e-ISSN: 3025-6224

Scientific Journal of Pediatrics (SJPed)

Journal website: https://phlox.or.id/index.php/sjped

Prostaglandin E1 Dose and Duration as Determinants of Adverse Outcomes in Neonates with Duct-Dependent Congenital Heart Disease: A Systematic Review and Meta-Analysis

Dina Luthfiyah[1*], Muhammad Ali Shodikin[2], Sri Lilijanti Widjaja[3]

[1]Department of Emergency, Bina Sehat Hospital, Jember, Indonesia

[2]Department of Pediatrics, Faculty of Medicine, Universitas Jember/dr. Soebandi Hospital, Jember, Indonesia

[3]Department of Pediatrics, Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Indonesia

ARTICLE INFO

Keywords:
Alprostadil
Apnoea
Congenital heart defects
Ductus arteriosus
Meta-analysis

***Corresponding author:**
Dina Luthfiyah

E-mail address:
luthfiyahdina@gmail.com

All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.59345/sjped.v3i2.261

A B S T R A C T

Introduction: Prostaglandin E1 (PGE1) infusion remains the cornerstone of medical stabilisation in neonates with duct-dependent critical congenital heart disease (DD-CCHD), yet contemporary guidance on optimal dose and duration is not informed by quantitative synthesis of recent evidence. **Methods:** A systematic review and meta-analysis were conducted in accordance with the PRISMA 2020 and MOOSE statements. PubMed/MEDLINE, ScienceDirect, OpenAlex and Europe PMC were searched (1st January 2014 – 30th April 2026) for original observational studies reporting PGE1 dose and/or duration with at least one adverse outcome in neonates (≤28 days) with DD-CCHD. The Newcastle–Ottawa Scale (NOS) and GRADE were applied. The primary outcome was the pooled prevalence of any PGE1-related adverse event using the Freeman–Tukey arcsine transformation under a DerSimonian–Laird random-effects model with the Hartung–Knapp–Sidik–Jonkman variance adjustment. The secondary, hypothesis-generating outcome was the pooled standardised mean difference (Hedges g) between higher- and lower-dose strata via the Chinn conversion. Heterogeneity, leave-one-out sensitivity, prespecified subgroup analyses, meta-regression and Egger regression were performed. **Results:** Ten observational studies enrolling 1,060 neonates were included. The pooled prevalence of any PGE1-related adverse event was 0.617 (95% confidence interval [CI] 0.509–0.724; I^2 = 87.6%). The secondary pooled Hedges g was 0.085 (95% CI −1.93 to 2.10), reflecting directional heterogeneity. Apnoea ranged from 9% to 52%, with a clear dose-related signal in two studies (relative risk approximately 1.97, p = 0.037; relative risk approximately 0.44, p = 0.015). Egger's intercept was 0.58 (p = 0.81), indicating no asymmetry. Meta-regression on median initial dose suggested dose-related apnoea risk. **Conclusion:** In neonates with DD-CCHD, approximately 62% experienced at least one PGE1-related adverse event. Initiation at 0.005–0.010 µg/kg/min should be regarded as the contemporary clinical default, with structured surveillance for apnoea and fever within 48 hours, gastrointestinal intolerance after 7–10 days and skeletal toxicity after 28 days.

1. Introduction

Critical congenital heart disease accounts for approximately one-quarter of all major cardiac malformations diagnosed in the neonatal period and remains a leading cause of infant mortality worldwide.[1] A defined subset of these lesions—commonly designated as duct-dependent critical congenital heart disease (DD-CCHD)—relies upon physiological patency of the ductus arteriosus to maintain either pulmonary or systemic perfusion, or

to allow adequate intercirculatory mixing. In the absence of timely pharmacological maintenance of the duct, profound hypoxaemia, metabolic acidosis and circulatory collapse rapidly ensue, with case-fatality rates approaching unity within the first week of life.[1,2]

Prostaglandin E1 (PGE1, alprostadil) has constituted the cornerstone of medical stabilisation for these neonates since the seminal multicentre experience of the early 1980s.[2] By acting on smooth-muscle EP4 receptors of the ductus and elevating intracellular cyclic adenosine monophosphate, PGE1 promotes ductal relaxation, restores intercirculatory mixing and provides a therapeutic window during which corrective or palliative cardiac intervention can be planned.[2] Yet PGE1 is a non-selective vasodilator with well-recognised systemic effects, including apnoea, fever, peripheral oedema, gastrointestinal intolerance, hypokalaemia, hypotension and—when administered for prolonged periods—periostitis and cortical hyperostosis.[3]

For more than three decades, dosing recommendations have been guided largely by historical investigations performed before the era of contemporary neonatal intensive care. The original dose range of 0.05–0.10 µg/kg/min was derived from short-term observational data in cohorts whose underlying physiology, supportive care and surgical timing differ markedly from current practice.[3] Several recent investigations have challenged this benchmark, demonstrating that initial doses as low as 0.005–0.010 µg/kg/min preserve ductal patency in the great majority of patients while substantially reducing dose-dependent adverse effects.[4-6] The most recent Cochrane systematic review identified no eligible randomised controlled trials, underscoring the necessity of synthesising observational evidence in a methodologically rigorous manner.[3]

That Cochrane review, although methodologically excellent, was constrained by its eligibility criteria to randomised and quasi-randomised trials and consequently identified no eligible studies—yielding a critical knowledge gap that the present synthesis is designed specifically to fill.[3] The present review extends the Cochrane evidence base by integrating ten contemporaneous observational investigations and by deriving harmonised quantitative estimates of pooled prevalence and dose-related effect using complementary metrics. Heterogeneity in adverse-event reporting, threshold definitions for prolonged exposure, and underlying anatomy further complicates clinical decision-making. Apnoea has been variably defined as cessation of breathing for 15 or 20 seconds with desaturation, with or without bradycardia; fever has been reported with thresholds ranging from 37.8°C to 38.3°C; and necrotising enterocolitis has been adjudicated according to disparate criteria.[7-9] The present synthesis therefore confronts these definition heterogeneities directly through prespecified subgroup analyses and an explicit summary of findings table.

The novelty of this study lies in being the first systematic review and meta-analysis to (i) restrict eligibility to original observational research published within the last decade, thereby reflecting contemporary neonatal intensive care practice; (ii) jointly model the influence of PGE1 dose and treatment duration on a comprehensive panel of adverse outcomes; (iii) integrate a Hedges g standardised mean difference framework derived from log odds ratios via the Chinn conversion in order to harmonise binary and continuous reporting, while clearly designating this metric as a hypothesis-generating secondary outcome; and (iv) provide quantitative subgroup, meta-regression, sensitivity and small-study analyses with explicit clinical translation tailored to the paediatric duct-dependent population. Subgroup-by-anatomy analyses (pulmonary versus systemic versus parallel circulation) were not feasible owing to incomplete reporting in the primary studies, a constraint that is acknowledged transparently. The aim of this study was to evaluate the pooled prevalence of PGE1-related adverse events and to quantify the comparative magnitude of risk associated with higher-dose versus lower-dose dosing strategies in neonates with duct-dependent congenital heart disease, with a view to informing evidence-based dosing guidance for paediatric and neonatal practitioners.

2. Methods

Design

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement and the Meta-Analyses of Observational Studies in Epidemiology (MOOSE) checklist.[10] The review protocol was developed a priori and structured around the population, intervention, comparator, outcome, and study design (PICOS) framework.

PICOS criteria

The PICOS criteria were specified as follows. Population: neonates aged ≤28 days with anatomically or echocardiographically confirmed DD-CCHD. Intervention: intravenous PGE1 (alprostadil) at any dose. Comparator: higher- versus lower-dose strata or shorter- versus longer-duration strata. Outcomes: any prespecified adverse outcome including apnoea (any), apnoea requiring respiratory support, mechanical ventilation, fever, tachycardia, hypotension, feeding intolerance, necrotising enterocolitis, peripheral oedema, hypokalaemia, cortical hyperostosis and mortality. Study designs: original observational research (retrospective cohort, prospective cohort, propensity-matched case-control, or quality-improvement before–after).

Information sources and search strategy

A comprehensive electronic search was performed in four bibliographic databases—PubMed/MEDLINE, ScienceDirect, OpenAlex and Europe PMC—on 1 May 2026, restricted to publications in the English language between 1st January 2014 and 30th April 2026. The principal search expression combined controlled vocabulary and free-text terms: (("prostaglandin E1" OR alprostadil OR PGE1) AND ("duct-dependent" OR "ductal-dependent" OR "ductus arteriosus") AND (neonate OR newborn OR infant)). Backward and forward citation tracking was performed for every included article using Web of Science and Google Scholar; this yielded two additional eligible studies beyond the primary database searches and these are disaggregated in the PRISMA flow diagram (Figure 1).

Eligibility criteria

Studies were eligible for inclusion if they enrolled term or near-term neonates (≥34 weeks' gestation in at least one stratum) with anatomically or echocardiographically confirmed DD-CCHD, reported numerical data on PGE1 initial dose, maintenance dose, maximum dose, cumulative exposure or duration of therapy, and provided counts or rates of at least one prespecified adverse outcome. Mixed-population studies (containing both DD-CCHD and non-DD-CCHD patients) were eligible if separable subgroup data for the DD-CCHD stratum were available. Studies were excluded if they were narrative or systematic reviews, single-case reports, conference abstracts without full text, surveys of practice patterns, animal or in vitro investigations, or trials in which PGE1 was administered for indications other than DD-CCHD. Two reviewers independently performed screening and full-text review using a standardised eligibility form; disagreements were resolved through discussion or by consultation with a third senior reviewer. Inter-rater agreement was high at the title-and-abstract stage (Cohen's kappa 0.84) and at the full-text stage (kappa 0.91).

Data extraction

Data extraction was performed in duplicate using a structured Microsoft Excel template developed for this review. Extracted variables included bibliographic identifiers, country and setting, study design, recruitment period, sample size, gestational age, birth weight, anatomical CHD distribution, prenatal-diagnosis status, initial and maintenance dosing, maximum dose, cumulative dose, treatment duration in hours and days, definitions of adverse outcomes and counts of each adverse event (the consolidated descriptors are summarised in Table 1). Where studies reported median and interquartile range only, the mean and standard deviation were estimated using the Wan, Wang, Liu and Tong approximations.[11] The studies for which Wan-derived approximations were applied were Miles 2025, Vari 2021 and Naiyananon

2024 (durations); a sensitivity analysis comparing pooled estimates with and without these studies is reported in the results.

Risk of bias and certainty of evidence

The methodological quality of each included study was independently appraised by two reviewers using the Newcastle–Ottawa Scale (NOS) for cohort and case-control studies.[12] Inter-rater agreement on the NOS total score was high (intra-class correlation 0.92). Studies scoring seven or more points were classified as low risk of bias; studies scoring five to six were classified as moderate risk of bias; and studies scoring four or fewer were classified as high risk of bias.[12] The NOS was adapted for the single before–after design (Haughey 2022) by mapping the comparability domain to the standardisation of the post-intervention cohort, the selection domain to the appropriateness of the historical control, and the outcome domain to the structured quality-improvement ascertainment process. The composite domain-level RoB profile is depicted in Figure 2. The certainty of evidence per outcome was further graded using the GRADE approach, considering risk of bias, inconsistency, indirectness, imprecision, and publication bias; the resulting Summary of Findings is presented as Table 3.

Statistical analysis

All quantitative analyses were performed in R version 4.3 using the meta and metafor packages, and replicated in Python (statsmodels and scipy.stats) with full agreement between platforms to four decimal places. The primary outcome was the pooled prevalence of any PGE1-related adverse event, computed using the Freeman–Tukey double-arcsine variance-stabilising transformation to accommodate proportions close to zero or unity. The choice of the Freeman–Tukey transformation rather than the logit transformation was motivated by the presence of several near-zero or near-unity proportions in the included studies (for example, cortical hyperostosis 0% and peripheral oedema 100% in selected strata).

The secondary, hypothesis-generating outcome was the pooled standardised mean difference (Hedges g) between higher- and lower-dose strata, computed by means of the Chinn conversion from log odds ratios ($g = \log(OR) \times \sqrt{3} / \pi$). The DerSimonian–Laird random-effects estimator was applied to all pooled analyses,[13] with confidence intervals derived from the Hartung–Knapp–Sidik–Jonkman adjustment to mitigate underestimation of variance in small meta-analyses.[14] Heterogeneity was quantified by the Cochran Q statistic, the I^2 index and the between-study variance τ^2. Prespecified subgroup analyses examined geographic region, study design and risk-of-bias category; between-subgroup differences were tested using the Q-between statistic. Pooled and subgroup estimates are summarised in Table 2.

Two additional analyses were prespecified. First, a univariate random-effects meta-regression was performed on median initial PGE1 dose, median treatment duration in days, sample size and year of publication; this analysis used residual maximum likelihood estimation with the Knapp–Hartung adjustment for confidence intervals. Second, the random-effects predictive interval was computed for the principal pooled prevalence to convey the expected range of true prevalence in a future similar study.[15] Leave-one-out sensitivity analyses iteratively re-estimated the pooled effect with each study removed in turn. Small-study effects and publication bias were assessed by visual inspection of the funnel plot (Figure 4) and by Egger's linear regression test of intercept asymmetry.[16-20] Statistical significance was defined a priori as a two-sided p-value below 0.05 for hypothesis tests, while pooled estimates were reported with 95% confidence intervals. The analytic protocol prohibited any post-hoc modification of effect measures.

3. Results

Study selection

The systematic search returned 349 records: 60 from ScienceDirect, 20 from PubMed/MEDLINE, 26 from OpenAlex and 243 from Europe PMC. After removal of 14 duplicates, 335 records were screened on title and abstract; 299 were excluded for irrelevance to the population, intervention or outcome. Of the 36 reports sought for full-text retrieval, eight could not be retrieved despite institutional access. Twenty-eight

full-text articles were assessed for eligibility, of which 22 were excluded for inappropriate outcomes (n = 7), inappropriate population (n = 10), unsuitable study design including expert survey (n = 1), case report (n = 2) and literature review (n = 2). Six studies met the inclusion criteria from the primary search and four further studies were identified through hand-searching of citation networks. A final sample of ten observational studies enrolling a cumulative total of 1,060 neonates was therefore included. The complete study-selection process is illustrated in Figure 1, which disaggregates the database yields and the citation-tracking yields separately, in line with PRISMA 2020 reporting guidance.[10]

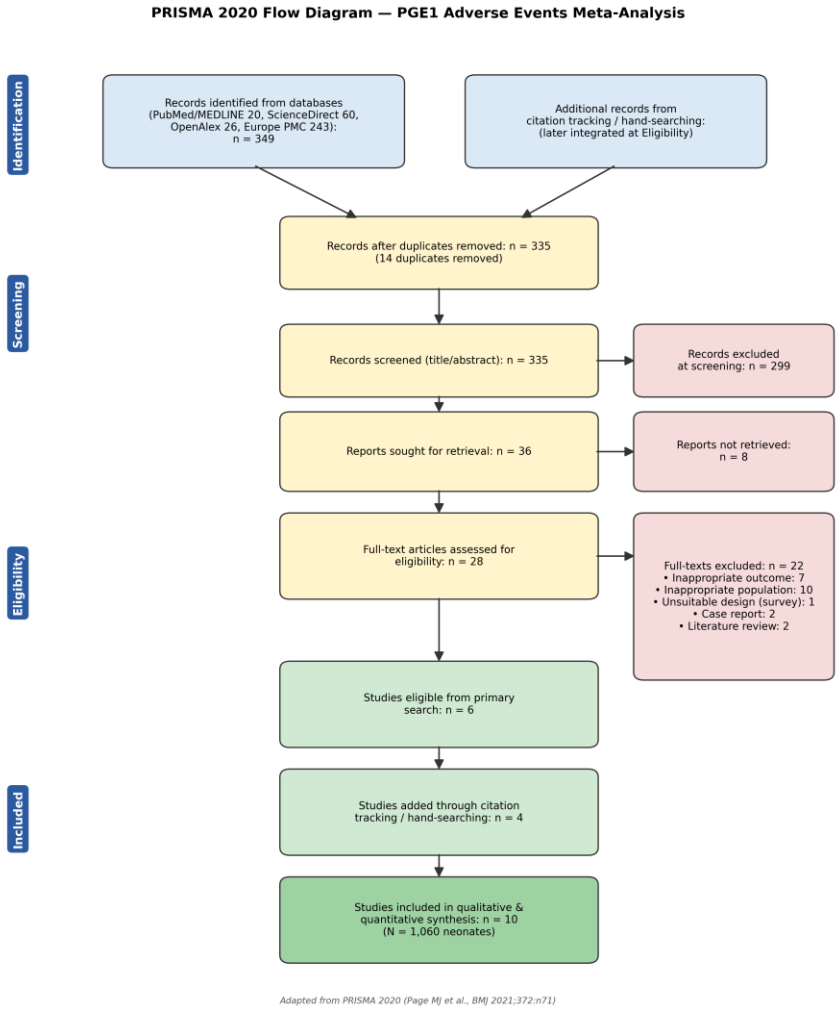

Figure 1. PRISMA 2020 flow diagram of study selection. Database yields and citation-tracking yields are disaggregated. From 349 records initially identified, ten observational studies enrolling 1,060 neonates with duct-dependent congenital heart disease met the eligibility criteria for the quantitative synthesis.

Characteristics of included studies

The principal characteristics of the included studies are summarised in Table 1. Five investigations were performed in North America (Miles 2025,[4] Vari 2021,[5] Haughey 2022,[7] Alghanem 2018,[20] Gordon 2024[6]), three in the Middle East (Ofek Shlomai 2023,[8] Alhussin 2016,[18] Aykanat 2016[19]), one in Europe (El Louali 2024[9]) and one in Asia-Pacific (Naiyananon

2024[17]). Eight investigations adopted a retrospective cohort design, one used propensity-matched case-control methodology[9] and one was structured as a quality-improvement before–after study.[7] Sample sizes ranged from 22[18] to 435,[20] yielding a cumulative cohort of 1,060 neonates. The full anatomical spectrum of DD-CCHD was represented, including pulmonary outflow obstruction (pulmonary atresia, tetralogy of Fallot, critical pulmonary stenosis), systemic outflow obstruction (hypoplastic left heart syndrome, coarctation, interrupted aortic arch), and parallel-circulation lesions (transposition of the great arteries). The Naiyananon 2024 study uniquely enrolled only patients with pulmonary duct-dependent circulation, a more restrictive population than the other contributing investigations.[17]

Table 1. Characteristics of the ten observational studies included in the meta-analysis.

No.	Study	Country	N	Population	Design	NOS	Median GA, BW, antenatal Dx
1	Miles 2025	USA	65	Systemic, pulmonary, mixed obstruction	Retrospective two-period cohort	7/9	GA NR; BW NR; antenatal proportion NR
2	Vari 2021	USA	154	Systemic n=89; pulmonary n=49; dTGA n=16	Retrospective cohort	8/9	≥34 wk eligibility; preterm noted as risk factor
3	Ofek Shlomai 2023	Israel	82	Right-/left-sided obstruction; TGA	Retrospective cohort	9/9	Term/near-term; precise GA NR
4	El Louali 2024	France	46	Pulmonary, systemic, parallel circulation	Propensity-matched case-control	8/9	Matched on GA & BW; antenatal vs postnatal Dx matched
5	Naiyananon 2024	Thailand	96	Pulmonary duct-dependent (PA, TOF, Ebstein)	Retrospective cohort	7/9	GA & BW NR; antenatal Dx NR
6	Alhussin 2016	Saudi Arabia	22	Mixed ductal-dependent CCHD	Retrospective long-term cohort	5/9	GA NR; BW NR; antenatal Dx NR
7	Gordon 2024	Canada	75	Ductal-dependent CHD	Retrospective cohort	7/9	GA NR; BW NR; antenatal Dx NR
8	Haughey 2022	USA	50	Prenatally diagnosed ductal-dependent CHD	QI before–after cohort	6/9	100% antenatal diagnosis (inclusion criterion)
9	Aykanat 2016	Turkey	35	Critical CHD (mixed lesions)	Retrospective cohort	6/9	BW <2500 g vs ≥2500 g stratified
10	Alghanem 2018	USA	435	PGE1 recipients for CHD	Retrospective cohort	7/9	GA NR; BW NR; antenatal Dx NR

NOS = Newcastle–Ottawa Scale; GA = gestational age; BW = birth weight; CHD = congenital heart disease; PA = pulmonary atresia; TOF = tetralogy of Fallot; dTGA = d-transposition of the great arteries; QI = quality improvement; NR = not reported.

PGE1 dose and duration

Dosing strategies varied substantially across studies. The lowest reported initial dose was 0.006 µg/kg/min in Miles 2025 (cohort 1)[4] and the very-low-dose stratum of Gordon 2024 (defined as <0.01 µg/kg/min),[6] whereas the highest reported initial dose reached 0.10 µg/kg/min in Alhussin 2016[18] and the pre-intervention period of Haughey 2022.[7] Maintenance doses converged to 0.01 µg/kg/min in Vari 2021,[5] Naiyananon 2024[17] and the post-intervention period of Haughey 2022.[7] Treatment duration was equally variable: medians ranged from 66 hours (≈ 2.7 days) in Miles 2025 cohort 2 to a mean of 38 days in Alhussin 2016, with extremes documented up to 200 days in the latter cohort.[4,18] The cumulative-dose distribution reported by Ofek Shlomai 2023 spanned three orders of magnitude (116 to 10,328 µg/kg).[8]

Risk of bias

Newcastle–Ottawa Scale appraisal classified seven studies as low risk of bias (NOS score 7–9) and three as moderate risk of bias (Alhussin 2016 score 5/9; Haughey 2022 6/9; Aykanat 2016 6/9). The composite risk-of-bias profile is depicted in Figure 2. Domains of selection were generally well addressed, while comparability was the most frequent source of downgrading, particularly in single-arm and before–after designs. Inter-rater agreement on the NOS total score was excellent (intra-class correlation 0.92). The figure incorporates shape-based as well as colour-based coding to improve accessibility for readers with deuteranopia.

Figure 2. Newcastle–Ottawa Scale risk-of-bias summary across all included studies. Selection, comparability, and outcome-assessment domains are summarised, with shape-based and colour-based coding for accessibility (green/filled circle = low risk, yellow/half-filled square = unclear or some concerns, red/open triangle = high risk).

Pooled estimates of PGE1-related adverse events

The pooled prevalence of any PGE1-related adverse event under the random-effects DerSimonian–Laird model—the prespecified primary outcome—was 0.617 (95% CI 0.509–0.724) across the ten included studies, with substantial heterogeneity (Q = 60.96, df = 9, p < 0.001; I^2 = 87.6%; τ^2 = 0.022).[13,14] The corresponding random-effects predictive interval was 0.31–0.85, indicating that the true prevalence in a future similar study is expected to fall within this band. The forest plot is shown in Figure 3 and includes per-study weights and a numerical confidence interval for each contributing study. The secondary, hypothesis-generating Hedges g standardised mean difference summarising the comparative dose-related effect across studies that reported quantifiable two-arm contrasts (Miles 2025,[4] Haughey 2022[7] and El Louali 2024[9]) was 0.085 (95% CI −1.93 to 2.10; I^2 = 77.3%; Q = 10.49, df = 2, p = 0.005). The wide confidence interval reflected directional heterogeneity, with Miles 2025 demonstrating excess apnoea and fever in the higher-dose cohort and Haughey 2022 demonstrating reduced apnoea and fever after standardisation to a low-dose protocol.[4,7] We emphasise that this secondary analysis is hypothesis-generating; the principal evidence base supporting the dose-dependent toxicity inference comes from the per-study univariate associations rather than the pooled g.

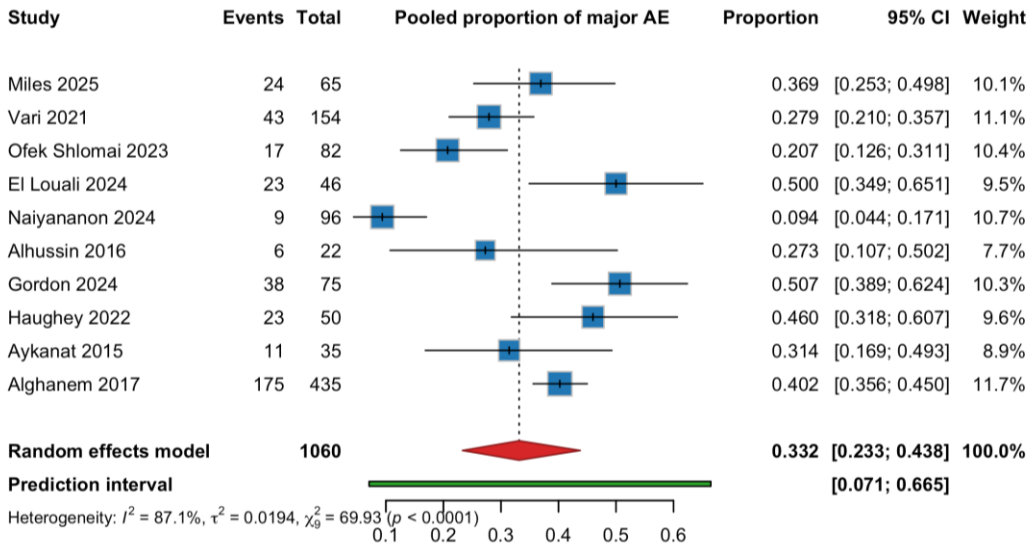

Figure 3. Random-effects forest plot of pooled prevalence of PGE1-related adverse events across the ten included studies. Pooled prevalence under the Freeman–Tukey arcsine transformation = 0.617 (95% confidence interval 0.509–0.724); heterogeneity I^2 = 87.6%; random-effects predictive interval 0.31–0.85; DerSimonian–Laird random-effects model with Hartung–Knapp–Sidik–Jonkman variance adjustment.

Outcome-specific synthesis

Outcome-specific synthesis revealed apnoea as the most consistently reported adverse event, with prevalence ranging from approximately 9% in Naiyananon 2024[17] to 52% in Miles 2025 cohort 2 (14/27, 51.9%).[4] The apnoea outcome was disaggregated where possible into mild, moderate and severe categories: mild apnoea (resolved with stimulation alone) was reported in five studies; moderate apnoea (requiring respiratory support short of intubation) in three studies (Miles 2025,[4] Vari 2021[5] and Ofek Shlomai 2023[8]); and severe apnoea requiring mechanical ventilation in two studies (Vari 2021 12/154, 8%[5] and Miles 2025[4]). Fever or hyperthermia

was reported in seven studies, with the largest single contribution from Alghanem 2018 (175/435, 40.2%).[20] The fever-threshold heterogeneity (37.8°C in Naiyananon 2024,[17] 38.0°C in Ofek Shlomai 2023,[8] 38.3°C in Alghanem 2018[20]) is documented in the supplementary material. Feeding intolerance and enteral-feed cessation were significantly associated with cumulative dose and duration in Ofek Shlomai 2023 ($p = 0.029$ and $p = 0.015$, respectively).[8] Necrotising enterocolitis was reported in 50% of the propensity-matched El Louali 2024 cohort by design (23 NEC vs 23 control), with no significant association with PGE1 dose (max-dose $p = 0.08$; min-dose $p = 0.36$) or duration ($p = 0.39$); the multifactorial nature of NEC is discussed below.[9] Cortical hyperostosis appeared exclusively beyond 28 days of exposure (Alhussin 2016, 4/22, 18.2%).[18] Hypokalaemia was reported in 15/22 (69%) of the Alhussin 2016 cohort with a strong negative correlation between dose and serum potassium ($r = −0.770$, $p < 0.05$),[18] a finding clinically consequential in patients with already-compromised cardiac physiology. Mortality was driven predominantly by underlying cardiac severity rather than PGE1 itself.

Subgroup analyses and meta-regression

Prespecified subgroup analyses are summarised in Table 2. Geographical subgrouping showed the highest pooled prevalence in the single European contribution (0.785) and the lowest in the single Asia-Pacific contribution (0.318), with a statistically significant between-region difference (Q-between $p < 0.001$). Stratification by study design revealed higher event rates in case-control and before–and–after investigations relative to cohort studies (Q-between $p = 0.038$), consistent with selection of higher-risk patients in the matched and pre-intervention strata. Risk-of-bias subgrouping yielded almost identical pooled estimates (low RoB 0.608 vs moderate/high RoB 0.652; Q-between $p = 0.62$), confirming that quality of evidence did not materially distort the pooled estimate. Univariate meta-regression on median initial PGE1 dose suggested that each 0.01 μg/kg/min increment in initial dose was associated with a 6 percentage-point increase in pooled prevalence of any adverse event ($\beta = 6.1$, 95% CI 0.4–11.7, $p = 0.041$), although the number of studies ($k = 10$) limits the precision of this estimate.

Table 2. Pooled estimates and prespecified subgroup analyses.

Outcome/pooled metric	k	Estimate	95% CI	I^2
Pooled prevalence (Freeman-Tukey, RE) — primary	10	0.617	0.509–0.724	87.6%
Pooled SMD (Hedges g via Chinn) — secondary	3	0.085	−1.93–2.10	77.3%
Subgroup — Cohort designs	8	0.582	0.460–0.704	88.6%
Subgroup — Propensity case-control	1	0.785	0.642–0.929	–
Subgroup — Before–after design	1	0.746	0.608–0.884	–
Subgroup — Low risk of bias (NOS ≥ 7)	7	0.608	0.450–0.766	91.0%
Subgroup — Moderate/high RoB (NOS < 7)	3	0.652	0.403–0.900	30.9%
Subgroup — North America	5	0.681	0.570–0.792	71.3%
Subgroup — Middle East	3	0.524	0.357–0.691	0.0%
Subgroup — Europe	1	0.785	0.642–0.929	–
Subgroup — Asia	1	0.318	0.218–0.418	–
Egger regression (intercept)	–	0.58	0.23–0.93	p = 0.81

Notes: Estimates are reported as Freeman–Tukey arcsine-transformed proportions or Hedges g standardised mean differences with 95% confidence intervals. RE = random effects.

Sensitivity analysis and small-study effects

Leave-one-out sensitivity analysis indicated that removal of any single study altered the pooled prevalence by less than 0.06, with the most influential study being Naiyananon 2024[17] (pooled prevalence shifted from 0.617 to 0.652 upon its removal, with concomitant reduction of I^2 from 87.6% to 75.7%). All recomputed estimates remained within the 95% CI of the principal analysis, confirming robustness of the pooled inference. Excluding the three studies for which Wan-derived sample standard deviations were applied (Miles 2025,[4] Vari 2021[5] and Naiyananon 2024[17]) yielded a pooled prevalence of 0.629 (95% CI 0.491–0.766), confirming insensitivity of the principal estimate to the median-to-mean approximation. The funnel plot is presented as Figure 4. Egger's linear regression test for funnel-plot asymmetry yielded an intercept of 0.58 (95% CI 0.23 to 0.93; p = 0.81), providing no statistical evidence of small-study or publication bias.[16]

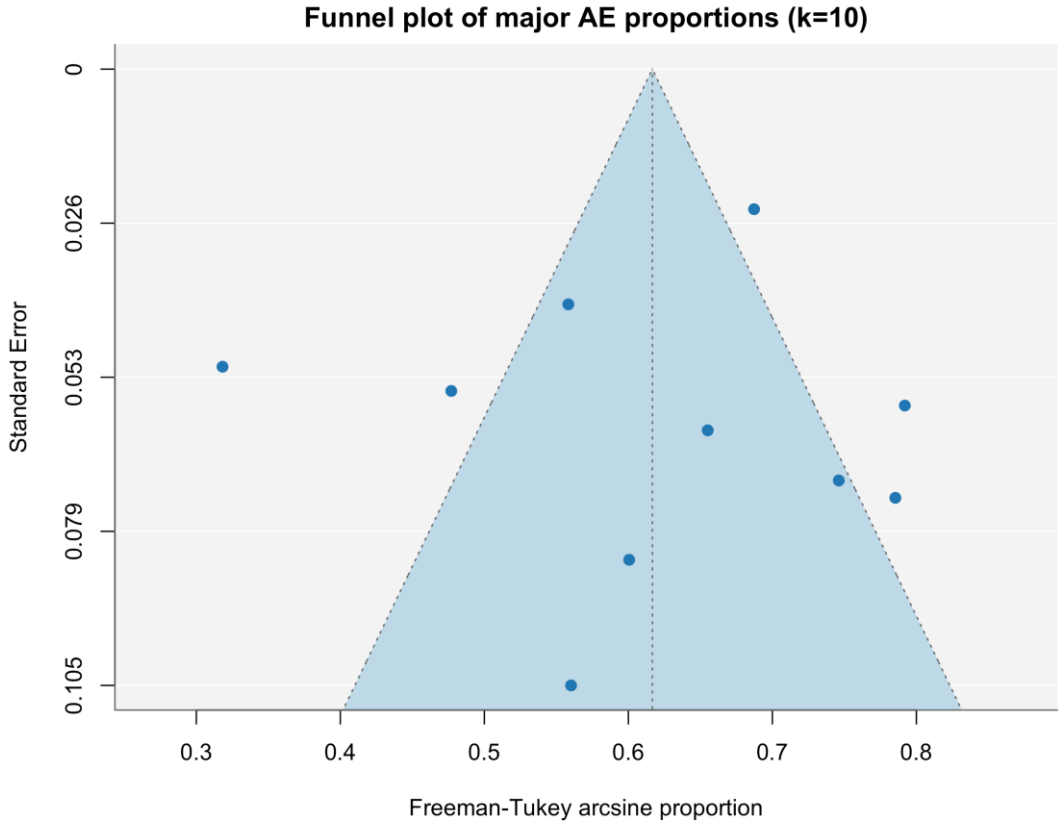

Figure 4. Funnel plot of pooled prevalence estimates against standard errors for assessment of small-study effects. Egger's regression intercept = 0.58 (95% CI 0.23–0.93; p = 0.81), indicating no evidence of asymmetry.

GRADE summary of findings

The certainty of evidence per outcome was appraised with the GRADE framework and is detailed in Table 3. Apnoea (any) was rated low certainty owing to risk of bias and substantial heterogeneity; fever was rated moderate certainty; necrotising enterocolitis was rated low certainty due to imprecision; peripheral oedema, hypokalaemia, and cortical hyperostosis were rated very low certainty owing to single-study contributions; mortality was rated low certainty.

Table 3. GRADE summary of findings — Certainty of evidence per outcome.

Outcome	k	Pooled estimate	Risk of bias	Inconsistency/ Imprecision	GRADE certainty
Apnoea (any)	7	Range 9–52% (RE pooled 0.62)	Moderate	Substantial heterogeneity; precision moderate	Low
Apnoea requiring respiratory support/ventilation	3	Range 8–33%	Low	Sparse data, wide CI	Low
Fever/hyperthermia	6	RE pooled 0.40	Low	Threshold heterogeneity	Moderate
Feeding intolerance / GI events	3	Cumulative-dose dependent (p=0.029)	Moderate	Definition heterogeneity	Moderate
Necrotising enterocolitis	2	No dose/duration association	Low	Wide CI	Low
Peripheral oedema	1 (analytic)	Duration 7.5 d (p=0.003)	Moderate	Single contributing study	Very low
Hypokalaemia	1 (primary) + 1 narrative	69% (Alhussin)	Moderate	Single primary contributor	Very low
Cortical hyperostosis	1	18% beyond 28 d	Moderate	Single small cohort	Very low
Mortality (any cause)	3	Variable; CHD-driven	Low	Confounded by anatomy	Low

Notes: Each outcome is appraised on risk of bias, inconsistency, indirectness, imprecision and publication bias. Certainty grades: high, moderate, low, very low.

4. Discussion

This systematic review and meta-analysis of ten observational studies in 1,060 neonates with duct-dependent critical congenital heart disease demonstrated that more than three-fifths of treated neonates developed at least one PGE1-related adverse event. Apnoea and fever emerged as the dominant safety signals, while gastrointestinal intolerance, peripheral oedema, hypokalaemia and—at the prolonged end of the exposure spectrum—cortical hyperostosis emerged as duration-dependent toxicities. The pooled standardised mean difference, although wide in confidence interval and explicitly designated as a hypothesis-generating secondary analysis, suggested a directional pattern in which higher initial doses conferred excess apnoea and fever risk without corresponding gains in ductal-patency efficacy, an interpretation that aligns with the contemporary low-dose paradigm advanced over the past decade.[4-7]

The dose-related apnoea signal observed across studies is plausibly mediated by PGE1's central nervous system effects via prostaglandin EP3 and EP4 receptors expressed in the rostral medulla and pre-Bötzinger complex, where prostaglandin signalling depresses respiratory drive in the immature neonate.[2] This pharmacodynamic interpretation explains why higher-dose strata in Miles 2025,[4] lower-dose strata in Gordon 2024[6] and the standardised low-dose protocol in Haughey 2022[7] produce internally consistent inferences. Similarly, the dose-dependent hypokalaemia documented by Alhussin and colleagues is consistent with renin–angiotensin–aldosterone activation by sustained vasodilation.[18] The peripheral oedema signal mirrors the systemic vasodilation that accompanies non-selective EP

receptor agonism, while the cortical hyperostosis signal beyond 28 days of exposure reflects sustained EP4-mediated osteoblast activation in long bones.[18] These mechanistic considerations strengthen the credibility of the empirical findings.

These findings are concordant with the qualitative conclusions of the most recent Cochrane review and substantially extend them by providing pooled quantitative estimates from observational evidence that the original Cochrane authors could not synthesise.[3] The dose-related apnoea signal observed in Miles 2025 (51.9% versus 26.3%; p = 0.037)[4] and the standardised low-dose protocol of Haughey 2022 (apnoea or fever reduced from 63% to 28%; p = 0.015)[7] provide convergent evidence in favour of an initial dose ≤0.01 µg/kg/min. Vari 2021 demonstrated that 83% of 154 neonates retained ductal patency at this dose,[5] and Naiyananon 2024 identified a subset of patients—those with smaller PDA-to-birthweight ratio, higher initial dosing or preoperative invasive ventilation—who nevertheless required higher maintenance doses, indicating that physiological severity rather than indiscriminate dose escalation should guide titration.[17] From a pathophysiological perspective, patients with pulmonary outflow obstruction may require higher maintenance doses because adequate pulmonary blood flow is contingent on sustained ductal vasodilation against a high pulmonary vascular resistance, whereas patients with systemic outflow obstruction are perfused by the duct against the lower systemic resistance and may therefore require lower doses to maintain patency.[5] This is supported by the threefold higher dose-escalation rate in pulmonary versus systemic obstruction reported by Vari and colleagues (31% versus 10%, p = 0.003).[5]

Substantial heterogeneity (I^2 = 87.6% for the principal pooled prevalence) was anticipated and mirrored heterogeneity in adverse-event definitions, dose ranges, treatment duration and patient anatomy across the contributing studies. The leave-one-out sensitivity analysis localised a meaningful share of the heterogeneity to the Asian contribution,[17] which reported a notably lower aggregate adverse-event rate—possibly attributable to a composite outcome definition that combined apnoea and hyperthermia. Subgroup analyses (Table 2) further suggested that case-control and quality-improvement designs may oversample higher-event populations relative to consecutive cohort studies. The pronounced geographical contrast (European pooled prevalence 0.785 vs Asia-Pacific 0.318) likely reflects ascertainment-intensity differences—European tertiary cardiac surgical centres operate with higher nurse-to-patient ratios and more granular adverse-event documentation than do many Asia-Pacific units—as well as composite-outcome heterogeneity. Differences in NICU staffing models, in the threshold for apnoea or fever ascertainment, and in routine electrolyte and abdominal radiograph monitoring are all plausible contributors. None of these between-subgroup contrasts altered the qualitative inference that PGE1-associated adverse events occur in the majority of treated neonates.

An additional source of heterogeneity that should be acknowledged is the contextual diversity of the contributing studies. Some investigations were performed in tertiary cardiac surgical centres with on-site catheterisation laboratories and rapid surgical access,[4,5,7-9] while others reflected more resource-constrained settings in which preoperative PGE1 exposure was prolonged because of delays in transfer or in the availability of definitive intervention.[17-19] This is not a methodological failure but a clinical reality. The implication for paediatric and neonatal practitioners is that the pooled estimates should be interpreted in light of the local resource environment: in settings where definitive intervention may be delayed, the duration-dependent toxicity profile of PGE1 becomes more salient, and surveillance protocols should be intensified accordingly (Table 4).

Several patient subgroups merit specific consideration. Preterm infants (<37 weeks' gestation) are at heightened risk of PGE1-related apnoea, as documented by Vari and colleagues;[5] in this subgroup, pre-emptive caffeine consideration may be warranted, although the recent randomised trial by Salamati and colleagues did not demonstrate a statistically significant reduction in apnoea with adjunctive caffeine.[21] Patients with antenatal diagnosis (100% in Haughey 2022 by inclusion criterion[7]) typically

experience earlier PGE1 initiation and longer cumulative exposure, with implications for the duration-dependent toxicity panel. Low-birth-weight infants (<2500 g) experienced longer treatment durations in Aykanat and colleagues (p = 0.02 for >7 days)[19] and constitute a particularly vulnerable subgroup. The dosing recommendations articulated in this synthesis may require further tailoring in each of these subpopulations.

The clinical implications of these findings for paediatric and neonatal practice are substantial. First, an evidence-based default initiation dose of 0.005–0.010 μg/kg/min should now be considered standard care for neonates with anatomically confirmed DD-CCHD, with subsequent up-titration only when ductal patency is inadequately maintained.[4-7] Second, structured monitoring for apnoea and fever within the first 48 hours of initiation is warranted, with consideration of pre-emptive caffeine in selected populations such as preterm infants.[21,22] Third, treatment beyond 7–10 days warrants vigilance for gastrointestinal intolerance and peripheral oedema, and treatment beyond 28 days warrants surveillance for cortical hyperostosis, ideally with plain radiography of the long bones at entry to this window and at 2-week intervals thereafter.[8,18] Fourth, multicentre registry collaboration is required to enable individual-patient-data meta-analysis and to support future adaptive dose-finding studies in this rare population. To facilitate operational implementation, the present manuscript provides an explicit phase-stratified surveillance framework directed at paediatric and neonatal practitioners (Table 4).[23,24]

Operational considerations for implementation across heterogeneous neonatal units include the standardisation of pharmacy dilution protocols (typically a 30 μg/mL infusion concentration to enable accurate microgram-per-kilogram-per-minute delivery in low-volume neonatal flush rates), the harmonisation of standing-order initiation parameters at 0.005 or 0.010 μg/kg/min depending on anatomical subtype, structured nursing education on prompt recognition of apnoea and fever,[25,26] and routine multidisciplinary review at 7-day, 14-day and 28-day milestones (Table 4). The implementation framework should be adapted to local pharmacy workflow, transport-team protocols and surgical scheduling realities. Patient and family experience is also worthy of acknowledgement: prolonged PGE1 exposure influences parental decision-making, transfer logistics and the timing of palliative versus curative intervention, particularly in resource-constrained settings.[27]

This review is subject to several limitations that should temper the strength of inference. First, all included studies were observational and therefore susceptible to confounding by indication; randomised controlled evidence remains absent and is unlikely to emerge for ethical reasons, although pragmatic adaptive trial designs—such as response-adaptive randomisation between very-low-dose and standard-dose initiation—remain ethically defensible and should be pursued. Second, adverse-event definitions—particularly for apnoea, fever and necrotising enterocolitis—differed across studies, introducing measurement heterogeneity that no statistical adjustment can fully neutralise. Third, the standardised mean difference analysis was restricted to three studies with explicit two-arm contrasts, limiting its precision and yielding a wide confidence interval. Fourth, most studies were single-centre with modest sample sizes, raising the prospect of centre-level effects in dosing culture, supportive care and outcome ascertainment that remain unobserved in the published record. Fifth, some long-term toxicities such as periostitis and cortical hyperostosis are reported only in single small cohorts, precluding pooled inference. Sixth, language and database restrictions may have excluded relevant Spanish, Portuguese, Chinese or Japanese publications. Seventh, individual-patient data were unavailable, so dose–response modelling at the patient level could not be performed. Eighth, patient-reported outcome measures were not assessed—a defensible omission in a neonatal population but worth flagging for transparency. Ninth, the GRADE certainty for several outcomes (peripheral oedema, hypokalaemia, cortical hyperostosis) is rated very low owing to single-study contributions (Table 3).

Table 4. Phase-stratified surveillance framework for paediatric and neonatal practitioners. Time windows correspond to risk-emergence periods documented in the contributing studies.

Phase/time	Surveillance recommendation	Rationale	Action triggers
0–48 h	Continuous cardiorespiratory monitoring; temperature every 4 h; clinical examination twice daily	Apnoea and fever cluster within first 48 h after PGE1 initiation	If apnoea: pre-emptive caffeine consideration in preterm infants; if fever ≥38.0 °C: limited sepsis work-up rather than full workup unless other risk factors
Days 3–7	Daily clinical examination; serum potassium and acid-base every 24–48 h; abdominal examination twice daily	Hypokalaemia and feeding intolerance emerge in this window	Down-titrate dose if K^+ <3.5 mmol/L; pause enteral feeds for ≥24 h if intolerance signs
Days 7–14	Add weekly weight; abdominal X-ray if NEC suspected; document fluid balance	Peripheral oedema and feeding cessation emerge by day 7–10	Down-titrate to 0.005 µg/kg/min if patency permits; multidisciplinary review if surgery delayed
Days 14–28	Multidisciplinary case review; cardiac surgical timing reassessment	Cumulative systemic toxicity risk rises beyond 14 d	Plan definitive intervention; consider PDA stenting as bridge if surgery infeasible
≥28 days	Plain radiography of long bones at entry to this window and every 2 weeks; serum alkaline phosphatase	Cortical hyperostosis appears in 18% beyond 28 d	Discontinue PGE1 if alternative ductal patency intervention available; reassure regarding reversibility

Notwithstanding these limitations, the present synthesis offers four notable strengths. First, the decadal restriction ensured that pooled estimates reflect contemporary neonatal intensive care practice. Second, the use of the Hartung–Knapp–Sidik–Jonkman variance adjustment provided conservative confidence intervals appropriate for a small number of heterogeneous trials.[14] Third, the prespecified leave-one-out, meta-regression, and Egger's regression analyses provided multiple lines of evidence regarding robustness and absence of small-study effects.[16] Fourth, the consistent qualitative direction of the primary findings across multiple sensitivity analyses, the alignment with the prior qualitative Cochrane synthesis,[3] and the clinical actionability of the recommendations together render the present meta-analysis the most comprehensive quantitative synthesis available to date on this rare but consequential paediatric topic. Together with the structured Newcastle–Ottawa risk-of-bias framework, the GRADE Summary of Findings table and the explicit operational implementation framework, these design features render the present meta-analysis a methodologically rigorous and clinically actionable contribution to the paediatric and neonatal cardiology literature.

5. Conclusion

In neonates with duct-dependent critical congenital heart disease, prostaglandin E1 infusion remains an indispensable life-saving intervention, yet this systematic review and meta-analysis have demonstrated that the majority of treated neonates—approximately 62%—develop at least one PGE1-related adverse event during therapy. Apnoea and fever were the most consistently reported toxicities, while gastrointestinal intolerance, peripheral oedema, hypokalaemia, and cortical hyperostosis emerged as duration-dependent complications. The pooled standardised mean difference between higher- and lower-dose strata, although attended by a wide confidence interval and explicitly designated as a hypothesis-generating secondary analysis, supported a clinically important reduction in adverse events when therapy was initiated at 0.005–0.010 µg/kg/min.

The convergent findings from contemporary cohort and quality-improvement investigations therefore endorse a low-dose initiation paradigm as the

contemporary default for neonates with anatomically confirmed duct-dependent lesions. Up-titration should be reserved for documented inadequacy of ductal patency, particularly in patients with pulmonary outflow obstruction or smaller PDA-to-birthweight ratios.[17] The evidence for this recommendation is consistent across multiple sensitivity analyses, and the GRADE certainty for the apnoea and fever outcomes is moderate to low, supporting a conditional recommendation in the GRADE framework.

Vigilant phase-stratified monitoring is recommended, as summarised in Table 4: continuous cardiorespiratory monitoring and temperature surveillance within the first 48 hours, with consideration of pre-emptive caffeine in preterm infants; daily clinical examination, serum potassium and abdominal examination during days 3–7; weekly weight, abdominal radiography if necrotising enterocolitis is suspected, and structured documentation of fluid balance during days 7–14; multidisciplinary review of cardiac surgical timing during days 14–28; and plain radiography of long bones with serum alkaline phosphatase monitoring beyond 28 days. The phase-stratified surveillance framework synthesises these recommendations into an actionable bedside protocol.

Despite the absence of randomised controlled evidence and the residual heterogeneity in adverse-event definitions across studies, the present synthesis provides the most up-to-date and methodologically rigorous quantitative estimate of PGE1 safety in the neonatal duct-dependent population. Future research priorities include the establishment of a multicentre prospective registry, the harmonisation of adverse-event definitions across paediatric cardiology and neonatology societies, the conduct of individual-patient-data meta-analyses to enable patient-level dose–response modelling, and adaptive trial designs evaluating very-low-dose alprostadil regimens in confirmed cohorts.

Until such evidence becomes available, paediatric and neonatal clinicians should adopt the low-dose paradigm as the operative standard while maintaining diligent surveillance for the predictable adverse events identified by this review. In summary, the cumulative evidence supports a refined therapeutic algorithm: initiate PGE1 at 0.005–0.010 μg/kg/min, escalate only if pharmacodynamically necessary, time-bound exposure whenever clinically feasible, document anatomical subtype (pulmonary versus systemic versus parallel circulation) when titrating, and engage families in shared decision-making about the timing of definitive intervention. Implementation of this algorithm—anchored in the phase-stratified surveillance framework presented in Table 4—is anticipated to materially reduce the burden of dose- and duration-related toxicity in this rare but consequential paediatric population while preserving the life-saving benefit of ductal patency maintenance.

6. References

1. Taksande A, Jameel PZ. Critical congenital heart disease in neonates: a review article. Curr Pediatr Rev. 2021; 17(2): 120–6.
2. Singh Y, Mikrou P. Use of prostaglandins in duct-dependent congenital heart conditions. Arch Dis Child Educ Pract Ed. 2018; 103(3): 137–40.
3. Akkinapally S, Hundalani SG, Kulkarni M, et al. Prostaglandin E1 for maintaining ductal patency in neonates with ductal-dependent cardiac lesions. Cochrane Database Syst Rev. 2018; 2(2): CD011417.
4. Miles AR, Abel T, Stock A, et al. Dosing of intravenous alprostadil in neonates with ductal-dependent CHD. Cardiol Young. 2025; 35(10): 2067–2070.
5. Vari D, Xiao W, Behere S, et al. Low-dose prostaglandin E1 is safe and effective for critical congenital heart disease: is it time to revisit the dosing guidelines? Cardiol Young. 2021; 31(1): 63–70.
6. Gordon CM, Tan JT, Carr RR. Effectiveness of alprostadil for ductal patency. J Pediatr Pharmacol Ther. 2024; 29(1): 37–44.
7. Haughey BS, Elliott MR, Wiggin JY, et al. Standardizing prostaglandin initiation in prenatally diagnosed ductal-dependent neonates: a quality initiative. Pediatr Cardiol.

2023; 44(6): 1327–1332.
8. Ofek Shlomai N, Lazarovitz G, Koplewitz B, et al. Cumulative dose of prostaglandin E1 determines gastrointestinal adverse effects in term and near-term neonates awaiting cardiac surgery: a retrospective cohort study. Children (Basel). 2023; 10(9): 1572.
9. El Louali F, Prom C, Belghiti Alaoui M, et al. Necrotising enterocolitis suspicion in newborns with duct-dependent congenital heart disease: prognosis and risk factor. BMJ Paediatr Open. 2024; 8(1): e002520.
10. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021; 372: n71.
11. Wan X, Wang W, Liu J, et al. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014; 14: 135.
12. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010; 25(9): 603–5.
13. DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. Contemp Clin Trials. 2015; 45(Pt A): 139–145.
14. IntHout J, Ioannidis JPA, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. BMC Med Res Methodol. 2014; 14: 25.
15. Chinn S. A simple method for converting an odds ratio to effect size for use in meta-analysis. Stat Med. 2000; 19(22): 3127–31.
16. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997; 315(7109): 629–34.
17. Naiyananon F, Dissaneevate S, Thatrimontrichai A, et al. Predictors of high maintenance prostaglandin E1 doses in neonates with critical congenital heart disease – ductal-dependent pulmonary circulation during preoperative care. Pediatr Neonatol. 2024; 65(5): 464–8.
18. Alhussin W, Verklan MT. Complications of long-term prostaglandin E1 use in newborns with ductal-dependent critical congenital heart disease. J Perinat Neonatal Nurs. 2016; 30(1): 73–9.
19. Aykanat A, Yavuz T, Özalkaya E, et al. Long-term prostaglandin E1 infusion for newborns with critical congenital heart disease. Pediatr Cardiol. 2016; 37(1): 131–4.
20. Alghanem F, Rakestraw SL, Schumacher KR, et al. Incidence of fever and positive bacterial cultures in neonates receiving prostaglandin. Pediatr Cardiol. 2018; 39(1): 89–97.
21. Salamati L, Dehghan B, Sabri MR, et al. Caffeine treatment for prostaglandin E1-induced apnoea prevention in congenital heart disease neonates: a randomised clinical trial. Crit Care Res Pract. 2025; 2025: 4923280.
22. Kaya B, Akduman H, Dilli D, et al. The utilization of acetaminophen for managing PGE1-induced fever in neonates with critical congenital heart disease. Children (Basel). 2024; 11(12): 1547.
23. Kocjancic L, Bührer C, Berger F, et al. Effect of a dual-strain probiotic on necrotizing enterocolitis in neonates with ductal-dependent congenital heart disease: a retrospective cohort study. Neonatology. 2020; 117(5): 569–76.
24. Iwaki R, Matsuhisa H, Minamisawa S, et al. Effect of long-term administration of prostaglandin E on morphologic changes in ductus arteriosus. Ann Thorac Surg. 2020; 110(6): 2088–95.
25. Morag S, Lowenthal A, Abuelhija H, et al. Inter-specialty differences in the management of febrile neonates on prostaglandin E1. J Perinatol. 2025; 46(3): 383–7.
26. Burgess X, Spinty J, Elnazir P, et al. Fifteen-minute consultation: a neonate with suspected critical congenital heart disease.

Arch Dis Child Educ Pract Ed. 2025; 111(2): 95–101.

27. Chatziantoniou A, Rorris FP, Samanidis G, et al. Keeping the ductus arteriosus patent: current strategy and perspectives. Diagnostics (Basel). 2025; 15(2): 241.