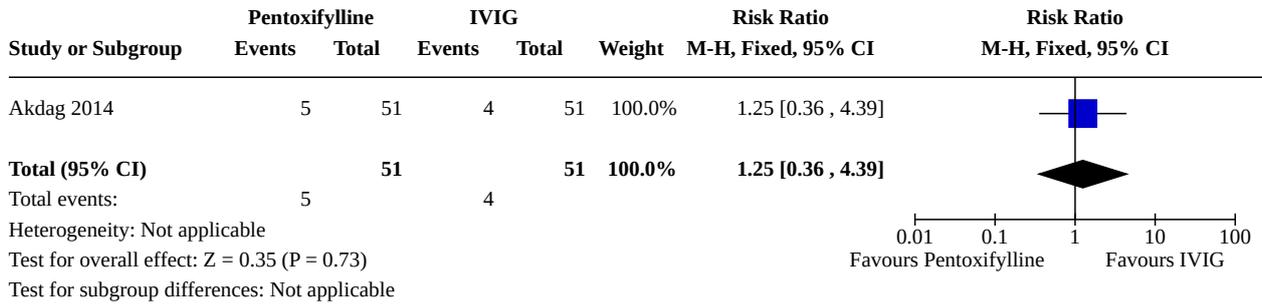
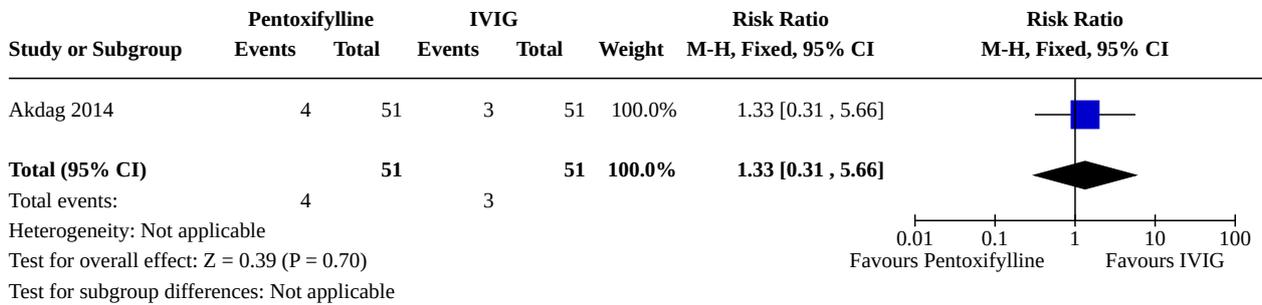### Analysis 3.2. Comparison 3: Pentoxifylline with antibiotics (any dose or duration) compared to adjunct treatments such as IgM-enriched IVIG with antibiotics, Outcome 2: Necrotising enterocolitis, any Bell stage

Study or Subgroup	Pentoxifylline Events	Total	IVIG Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Akdag 2014	4	51	3	51	100.0%	1.33 [0.31 , 5.66]	
Total (95% CI)		51		51	100.0%	**1.33 [0.31 , 5.66]**	
Total events:	4		3				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.39 (P = 0.70)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Favours Pentoxifylline   Favours IVIG

APPENDICES

Appendix 1. Cochrane CRS strategy

	Cochrane CRS	
	31-Jul-22	
1	MESH DESCRIPTOR Pentoxifylline AND CENTRAL:TARGET	3094
2	(agapurin or artal or azupentat or azutrenat or bl 191 or bl191 or c-vex or carpental or cental or ceretal or claudicat retard or "eht 0201" or eht0201 or elorgan or erytral or fixoten or flexital or harin or harine or hemovas or ikomio or ipentol or kentadin or oxopurin 400 sr or oxpentifylline or oxpentiphylline or oxypentifylline or penphylline or pentong or pentopak or pentox* or pentyllin or perencal or perental or peridane or pexal or pexol or platof or ralofect or ralofekt or relofekt or rentylin or tarontal or thrental or torental or torestal or trenfyl or trenlin or trental or trepal-400 or vazofen):ti,ab,kw AND CENTRAL:TARGET	1400
3	#1 OR #2	3917
4	MESH DESCRIPTOR Phosphodiesterase Inhibitors EXPLODE ALL AND CENTRAL:TARGET	7724

(Continued)

5	(Phosphodiesteras* adj2 Inhibit*):ti,ab,kw AND CENTRAL:TARGET	1967
6	#5 OR #4	8922
7	MESH DESCRIPTOR enterocolitis EXPLODE ALL AND CENTRAL:TARGET	473
8	MESH DESCRIPTOR sepsis EXPLODE ALL AND CENTRAL:TARGET	5041
9	(sepsis* or septic* or Pyemia* or Pyohemi* or Pyaemi* or ((blood* or blood-stream*) adj2 (infect* or poison*))):ti,ab,kw AND CENTRAL:TARGET	14931
10	#9 OR #8 OR #7	17148
11	MESH DESCRIPTOR Infant, Newborn EXPLODE ALL AND CENTRAL:TARGET	17912
12	MESH DESCRIPTOR Intensive Care, Neonatal EXPLODE ALL AND CENTRAL:TARGET	363
13	MESH DESCRIPTOR Intensive Care Units, Neonatal EXPLODE ALL AND CENTRAL:TARGET	903
14	MESH DESCRIPTOR Gestational Age EXPLODE ALL AND CENTRAL:TARGET	2928
15	(babe or babes or baby* or babies or gestational age? or infant? or infantile or infancy or low birth weight or low birthweight or neonat* or neo-nat* or newborn* or new born? or newly born or premature or pre-mature or pre-matures or prematures or prematurity or pre-maturity or preterm or preterms or pre term? or preemie or preemies or premies or premie or VLBW or VLBWI or VLBW-I or VLBWs or LBW or LBWI or LBWs or ELBW or ELBWI or ELBWs or NICU or NICUs):ti,ab,kw AND CENTRAL:TARGET	77904
16	#11 OR #12 OR #13 OR #14 OR #15	81312
17	#3 AND #16	103
18	#6 AND #10 AND #16	17
19	#18 OR #17	108

Appendix 2. MEDLINE strategy

	Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions 1946 to July 29, 2022	
#	Searches	Results
1	pentoxifylline/ [MeSH/EMTREE]	4320
2	(agapurin or artal or azupentat or azutrenat or bl 191 or bl191 or c-vex or car-pental or cental or ceretal or claudicat retard or "eht 0201" or eht0201 or elor-gan or erytral or fixoten or flexital or harin or harine or hemovas or ikomio or ipentol or kentadin or oxopurin 400 sr or oxpentifylline or oxpentiphylline or	7236

	oxypentifylline or penphylline or pentong or pentopak or pentox* or pentyllin or perencal or perental or peridane or pexal or pexol or platof or ralofect or ralofekt or relofekt or rentylin or tarontal or thrental or torental or torestal or trenfyl or trenlin or trental or trepal-400 or vazofen).ti,ab,kw,kf.	
3	or/1-2 [Pentoxifylline]	7879
4	exp Phosphodiesterase Inhibitors/	88829
5	(Phosphodiesteras* adj2 Inhibit*).ti,ab,kw,kf.	13372
6	or/4-5 [Drug category]	93687
7	exp sepsis/	136863
8	exp enterocolitis/ [includes necrotising]	14504
9	(sepsis* or septic* or Pyemia* or Pyohemi* or Pyaemi* or ((blood* or blood-stream*) adj2 (infect* or poison*))).ti,ab,kw,kf.	197502
10	(enterocoliti* or colienteriti* or NEC).ti,ab,kw,kf.	22328
11	or/7-10 [NEC or Sepsis]	285286
12	exp Infant, Newborn/ or Intensive Care, Neonatal/ or Intensive Care Units, Neonatal/ or Gestational Age/	707018
13	(babe or babes or baby* or babies or gestational age? or infant? or infantile or infancy or low birth weight or low birthweight or neonat* or neo-nat* or newborn* or new born? or newly born or premature or pre-mature or pre-matures or prematures or prematurity or pre-maturity or preterm or preterms or pre term? or preemie or preemies or premies or premie or VLBW or VLBWI or VLBW-I or VLBWs or LBW or LBWI or LBWs or ELBW or ELBWI or ELBWs or NICU or NICUs).ti,ab,kw,kf.	1004443
14	or/12-13 [Filter: Neonatal Population 04-2022-MEDLINE]	1313879
15	randomized controlled trial.pt.	574087
16	controlled clinical trial.pt.	94966
17	randomized.ti,ab.	619035
18	placebo.ti,ab.	236764
19	drug therapy.fs.	2516603
20	randomly.ti,ab.	389079
21	trial.ti,ab.	709192
22	groups.ti,ab.	2415024
23	or/15-22 [Cochrane HSSS-SM Filter; Box 6.4.a Cochrane Handbook]	5488787
24	(quasirandom* or quasi-random* or randomi* or randomly).ti,ab,kw,kf.	1058014

(Continued)

25	(control* adj2 (group? or random* or trial? or study)).ti,ab,kw,kf.	1053768
26	or/24-25 [Additional terms to increase sensitivity]	1636420
27	exp animals/ not humans/	5033285
28	(or/23,26) not 27 [RCT Filter: Medline]	5031488
29	meta-analysis/ or "systematic review"/ or network meta-analysis/ [/ finds same as.pt. syntax]	281523
30	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf,kw.	278904
31	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf,kw.	35286
32	(data synthes* or data extraction* or data abstraction*).ti,ab,kf,kw.	36171
33	(hand search* or handsearch*).ti,ab,kf,kw.	10608
34	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf,kw.	32709
35	meta-analysis as topic/ or network meta-analysis/	25398
36	(meta analy* or metanaly* or meta regression* or metaregression*).ti,ab,kf,kw.	243644
37	(medline or cochrane or pubmed or medlars or embase or cinahl).ab.	297414
38	(cochrane or systematic review?).jw.	19418
39	or/29-38 [SR filter-Medline; based on CADTH https://searchfilters.cadth.ca]	562706
40	3 and 14 [Pentoxifylline AND Neonatal Terms]	197
41	6 and 11 and 14 [Drug Cateory AND NEC/Sepsis AND Neonatal Terms]	118
42	or/40-41 [Results before filters]	270
43	42 and 28 [RCT Results]	130
44	42 and 39 and 202*.yr. [Systematic reviews 2020 forward]	1
45	or/43-44 [All Results]	130

Appendix 3. Embase strategy

	Embase 1974 to 2022 July 29	
#	Searches	Results

1	pentoxifylline/ [MeSH/EMTREE]	14466
2	(agapurin or artal or azupentat or azutrenat or bl 191 or bl191 or c-vex or car-pental or cental or ceretal or claudicat retard or "eht 0201" or eht0201 or elor-gan or erytral or fixoten or flexital or harin or harine or hemovas or ikomio or ipentol or kentadin or oxopurin 400 sr or oxpentifylline or oxpentiphylline or oxypentifylline or penphylline or pentong or pentopak or pentox* or pentyllin or perencal or perental or peridane or pexal or pexol or platof or ralofect or ralofekt or relofekt or rentylin or tarontal or thrental or torental or torestal or trenfyl or trenlin or trental or trepal-400 or vazofen).ti,ab,kw,kf,du,dy,tn.	18581
3	or/1-2 [Pentox]	18581
4	exp phosphodiesterase inhibitor/ [EMTREE]	190909
5	(Phosphodiesteras* adj2 Inhibit*).ti,ab,kw,kf.	17888
6	or/4-5 [Drug Category]	194223
7	enterocolitis/ or necrotizing enterocolitis/	20263
8	exp sepsis/	309684
9	(sepsis* or septic* or Pyemia* or Pyohemi* or Pyaemi* or ((blood* or blood-stream*) adj2 (infect* or poison*))).ti,ab,kw,kf.	287232
10	(enterocoliti* or colienteriti* or NEC).ti,ab,kw,kf.	29444
11	or/7-10 [NEC or Sepsis]	444609
12	newborn/ or prematurity/ or newborn intensive care/ or newborn care/ or ges-tational age/	751844
13	(babe or babes or baby* or babies or gestational age? or infant? or infantile or infancy or low birth weight or low birthweight or neonat* or neo-nat* or newborn* or new born? or newly born or premature or pre-mature or pre-ma-tures or prematures or prematurity or pre-maturity or preterm or preterms or pre term? or preemie or preemies or premies or premie or VLBW or VLBWI or VLBW-I or VLBWs or LBW or LBWI or LBWs or ELBW or ELBWI or ELBWs or NICU or NICUs).ti,ab,kw,kf.	1184279
14	or/12-13 [Filter: Neonatal Population 03-2022-OVID EMBASE]	1443014
15	Randomized controlled trial/ or Controlled clinical study/	910289
16	random$.ti,ab,kw.	1820756
17	Randomization/	94488
18	placebo.ti,ab,kw.	344497
19	((double or single or doubly or singly) adj (blind or blinded or blind-ly)).ti,ab,kw.	258905
20	double blind procedure/	197173
21	(controlled adj7 (study or design or trial)).ti,ab,kw.	414061

(Continued)

22	parallel group$1.ti,ab.	29761
23	(crossover or cross over).ti,ab.	117344
24	((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.	384521
25	(open adj label).ti,ab.	98477
26	(quasirandom* or quasi-random* or randomi* or randomly).ti,ab,kw,kf.	1485045
27	(control* adj2 (group? or random*)).ti,ab,kw,kf.	1209091
28	or/15-27 [Terms based on Cochrane Central strategy- How Central is Created]	3113755
29	(exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/) and (human/ or normal human/ or human cell/)	23905129
30	exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/	30852508
31	30 not 29 [Animal Exclusion-https://community-cochrane-org.ezproxy.uvm.e-du/sites/default/files/uploads/inline-files/Embase%20animal%20filter.pdf]	6947379
32	28 not 31 [Filter: RCT-EMBASE]	2676548
33	meta-analysis/ or "systematic review"/ or "meta analysis (topic)"/ [EMTREE]	518355
34	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kw.	337771
35	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kw.	49513
36	(data synthes* or data extraction* or data abstraction*).ti,ab,kw.	44044
37	(hand search* or handsearch*).ti,ab,kw.	12873
38	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kw.	43117
39	(meta analy* or metanaly* or meta regression* or metaregression*).ti,ab,kw.	310131
40	(medline or cochrane or pubmed or medlars or embase or cinahl).ab.	373572
41	(cochrane or systematic review?).jn,jx.	30454
42	(overview adj2 reviews).ti.	118
43	or/33-42 [SR Filter: EMBASE based on CADTH filter: https://searchfilter-s.cadth.ca]	798026
44	3 and 14 [Pentoxifylline AND Neonatal Terms]	478
45	6 and 11 and 14 [Drug Category AND Sepsis/NEC AND Neonatal Terms]	712

(Continued)

46	or/44-45 [Results before filters]	1153
47	46 and 32 [RCT Results]	160
48	46 and 43 [Systematic Review Results]	78
49	or/47-48 [All results]	206

Appendix 4. CINAHL strategy

	CINAHL Complete; EBSCOHost	
	July-31-2022	
	Advanced Search; Search mode: Boolean/Phrase	
#	Query	Results
1	(MH "Pentoxifylline")	518
2	TI ((agapurin or artal or azupentat or azutrenat or bl 191 or bl191 or c-vex or carpental or cental or ceretal or claudicat retard or "eht 0201" or eht0201 or elorgan or erytral or fixoten or flexital or harin or harine or hemovas or ikomio or ipentol or kentadin or oxopurin 400 sr or oxpentifylline or oxpentiphylline or oxypentifylline or penphylline or pentong or pentopak or pentox* or pentyllin or perencal or perental or peridane or pexal or pexol or platof or ralofect or ralofekt or relofekt or rentylin or tarontal or thrental or torental or torestal or trenfyl or trenlin or trental or trepal-400 or vazofen)) OR AB ((agapurin or artal or azupentat or azutrenat or bl 191 or bl191 or c-vex or carpental or cental or ceretal or claudicat retard or "eht 0201" or eht0201 or elorgan or erytral or fixoten or flexital or harin or harine or hemovas or ikomio or ipentol or kentadin or oxopurin 400 sr or oxpentifylline or oxpentiphylline or oxypentifylline or penphylline or pentong or pentopak or pentox* or pentyllin or perencal or perental or peridane or pexal or pexol or platof or ralofect or ralofekt or relofekt or rentylin or tarontal or thrental or torental or torestal or trenfyl or trenlin or trental or trepal-400 or vazofen))	638
3	S1 OR S2	797
4	(MH "Phosphodiesterase Inhibitors+")	3,586
5	TI (Phosphodiesteras* N2 Inhibit*) OR AB (Phosphodiesteras* N2 Inhibit*)	1,619
6	S4 OR S5	4,310
7	(MH "Sepsis+") OR (MH "Neonatal Sepsis")	30,959
8	(MH "Enterocolitis+") OR (MH "Enterocolitis, Necrotizing")	3,647
9	TI ((sepsis* or septic* or Pyemia* or Pyohemi* or Pyaemi* or ((blood* or bloodstream*) N2 (infect* or poison*)))) OR AB ((sepsis* or septic* or Pyemia* or Pyohemi* or Pyaemi* or ((blood* or bloodstream*) N2 (infect* or poison*))))	44,927

(Continued)

10	TI ((enterocoliti* or colienteriti* or NEC)) OR AB ((enterocoliti* or colienteriti* or NEC))	4,397
11	S7 OR S8 OR S9 OR S10	60,120
12	(MH "Infant, Newborn+") OR (MH "Infant, Large for Gestational Age") OR (MH "Infant, Low Birth Weight+") OR (MH "Infant, Postmature") OR (MH "Infant, Premature") OR (MH "Intensive Care, Neonatal+") OR (MH "Intensive Care Units, Neonatal") OR (MH "Gestational Age")	171,731
13	TI ((babe or babes or baby* or babies or gestational age# or infant# or infantile or infancy or low birth weight or low birthweight or neonat* or neo-nat* or newborn* or new born# or newly born or premature or pre-mature or pre-matures or prematures or prematurity or pre-maturity or preterm or preterms or pre term# or preemie or preemies or premies or premie or VLBW or VLBWI or VLBW-I or VLBWs or LBW or LBWI or LBWs or ELBW or ELBWI or ELBWs or NICU or NICUs) OR AB (babe or babes or baby* or babies or gestational age# or infant# or infantile or infancy or low birth weight or low birthweight or neonat* or neo-nat* or newborn* or new born# or newly born or premature or pre-mature or pre-matures or prematures or prematurity or pre-maturity or preterm or preterms or pre term# or preemie or preemies or premies or premie or VLBW or VLBWI or VLBW-I or VLBWs or LBW or LBWI or LBWs or ELBW or ELBWI or ELBWs or NICU or NICUs)	257,845
14	S12 OR S13	321,168
15	(MH "Single-Blind Studies") OR (MH "Triple-Blind Studies") OR (MH "Randomized Controlled Trials+") OR (MH "Double-Blind Studies")	171,721
16	(MH "Clinical Trials+")	341,694
17	TI (randomi#ed or randomly) OR AB (randomi#ed or randomly) OR AB (randomi#ed or randomly) OR AB (randomi#ed or randomly)	359,579
18	AB randomly	104,951
19	AB placebo	64,957
20	AB (trial)	331,183
21	AB groups	876,324
22	TI (quasirandom* or quasi-random*) OR AB (quasirandom* or quasi-random*)	2,195
23	S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22	1,283,162
24	(MH "Animal Studies")	148,280
25	(MH "Human")	2,584,163
26	S24 NOT S25	123,454
27	S23 NOT S26	1,244,112
28	(MH "Systematic Review")	112,201
29	(MH "Meta Analysis")	64,235

(Continued)

30	(TI ((systematic* N3 (review* or overview*)) or (methodologic* N3 (review* or overview*)))) OR (AB ((systematic* N3 (review* or overview*)) or (methodologic* N3 (review* or overview*))))	138,072
31	(TI ((integrative N3 (review* or overview*)) or (collaborative N3 (review* or overview*)) or (pool* N3 analy*))) OR (AB ((integrative N3 (review* or overview*)) or (collaborative N3 (review* or overview*)) or (pool* N3 analy*)))	18,428
32	(TI (data synthes* or data extraction* or data abstraction*)) OR (AB (data synthes* or data extraction* or data abstraction*))	13,853
33	AB (hand search* or handsearch*)	4,877
34	AB (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*)	9,417
35	(TI met analy* or metanaly* or meta regression* or metaregression*)) OR (AB met analy* or metanaly* or meta regression* or metaregression*))	4,805
36	AB (medline or cochrane or pubmed or medlars or embase OR CINAHL)	115,502
37	S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36	244,269
38	S4 AND S14	167
39	S6 AND S11 AND S14	6
40	S38 OR S39	170
41	S40 AND S27	55
42	(S40 AND S37) AND DT 202*	1
43	S41 OR S42	55

Appendix 5. Trial registry strategies

Date	Source	Terms	
July-31-2022	Clinicaltrials.gov	Pentoxifylline (Other terms) AND age Child (birth to17)	19
July-31-2022	Clinicaltrials.gov	Pentoxifylline (Other terms) AND neonatal [Condition or disease]	5
July-31-2022	Clinicaltrials.gov	Pentoxifylline (Other terms) AND sepsis [Condition or disease]	3
July-31-2022	Clinicaltrials.gov	Pentoxifylline (Other terms) AND enterocolitis [Condition or disease]	1
July-31-2022	ICTRP	Pentoxifylline (Title) AND Neonatal (Condition)	6
July-31-2022	ICTRP	Pentoxifylline (Title] AND Neonate (Condition)	0

(Continued)

July-31-2022	ICTRP	Pentoxifylline (Title) AND Neonatal (Condition)	6
July-31-2022	ICTRP	Pentoxifylline (Title] AND Sepsis [Condition]	6
July-31-2022	ICTRP	Pentoxifylline (Title] AND Enterocolitis [Condition]	3
July-31-2022	ICTRP	Pentoxifylline (Intervention) AND Neonatal (Condition)	5
July-31-2022	ICTRP	Pentoxifylline (Intervention] AND Sepsis [Condition]	5
July-31-2022	ICTRP	Pentoxifylline (Intervention] AND Enterocolitis [Condition]	3
July-31-2022	ICTRP	Pentoxifylline (Intervention] AND Neonate (Title)	0
July-31-2022	ISRCTN	Pentoxifylline (Text word] AND Neonatal [condition	0
July-31-2022	ISRCTN	Pentoxifylline (Intervention] AND Neonatal [condition	0
July-31-2022	ISRCTN	Pentoxifylline (Intervention] AND Sepsis [condition]	0
July-31-2022	ISRCTN	Pentoxifylline (Intervention] AND Enterocolitis [condition]	0
July-31-2022	ISRCTN	Pentoxifylline [Text search] found 18 but none in neonate or child population	0
August-18-2022	ANZCTR	Pentoxifylline [Description of intervention /exposure	4
Total			66

Appendix 6. Risk of bias tool

1. Sequence generation (checking for possible selection bias). Was the allocation sequence adequately generated?

For each included study, we categorised the method used to generate the allocation sequence as:

- low risk (any truly random process, e.g. random number table; computer random number generator);
- high risk (any non-random process, e.g. odd or even date of birth; hospital or clinic record number); or
- unclear risk.

2. Allocation concealment (checking for possible selection bias). Was allocation adequately concealed?

For each included study, we categorised the method used to conceal the allocation sequence as:

- low risk (e.g. telephone or central randomisation; consecutively numbered, sealed, opaque envelopes);
- high risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth); or
- unclear risk.

3. Blinding of participants and personnel (checking for possible performance bias). Was knowledge of the allocated intervention adequately prevented during the study?

For each included study, we categorised the methods used to blind study participants and personnel from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or class of outcomes. We categorised the methods as:

- low risk, high risk, or unclear risk for participants; and
- low risk, high risk, or unclear risk for personnel.

4. Blinding of outcome assessment (checking for possible detection bias). Was knowledge of the allocated intervention adequately prevented at the time of outcome assessment?

For each included study, we categorised the methods used to blind outcome assessment. We assessed blinding separately for different outcomes or class of outcomes. We categorised the methods as:

- low risk for outcome assessors;
- high risk for outcome assessors; or
- unclear risk for outcome assessors.

5. Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations). Were incomplete outcome data adequately addressed?

For each included study and for each outcome, we described the completeness of data including attrition and exclusions from the analysis. We noted whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported or supplied by the trial authors, we re-included missing data in the analyses. We categorised the methods as:

- low risk (< 20% missing data);
- high risk (≥ 20% missing data); or
- unclear risk.

6. Selective reporting bias. Are reports of the study free of the suggestion of selective outcome reporting?

For each included study, we described how we investigated the possibility of selective outcome reporting bias and what we found. For studies in which study protocols were published in advance, we compared the prespecified outcomes versus outcomes reported in the published results. If the study protocol was not published in advance, we contacted the study authors to gain access to it. We assessed the methods as:

- low risk (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- high risk (where not all the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified outcomes of interest and are reported incompletely and so cannot be used; the study fails to include results of a key outcome that would be expected to have been reported); or
- unclear risk.

7. Other sources of bias. Did the study appear to be free of other problems that could put it at high risk of bias?

For each included study, we described any important concerns we had about other possible sources of bias (e.g. whether there was a potential source of bias related to the specific study design, or if the trial was stopped early due to some data-dependent process). We assessed whether each study was free of other problems that could put it at risk of bias as:

- low risk;
- high risk; or
- unclear risk.

If needed, we explored the impact of the level of bias through undertaking sensitivity analyses.

WHAT'S NEW

Date	Event	Description
20 June 2023	New search has been performed	We updated the search in July 2022. No new trials were included, but we found one ongoing trial (ACTRN12616000405415), and excluded two trials (Hamilcikan 2017a; Hamilcikan 2017b). One outcome, retinopathy of prematurity, was included post hoc.
20 June 2023	New citation required but conclusions have not changed	The data analyses and conclusions remain the same.

HISTORY

Protocol first published: Issue 2, 2003
Review first published: Issue 4, 2003

Date	Event	Description
29 June 2014	New citation required but conclusions have not changed	No changes to conclusions
29 June 2014	New search has been performed	We updated the search in May 2014 and added two new studies (Shabaan 2015 and Akdag 2014). We revised the review by adding a summary of findings table and changing the ongoing study (ZTB 2009) to an included study (Akdag 2014). We used the GRADE approach to rate the quality of evidence as high, moderate, low, or very low.
8 July 2011	New citation required but conclusions have not changed	No change to conclusions
8 July 2011	New search has been performed	This updates the review 'Pentoxyfilline for treatment of sepsis and necrotizing enterocolitis in neonates' published in the Cochrane Database of Systematic Reviews (Haque 2003).

Search updated 8 July 2011. We included two new trials and added one ongoing study to the review. |
| 7 December 2010 | Amended | Contact details updated. |
| 21 February 2008 | Amended | Converted to new review format |
| 11 September 2007 | New search has been performed | This updates the review 'Pentoxifylline for neonatal sepsis' published in the Cochrane Database of Systematic Reviews, Issue 2, 2003 (Haque 2003).
The updated search did not identify any new trials. Two ongoing trials using pentoxifylline in the treatment of necrotising enterocolitis were identified.
The title and the review have been modified to include pentoxifylline treatment for necrotising enterocolitis, in view of emerging evidence for potential benefits of the use of pentoxifylline for this condition. |
| 28 January 2003 | New citation required and conclusions have changed | Substantive amendment |

CONTRIBUTIONS OF AUTHORS

Mohan Pammi:

- Updated the review
- Assisted in writing the protocol and review
- Independently assessed study methodology and extracted data from eligible studies
- Entered and checked data in Review Manager 5 for the review updates
- Assisted in contacting authors for more information on published articles and in tracing unpublished articles

Khalid Haque:

- Assessed methodology
- Extracted relevant data from eligible studies
- Contacted study authors for more data on published and unpublished trials
- Wrote the text of the review
- Assisted in updating the review

DECLARATIONS OF INTEREST

Mohan Pammi is an Associate Editor with the Cochrane Neonatal Group, but has taken no part in the editorial processes for this review, and otherwise declares no conflict of interest.

Khalid Haque declares that he has no conflict of interest.

SOURCES OF SUPPORT

Internal sources

- Epsom & St. Helier NHS Trust, UK

  Administrative support for previous versions of this review
- National Perinatal Epidemiology Unit, Headington, Oxford, UK

  Administrative support for previous versions of this review

External sources

- Vermont Oxford Network, USA

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. The secondary outcome of NEC was modified as a) NEC (any Bell stage) and b) Bell's stage 2 or 3
2. Retinopathy of prematurity a) ROP any stage, b) ROP stage III-IV were added as a secondary outcome.
3. We updated the risk of bias assessment to include seven categories.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [adverse effects]; *Enterocolitis, Necrotizing [drug therapy]; Immunoglobulin M; Immunoglobulins, Intravenous [therapeutic use]; Infant, Premature; *Lung Diseases; *Neonatal Sepsis [drug therapy]; *Pentoxifylline [adverse effects]; *Retinopathy of Prematurity; *Sepsis [drug therapy]

MeSH check words

Humans; Infant, Newborn