National Institute for Health and Care Excellence

Neonatal infection: antibiotics for prevention and treatment

[R] Technical appendices for switching from intravenous to oral antibiotics for suspected early-onset neonatal bacterial infection

NICE guideline NG195

Technical data underpinning evidence review [R]

February 2026

Draft

Contents

Appendix A - Review protocols

This evidence review was based on an existing systematic review from an external source. The review protocol for the existing review was pre-registered. The full protocol can be found at: CRD420251044158.

Appendix B - Literature search strategies

A search was not conducted for this evidence review because an existing systematic review from an external source was used. Details of the search methods used in the existing review are available in the preprint article.

Appendix C - Study selection – effectiveness evidence

The PRISMA diagram for the existing review is available in the preprint article.

Appendix D - Effectiveness evidence tables

Whear, 2025

Bibliographic Reference	Whear R; Abbott R; Aughey H; Rogers M; Bethel A; Logan S; Boxall K; Thompson Coon J; Effectiveness, cost effectiveness and experiences of switching from intravenous to oral antibiotics in neonates with probable early onset sepsis: a systematic review; medRxiv; 2025

Study Characteristics

Study design	Systematic review
Study details	Dates searched Search conducted in April 2025 with no date restrictions, exact start date and end date of search not reported. Citation analysis conducted in June 2025. Databases searched • Medline, Embase, PsycINFO, HMIC and SPP (via Ovid) • CENTRAL (via Cochrane Library) • CINAHL (via EBSCOhost) • Conference Abstracts (via Web of Science) • Cochrane Database of Systematic Reviews • Epistemonikos • clinicaltrials.gov • WHO International Clinical Trials Registry Platform • Google (advanced search for publications on nhs.uk and gov.uk web domains)

	• Other websites:
	  ○ The Neonatal Society
	  ○ British Association of Perinatal Medicine
	  ○ Royal College of Paediatrics and Child Health
	  ○ European Society of Paediatric and Neonatal Intensive Care
	  ○ Union of European Neonatal & Perinatal Societies
	  ○ European Society for Paediatric Research
	  ○ American Academy of Pediatrics
	
	Sources of funding
	
	National Institute for Health and Care Research Applied Research Collaboration South West Peninsula.

Inclusion criteria	Population: clinically stable, term and late pre-term (>35 weeks gestation) babies with suspected early-onset sepsis (within the first 72 hours of life) Intervention: switch from intravenous to oral antibiotics Comparator: remain on intravenous antibiotics Outcomes: mortality and morbidity, cost and resource use, process outcomes, family-related outcomes, and views, perceptions and experiences of healthcare professionals, parents and families Setting: hospitals Study design: all comparative study designs (randomised and non-randomised), qualitative studies Conference abstracts, protocols and ongoing trials
Exclusion criteria	Population: babies born under 35 weeks gestation, suspected infection more than 72 hours after birth

	Outcomes: pharmacokinetic outcomes Study design: ex vivo and in vitro studies, systematic reviews, scoping reviews, narrative reviews Letters, editorials, discussion pieces

Intervention(s)	Intervention: switch to oral antibiotics
	
	Antibiotics listed in the protocol: amoxicillin, ampicillin, augmentin, cefalexin, cefpodoxim, chloramphenicol, cloxacillin, coamoxiclav, flucloxacillin, nafcillin, penicillin
	
	Comparator: remain on intravenous antibiotics
	
	No further details provided in the protocol regarding eligibility criteria of interventions and comparators (such as dose and timing of switch to oral antibiotics)
	
	Included studies:
	
	• *Gyllensvärd 2020*
	  ○ Intervention (N=59): 3 days IV penicillin (50mg/kg, every 8 to 12 hours) plus amikacin (15mg/kg every 24 hours), followed by 2 days oral amoxicillin (20mg/kg, 3 times per day)
	  ○ Comparator (N=61): 5 to 7 days IV penicillin (50mg/kg) plus amikacin (15mg/kg every 24 hours)
	• *Keij 2022*
	  ○ Intervention (N=252): 2 days IV penicillin and gentamicin (dose NR, 3 times per day), followed by 5 days oral amoxicillin (75mg/kg) plus clavulanic acid (18.75mg/kg) per day in 3 doses
	  ○ Comparator (N=252): 7 days IV penicillin and gentamicin (dose NR, 3 times per day)
	• *Malchau Carlsen 2024*
	  ○ Intervention (N=478): 7 days total treatment, of which 1.5 to 2 days IV benzylpenicillin and gentamicin (dose NR), followed by oral amoxicillin (50mg/kg, 3 times per day) for remainder of treatment

	○ Comparator (N=53): 7 days IV benzylpenicillin and gentamicin (dose NR) • *Manzoni 2009* ○ Intervention (N=17): 3 days IV ampicillin and sulbactam (100mg/kg, 3 times per day) plus amikacin (15mg/kg once per day), followed by 5 days oral cefpodoxime proxetil (10mg/kg, once per day) ○ Comparator (N=37): 8 days IV ampicillin and sulbactam (100mg/kg, 3 times per day) plus amikacin (15mg/kg once per day) for first 3 days
Outcome(s)	Bacterial re-infection rate or late onset sepsis Re-presentation at or readmission to the hospital for infection within 28 days of birth Adverse events e.g. cannulation attempts, allergic reaction to antibiotics Completion of antibiotic course Impact on gut biome including long term impact Mortality Breastfeeding rates Sleep quality Parental anxiety Parent/child bonding Quality of life

	Parent perspectives/willingness to give antibiotics Length of stay in hospital Additional healthcare visits including GP, midwife, health visitor, 111, and emergency department Drug and equipment costs Costs to the family Views, perceptions and experiences of health care professionals, parents and families of switching from intravenous to oral administration of antibiotics
Number of studies included in the systematic review	4 (1 open-label non-inferiority RCT, 3 non-randomised studies: 1 prospective cohort study, 1 pre-post study, 1 case-control study)
Additional comments	Protocol deviations: indirect outcomes were included for readmission, adverse events, and treatment completion which do not exactly match those prespecified in the protocol. Definitions of suspected early-onset infection were extracted from the primary studies because they were not reported in the review: • *Gyllensvärd 2020*: blood culture negative with clinical signs of infection and CRP >20mg/L or IL-6 >350ng/L • *Keij 2022*: blood culture negative with clinical symptoms or maternal risk factors and CRP ≥10mg/L or elevated procalcitonin concentrations • *Malchau Carlsen 2024*: blood culture negative with clinical signs of maternal risk factors and CRP above 35 to 50mg/L • *Manzoni 2009*: presumed infection defined as >2 pathological findings in medical history or symptoms suggesting infection and >1 biological abnormality (leukopenia, leuokocytosis, <0.2 ratio of immature to total neutrophil, thrombocytopenia, thrombocytosis, or CRP >25mg/L 12 to 48 hours after first blood sample). Also included

proven infections, defined as positive blood or urine culture (52.7% in oral antibiotics group and 48.6% in intravenous antibiotics group)

Effect estimates (risk ratios or risk differences) were not reported for any outcomes in the review. These were calculated based on the raw data reported in the review.

The Effective Public Health Practice Project (EPHPP) tool was used in the review to critically appraise the included studies.

No evidence was identified by the review for the outcomes:

- Impact on gut biome
- Parental anxiety
- Parent/child bonding
- Quality of life
- Parent perspectives/willingness to give antibiotics
- Costs to the family
- Views, perceptions and experiences of health care professionals, parents and families of switching from intravenous to oral administration of antibiotics

The review also reported safety procedures implemented in each study:

- *Gyllensvärd 2020*: routine visit on day 7 in both arms for clinical assessment and CRP measurement
- *Keij 2022*: parents/guardians provided information on antibiotic intake, fever or other infection signs and adverse events on day 4 and 7 (telephone), day 7 and 21 (digital questionnaire), and day 35 (outpatient clinic appointment)
- *Malchau Carlsen 2024*: parents given information about signs of reinfection. Followed up 2 days after switch for clinical assessment and CRP measurement and 2 to 4 days after treatment end for clinical assessment
- *Manzoni 2009*: not reported

Abbreviations: CENTRAL: Cochrane Central Register of Controlled Trials; CINAHL: Cumulative Index to Nursing and Allied Health Literature; CRP: C-reactive protein; HMIC: Healthcare Management Information Consortium; IL-6: interleukin 6; IV: intravenous; RCT: randomised controlled trial; SPP: Social Policy and Practice; WHO: World Health Organization

Critical appraisal - ROBIS systematic review checklist

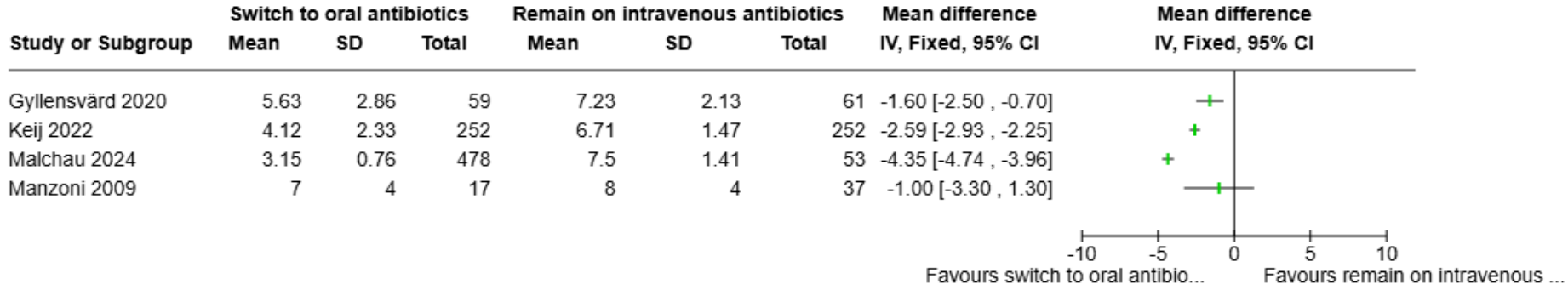
Section	Question	Answer
Overall study ratings	Overall risk of bias	Unclear *(A) Concerns about the lack of consideration of the quality of the included studies in the synthesis were partially addressed by the review authors in the discussion, but concern remains about the lack of consideration of the impact of confounding on the findings of the review. B) The review authors discuss the relevance of the included studies for UK practice, but do not perform formal assessment of applicability of the included studies. C) The review authors consider all findings as part of the conclusions, not just statistically significant results.*
Overall study ratings	Applicability as a source of data	Fully applicable

Appendix E - Forest plots

The forest plot below presents results for the same outcome reported across multiple studies but not pooled in a meta-analysis. Outcomes from single studies are not presented here; the quality assessment for such outcomes is provided in the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) summary tables in appendix F.

Switching to oral antibiotics versus remaining on intravenous antibiotics for neonates with suspected early-onset bacterial infection

Figure 1 Duration of hospital stay (days)



Abbreviations: CI: confidence intervals; IV: inverse variance; SD: standard deviation

Appendix F - GRADE summary

Table 1 Effectiveness evidence summary: switching to oral antibiotics versus remaining on intravenous antibiotics for neonates with suspected early-onset bacterial infection

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE) and clinical importance	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with remaining on intravenous antibiotics	Risk difference with switching to oral antibiotics
Bacterial reinfection within 28 days of treatment completion (defined using clinical symptoms, inflammatory markers and need for prolonged treatment)	504 (1 RCT) Keij 2022	Low[a,b] **EV. OF NO EFFECT**	**RD 0.00** (-0.01 to 0.01)	4 per 1,000	**0 more per 1,000** (10 fewer to 10 more)
Reinfection within 3 days of treatment completion (definition unclear)	120 (1 pre-post study) Gyllensvärd 2020	Very low[a,b,c] **EV. OF NO EFFECT**	**RD 0.00** (-0.03 to 0.03)	0 per 1,000	**0 more per 1,000** (30 fewer to 30 more)
Readmission within 28 days of treatment completion	504 (1 RCT) Keij 2022	Very low[a,b,d,e] **EV. OF NO EFFECT**	**RR 1.11** (0.46 to 2.69)	36 per 1,000	**4 more per 1,000** (19 fewer to 60 more)
Readmission within 3 days of treatment completion	120 (1 pre-post study) Gyllensvärd 2020	Very low[a,b,c,f] **EV. OF NO EFFECT**	**RD 0.02** (-0.03 to 0.06)	0 per 1,000	**20 more per 1,000** (30 fewer to 60 more)

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE) and clinical importance	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with remaining on intravenous antibiotics	Risk difference with switching to oral antibiotics
Readmission due to infection within 60 days of treatment completion	531 (1 prospective cohort study) Malchau Carlsen 2024	Very low[a,b,g] **EV. OF NO EFFECT**	**RD -0.02** (-0.06 to 0.03)	19 per 1,000	**20 fewer per 1,000** (60 fewer to 30 more)
Post-discharge admissions (timepoint NR)	54 (1 case-control study) Manzoni 2009	Very low[b,e,h,i] **EV. OF NO EFFECT**	**RR 1.09** (0.11 to 11.19)	54 per 1,000	**5 more per 1,000** (48 fewer to 551 more)
Any adverse event within 35 days of treatment initiation (reported via parent questionnaires and at follow-up visits)	504 (1 RCT) Keij 2022	Very low[a,b,j,k] **EV. OF DISBENEFIT**	**RR 1.12** (0.94 to 1.35)	448 per 1,000	**54 more per 1,000** (27 fewer to 157 more)
Serious adverse events within 35 days of treatment initiation (fatal or life-threatening, including readmissions to hospital)	504 (1 RCT) Keij 2022	Very low[a,b,e] **EV. OF NO EFFECT**	**RR 1.16** (0.64 to 2.09)	75 per 1,000	**12 more per 1,000** (27 fewer to 82 more)
Complications of treatment (timepoint NR; drug-related adverse events, unclear definition)	54 (1 case-control study) Manzoni 2009	Very low[b,c,h,l] **EV. OF NO EFFECT**	**RD 0.00** (-0.08 to 0.08)	0 per 1,000	**0 more per 1,000** (80 fewer to 80 more)
Clinical deterioration within intervention (7 days; symptoms or readmission due to symptoms relating to infection, unclear how symptoms were assessed)	504 (1 RCT) Keij 2022	Very low[a,b,m] **EV. OF NO EFFECT**	**RD 0.01** (-0.01 to 0.02)	0 per 1,000	**10 more per 1,000** (10 fewer to 20 more)

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE) and clinical importance	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with remaining on intravenous antibiotics	Risk difference with switching to oral antibiotics
Weight loss on day 4 (% of birthweight)	54 (1 case-control study) Manzoni 2009	Very low[b,h,l] **EV. OF NO EFFECT**	-	The mean weight loss on day 4 (% of birthweight) was **9** %	MD **1 % lower** (2.72 lower to 0.72 higher)
Number of cannula reinsertion attempts during treatment	504 (1 RCT) Keij 2022	Not assessed	-	The median number of cannula reinsertion attempts during treatment was **2 (IQR 1 to 3)**	-
Protocol violation (timepoint NR)	504 (1 RCT) Keij 2022	Very low[a,b,n] **EV. OF BENEFIT**	**RR 0.34** (0.20 to 0.56)	210 per 1,000	**139 fewer per 1,000** (168 fewer to 93 fewer)
Treatment discontinuation (timepoint NR; defined as premature treatment discontinuation)	531 (1 prospective cohort study) Malchau Carlsen 2024	Very low[a,b] **EV. OF NO EFFECT**	**RD 0.00** (-0.03 to 0.03)	0 per 1,000	**0 more per 1,000** (30 fewer to 30 more)
Oral medication accepted by neonate (timepoint NR)	531 (1 prospective cohort study) Malchau Carlsen 2024	Not assessed	478/478 (100%) in oral antibiotics arm	-	-
Mortality within 30 days (eligible causes of death NR)	120 (1 pre-post study) Gyllensvärd 2020	Very low[a,b,c] **EV. OF NO EFFECT**	**RD 0.00** (-0.03 to 0.03)	0 per 1,000	**0 more per 1,000** (30 fewer to 30 more)

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE) and clinical importance	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with remaining on intravenous antibiotics	Risk difference with switching to oral antibiotics
Mortality in first month of life (eligible causes of death NR)	54 (1 case-control study) Manzoni 2009	Very low[b,c,h,l] **EV. OF NO EFFECT**	**RD 0.00** (-0.08 to 0.08)	0 per 1,000	**0 more per 1,000** (80 fewer to 80 more)
Mortality (timepoint NR; eligible causes of death NR – deaths that occurred were not due to infection)	531 (1 prospective cohort study) Malchau Carlsen 2024	Very low[a,b,o] **EV. OF BENEFIT**	**RD -0.04** (-0.09 to 0.02)	38 per 1,000	**40 fewer per 1,000** (90 fewer to 20 more)
Exclusively breastfed at 1 month after treatment completion	504 (1 RCT) Keij 2022	Low[a,b] **EV. OF NO EFFECT**	**RR 1.01** (0.84 to 1.22)	464 per 1,000	**5 more per 1,000** (74 fewer to 102 more)
Exclusively breastfed at discharge	54 (1 case-control study) Manzoni 2009	Very low[b,h,k,l] **EV. OF BENEFIT**	**RR 1.24** (1.00 to 1.55)	757 per 1,000	**182 more per 1,000** (0 fewer to 416 more)
Sleep good quality at 1 week (parent-reported, not using a validated scale)	504 (1 RCT) Keij 2022	Low[a,b] **EV. OF NO EFFECT**	**RR 1.07** (0.98 to 1.17)	778 per 1,000	**54 more per 1,000** (16 fewer to 132 more)
Sleep good quality at 1 month (parent-reported, not using a validated scale)	504 (1 RCT) Keij 2022	Low[a,b] **EV. OF NO EFFECT**	**RR 1.09** (0.97 to 1.23)	655 per 1,000	**59 more per 1,000** (20 fewer to 151 more)

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE) and clinical importance	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with remaining on intravenous antibiotics	Risk difference with switching to oral antibiotics
Duration of hospital stay (days) Lower is better	504 (1 RCT) Keij 2022	Moderate[a] **EV. OF BENEFIT**	-	The mean duration of hospital stay was **6.71** days	MD **2.59 days lower** (2.93 lower to 2.25 lower)
Duration of hospital stay (days) Lower is better	120 (1 pre-post study) Gyllensvärd 2020	Very low[a,p] **EV. OF BENEFIT**	-	The mean duration of hospital stay was **7.23** days	MD **1.6 days lower** (2.5 lower to 0.7 lower)
Duration of hospital stay (days) Lower is better	531 (1 prospective cohort study) Malchau Carlsen 2024	Very low[a] **EV. OF BENEFIT**	-	The mean duration of hospital stay was **7.5** days	MD **4.35 days lower** (4.74 lower to 3.96 lower)
Duration of hospital stay (days) Lower is better	54 (1 case-control study) Manzoni 2009	Very low[h,l,q] **EV. OF BENEFIT**	-	The mean duration of hospital stay was **8** days	MD **1 day lower** (3.3 lower to 1.3 higher)
Healthcare professional visit between day 7 and 35 (reason for visit NR)	504 (1 RCT) Keij 2022	Very low[a,b,k] **EV. OF NO EFFECT**	**RR 1.26** (0.93 to 1.69)	230 per 1,000	**60 more per 1,000** (16 fewer to 159 more)

Abbreviations: CI: confidence interval; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations; IQR: interquartile range; MD: mean difference; NR: not reported; RCT: randomised controlled trial; RD: risk difference; RR: risk ratio

Explanations

a. Serious risk of bias in the evidence contributing to the outcome. The evidence came from a study of moderate methodological quality, assessed by the existing evidence review as per the Effective Public Health Practice Project tool
b. Single study - downgraded once for inconsistency, as single study outcomes may otherwise receive favourable ratings for inconsistency by default
c. Very serious imprecision because N<200
d. Serious indirectness because of outcome indirectness - included readmissions that were not due to infection
e. Very serious imprecision because 95% CI crosses 2 MIDs (MIDs: 0.8 and 1.25)
f. Serious indirectness because of outcome indirectness - included readmissions that were not due to infection and the timepoint of outcome assessment was earlier than specified in the protocol
g. Serious indirectness because of outcome indirectness - the timepoint of outcome assessment was later than specified in the protocol
h. Very serious risk of bias in the evidence contributing to the outcome. The evidence came from a study of weak methodological quality, assessed by the existing evidence review as per the Effective Public Health Practice Project tool
i. Very serious indirectness because of outcome indirectness and population indirectness - included readmissions that were not due to infection, the timepoint of outcome assessment was not specified and approximately 50% of the population had confirmed infections (not suspected infections)
j. Any adverse event included vomiting, changes in defecation pattern, rash, hyperbilirubinaemia, oral candidiasis for which treatment was indicated, excessive crying, elevated liver enzymes, anaemia with need for ferrous fumarate or transfusion, other
k. Serious imprecision because 95% CI crosses 1 MID (MIDs: 0.8 and 1.25)
l. Serious indirectness because of population indirectness - approximately 50% of the population had confirmed infections (not suspected infections)
m. Serious indirectness because of outcome indirectness - could be related to ongoing infection or new infection
n. Serious indirectness because of outcome indirectness - not all protocol violations were due to not completing antibiotic treatment. 49 neonates in intravenous antibiotics arm did not complete treatment because of issues with venous access, of which 33 continued treatment orally. Primary study reports that 6 neonates in the oral antibiotics arm did not complete treatment, but this was not reported in the review
o. Primary study reports 3 deaths: 1 neonate with E. coli septicaemia died on day 4 of intravenous treatment and 2 neonates who only received intravenous antibiotics died from severe perinatal asphyxia and hydrops foetalis of unknown origin. 3 deaths in the intravenous antibiotics group were originally reported in the existing review, but this was later revised by the authors of the existing review to 2 deaths in the intravenous antibiotics group following clarification from the primary study authors as only 2 deaths occurred in neonates who were blood culture negative, which was the population of interest
p. Serious imprecision because 95% CI crosses 1 MID (+/- 1 day)
q. Very serious imprecision because 95% CI crosses 2 MIDs (+/- 1 day)

Appendix G - Economic evidence study selection

The PRISMA diagram for the existing review is available in the preprint article.

Appendix H - Economic evidence tables

A search was not undertaken for health economic evidence for this review question.

Appendix I - Excluded studies

The list of studies that were excluded at full-text from the existing review with reasons for exclusion are available in the preprint article.

Appendix J - Methods

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are outlined below.

Assessing inconsistency

All outcomes based on single studies were downgraded once for inconsistency, as they would otherwise receive a favourable rating by default. For the outcome duration of hospital stay, studies were downgraded for inconsistency if <80% of point estimates were within the same range of effect (±1 day).

Assessing indirectness

Each individual study was classified into one of three groups for directness, based on if there were concerns about the population, intervention, comparator and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, intervention, comparator and/or outcomes.
- Partially indirect – Important deviations from the protocol in one of the following areas: population, intervention, comparator and/or outcomes.
- Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention, comparator and/or outcomes.

Assessing imprecision

For dichotomous outcomes, minimally important difference (MID) thresholds corresponding to relative risks (RRs) of 0.8 and 1.25 were used to assess imprecision. If risk difference (RD) was used for analysis, imprecision was assessed based on sample size using 200 and 400 as cut-offs for very serious and serious imprecision, respectively. For continuous outcomes, a

MID of ±1 day was used for duration of hospital stay, and ≥10% of birthweight was used for weight loss.

Assessing clinical importance

For dichotomous outcomes, the assessment of clinical benefit, disbenefit or no effect was based on the point estimate of absolute effect. The committee considered for most of the outcomes if at least 100 more participants per 1000 (10%) achieved the outcome of interest in the intervention group compared to the comparison group for a positive outcome then this intervention was considered beneficial. The same point estimate but in the opposite direction applied for a negative outcome. For adverse events 50 events or more per 1000 (5%) represented clinical disbenefit. For the critical outcome of mortality any reduction represented a clinical benefit. For the continuous outcome of duration of hospital stay, the committee considered a one-day difference to be considered clinically important. For the continuous outcome of weight loss, a reduction of 10% of birth weight was considered clinically important, based on recommendations from the NICE Guideline on Faltering growth: recognition and management of faltering growth in children (NG75).

Approach to analysis of studies with zero events

For studies reporting zero events in one or both arms, the risk difference (RD) was used as the effect measure. The absolute effect was derived based on the RD.

Informative statements

Informative statements were developed by considering both clinical importance and the certainty of the evidence. They were adapted from GRADE Guidance 26.

An example of how these statements were drafted is provided in the table below.

Effect estimate (clinical importance)	Suggested statements (replace X with intervention, replace 'reduce/increase' with direction of effect, replace 'outcome' with name of outcome, replace Y with name of comparator).
HIGH Certainty of the evidence (GRADE)	
Effect (Evidence of benefit or disbenefit)	The evidence shows that X reduces/increases [outcome] compared to Y.
Trivial, small unimportant effect or no effect (Evidence of no effect)	The evidence shows that X results in little to no difference in [outcome] compared to Y.
MODERATE Certainty of the evidence	
Effect (Evidence of benefit or disbenefit)	The evidence shows that X probably reduces/increases [outcome] compared to Y.
Trivial, small unimportant effect or no effect (Evidence of no effect)	The evidence shows that X probably results in little to no difference in [outcome] compared to Y.
Uncertain effect	The evidence is probably uncertain about the effect of X on [outcome] compared to Y.
LOW Certainty of the evidence	
Effect (Evidence of benefit or disbenefit)	The evidence suggests X reduces/increases [outcome] compared to Y.
Trivial, small unimportant effect or no effect (Evidence of no effect)	The evidence suggests that X results in little to no difference in [outcome] compared to Y.
Uncertain effect	The evidence is uncertain about the effect of X on [outcome] compared to Y. The evidence suggests that X does not reduce/increase [outcome] compared to Y, but the evidence is uncertain
VERY LOW Certainty of the evidence	
Any effect	The evidence is very uncertain about the effect of X on [outcome] compared to Y. X may reduce/increase/have little to no effect on outcome but the evidence is very uncertain.

Abbreviations: GRADE: Grading of Recommendations Assessment, Development and Evaluation

Appendix K - Research recommendations

No research recommendations were made for this review question.

1 Appendix L - Expert witness testimonial

Section A: Developer to complete	
Name:	Expert 1 - Dr Harriet Aughey Expert 2 - Dr Katie Evans Expert 3 - Dr Peter Reynolds Expert 4 - Dr Niamh Scally
Role:	Expert 1 - Neonatal Paediatrician Expert 2 - Neonatal ST8 Speciality Trainee Expert 3 - Neonatal Paediatrician Expert 4 - Paediatric Registrar
Institution/Organisation (where applicable): **Contact information:**	Expert 1 - Royal Devon University Healthcare NHS Foundation Trust Expert 2 - Ashford and St Peter's Hospitals NHS Foundation Trust Expert 3 - Ashford and St Peter's Hospitals NHS Foundation Trust Expert 4 - St George's University Hospitals NHS Foundation Trust Expert 1 - Barrack road, Exeter, Devon, EX2 5DW - Harriet.aughey2@nhs.net Expert 2 - Guildford Road, Chertsey, Surrey, KT16 0PZ - katie.evans7@nhs.net Expert 3 - Guildford Road, Chertsey, Surrey, KT16 0PZ - peter.reynolds1@nhs.net Expert 4 - Blackshaw Road Tooting, London SW17 0QT - n.scally@nhs.net
Guideline title:	Neonatal Infection
Guideline Committee:	Guideline Committee meeting on 19th November 2025
Subject of expert testimony:	Switching from IV to oral antibiotics in neonates with suspected or probable early onset neonatal infection: Local data on the effectiveness and safety of this approach, experiences of families and practitioners using this approach, and any implementation and resource impact issues.

Evidence gaps or uncertainties:	Review question: What is the impact of switching from intravenous (IV) to oral antibiotics for babies with suspected early-onset bacterial infection on morbidity and mortality, family outcomes, cost and resource use, and the views, experiences, and perceptions of healthcare professionals, parents or carers and families?

The objective of the review question was to determine whether switching from intravenous (IV) antibiotics to oral antibiotics in term and late preterm babies with suspected early onset neonatal sepsis (within the first 72 hours of life) is clinically effective, cost-effective, and safe. The committee sought evidence on outcomes such as reinfection rates, readmission to hospital, adverse events, mortality, duration of hospital stay, breast feeding rate, sleep quality and parental experience.

One external systematic review (Whear 2025) highlighted limited and mostly very low-certainty evidence on this topic. Only one open label RCT (Keij 2022) and three observational studies (Gyllensvärd 2020, Malchau 2024, Manzoni 2009) were identified. The RCT suggested that switching to oral antibiotics probably reduces duration of hospital stay (moderate-certainty evidence). Observational studies supported this finding, although the certainty of evidence was very low because of methodological limitations. Evidence for mortality, serious adverse events, reinfection rates, readmission to hospital, exclusive breastfeeding, and sleep quality appeared similar between oral and IV antibiotic groups, but the certainty was low to very low. No economic evaluations were available, and there was no evidence on parental perspectives. In light of these limitations, the committee invited expert witnesses to provide additional insights.

This approach of switching to oral antibiotics for early onset sepsis has been implemented locally in a few areas in the UK, including collection of data that has not (yet) been published in peer-reviewed journals. Evidence from these local areas around safety and effectiveness, implementation, resource impact and experiences from affected families and practitioners can help the committee to assess its applicability and usefulness in the UK context.

Section B: Expert to complete

Summary testimony:	[Please use the space below to summarise your testimony in 250–1000 words. Continue over page if necessary]

Early-onset neonatal infection (EOI) remains a significant cause of morbidity in the first days of life. Between 8-12% of babies are screened for EOI and commenced on IV antibiotics. Current interpretation of NICE NG195 typically results in term babies with negative blood cultures but ongoing infection concerns being treated with 5–7 days of intravenous antibiotics. This extended IV therapy requires prolonged hospitalisation, repeated cannulation and avoidable aminoglycoside exposure. International evidence now suggests that, in selected clinically improving term babies, switching early to oral antibiotics is safe, effective and acceptable to families.

Three UK quality-improvement initiatives — at the Royal Devon, St George's Hospital and across the Kent, Surrey and Sussex (KSS) network — now provide the first UK real-world evidence to support this. Across all three programmes, there has been widening national interest, including implementation discussions across Wales and London and high engagement from services seeking to adopt similar pathways. The NOAH resources have been downloaded more than 100 times across 60 NHS trusts.

Description of UK Oral-Switch Pathways

Royal Devon (NOAH)
The Neonatal Oral Antibiotics at Home (NOAH) pathway was introduced in June 2024. Eligibility criteria included term babies (≥37 weeks) who were clinically well, tolerating feeds, had negative cultures at 36 hours, a peak CRP below 50 and ongoing concerns suggesting the need for extended treatment. Babies switched to oral antibiotics at 36 hours. Initially, the oral antibiotic given was co-amoxiclav (dosing as per BNFc). This was later amended to Amoxicillin in order to achieve better Group B Streptococcus coverage and to align with the similar oral switch projects in other parts of the country. Following a supported first dose given in the hospital, babies completed a 7-day course at home and received structured day-five telephone follow-up. The pathway has since been adopted across additional South West sites.

St George's Hospital (PEARL)
The Postnatal Early Antibiotic Review for Low-Risk Babies (PEARL) was launched in September 2024. It applies to babies ≥35 weeks and ≥2000 g who are clinically well, feeding effectively, have negative cultures and meet defined CRP thresholds (peak CRP <100). The treatment protocol is amoxicillin 30mg/kg TDS for total of 7 days (duration inclusive of IV antibiotics already administered). Babies receive their first oral dose under supervision before discharge. Follow-up calls occur at days 5–7 and again at 28 days for audit and evaluation purposes.

KSS Oral Switch Initiative
Launched in April 2024 and gradually adopted across five KSS Trusts, this programme applies to clinically well babies ≥36 weeks with two CRP

measurements less than 50, good feeding and clinician agreement that they are suitable for oral antibiotics. Initially the antibiotic used was co-amoxiclav (dosing as per the RAIN study at 1ml/kg/dose TDS of 125/31 solution) which is a higher dose than the BNFc. This is imminently changing to amoxicillin at the BNFc dose of 30mg/kg TDS to align with other units, simplify pharmacy processes and also upkeep of antimicrobial stewardship principles. Caregivers administer the first dose with the clinical team before discharge, followed by structured telephone follow-up 48-72 hours later. The protocol aims to give the first dose of oral antibiotic 3-6 hrs after the last IV dose - based on the known absorption and pharmacokinetics of oral amoxycillin in babies in order to maintain adequate Minimum Inhibitory Concentrations (MICs) necessary for antibiotic effectiveness.

Evidence of Safety and Effectiveness

These 3 projects collectively demonstrate strong alignment with the published research. A consistent finding across NOAH, PEARL and KSS was the avoidance of between 2 and 2.7 inpatient days per baby when compared with traditional IV therapy.

Gentamicin exposure reduced substantially, with NOAH showing a fall from around three doses per baby to approximately 1.7. Pathways also reduced the need for repeated cannulation; KSS sites found that one-third of babies on the oral-switch pathway required only a single cannula attempt. All babies completed their full oral antibiotic courses.

Presentations to hospital after discharge were uncommon, with very few suspected infections and no missed or deteriorating cases requiring unplanned escalation of care.

Site / Project	Timeframe	Number screened for EOI	Number given prolonged course of antibiotics	Number switched to oral antibiotics	Re-presentations with ?infection	Readmissions due to concerns about systemic infection	Confirmed late sepsis within 28 days
Royal Devon (NOAH)	16 months 01/06/24 – 31/10/25	421	128	73	1	1**	0
St George's (PEARL)	12 months 23/9/24 - 22/9/25	352	135	78	0	0	0
KSS – St Peter's site-level	16 months 01/05/24 - 08/10/25	162	68	44	0	0	0
KSS – Darent Valley	8 months 07/04/2025 – 31/10/2025	181	x	60	1	1***	0

KSS – Wider Network (excluding St Peter's and Darent Valley)	17 months* 29/4/2024 to 08/10/2025	x	x	51	2	1****	0
SW – wider network (excluding Royal Devon)	7 months	121	58	25	0	0	0
Total		x	x	331	4	3	0

x Data not currently available
**Gradual adoption across the KSS network throughout this timeframe*
***One NOAH baby was admitted with suspected infection and was treated with IV antibiotics for 36 hours; all cultures were negative & CRPs were low*
**** One baby was admitted on day 16 with suspected infection and was treated with IV antibiotics for 36 hours; all cultures were negative & CRPs were low*
*****One baby in the KSS network was readmitted to another hospital on day 12 of life and received 7 days IV Abx with a raised CRP*

Family Experience

Family experience has been consistently positive across all three programmes. Parents valued going home earlier, avoiding separation, and establishing bonding and breastfeeding in a familiar environment. They reported confidence in giving oral antibiotics and knowing what to look out for.

• 100% of NOAH parents and 98% in KSS were happy to switch.
• Parents understood how to give oral antibiotics (100% in NOAH; 93% in KSS found them easy to administer).
• Confidence in recognising deterioration was very high (100% in NOAH; 99% in KSS).

Staff Experience

Staff experience was similarly positive. In NOAH's evaluation, 90% of staff were aware of the pathway before launch, 100% understood its aims, 97% supported implementation and 93% felt confident carrying out their roles. Practitioners across all sites reported that the approach was straightforward, improved family-centred care and did not generate additional workload pressure.

Cost and Resource Impact

Length-of-stay reductions translate into substantial cost avoidance. Using the 2024/25 Neonatal Critical Care, Special Care, with External Carer resident, National Average Unit Cost (£941.70 per cot-day), estimates for PEARL and NOAH suggest £1900–£2500 avoided per baby.

Nationally, these projects indicate that 1.5–2% of all babies born may be eligible for an early oral switch — approximately 9,000–12,000 babies per

year. This corresponds to 18,000–32,000 cot-days avoided, with a potential national cost avoidance of £17–30 million annually.

No additional staffing was required for implementation, and resource needs were minimal once eligibility criteria, parent information and follow-up processes were established.

Environmental Impact

Reducing the length of hospital stay, travel to and from neonatal units and the use of disposable equipment associated with IV therapy produces measurable carbon savings. At the Royal Devon alone, the NOAH pathway is estimated to save 8,230 kg CO_2 per year.

Alignment with National Priorities

The oral-switch approach supports national policy priorities, including the Maternity Incentive Scheme, the Three-Year Delivery Plan for Maternity and Neonatal Services, UKHSA IV-to-oral switch criteria, BAPM service standards, GIRFT neonatal recommendations and the NHS Net Zero agenda.

Implications for NICE

These quality improvement projects demonstrate UK real-world findings that an early IV-to-oral switch at 36–48 hours is safe, effective and highly acceptable in carefully selected term babies with negative cultures and improving clinical condition. A NICE recommendation supporting this practice would enable safe adoption, improve family experience, support antimicrobial stewardship and deliver significant environmental and economic benefits.

References to other work or publications to support your testimony' (if applicable):

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