



# Association Between Postnatal Steroid Use and Long-term Neurodevelopmental Impairment : A Systematic Review

<sup>1</sup> Deskafiani Putri, <sup>2</sup> Firman Syahbana

<sup>1</sup> General Practitioner, Annisa Mother and Child Hospital, Pekanbaru, Indonesia

<sup>2</sup> Pediatrician, Annisa Mother and Child Hospital, Pekanbaru, Indonesia

Corresponding Email : deskafianiputri@yahoo.com

## Article History :

Received date : 2026/02/17

Revised date : 2026/03/03

Accepted date : 2026/04/23

Published date : 2026/05/14



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E-ISSN :

ISSN 3048-1368



P-ISSN

ISSN 3048-1376



## ABSTRACT

**Introduction:** Postnatal systemic corticosteroids are used to prevent or treat bronchopulmonary dysplasia (BPD) in preterm infants, but concerns persist regarding their association with long-term neurodevelopmental impairment (NDI). This systematic review synthesizes evidence on the association between postnatal steroid use (dexamethasone and hydrocortisone) and long-term neurodevelopmental outcomes.

**Methods:** A systematic review was conducted following PRISMA guidelines. We screened studies based on predefined criteria: neonatal exposure to systemic postnatal corticosteroids, comparison groups, neurodevelopmental outcomes assessed at  $\geq 12$  months corrected age, and RCT or high-quality observational design. Data extraction covered study design, population, steroid regimen, neurodevelopmental outcomes, follow-up timing, association results, and confounding factors. A total of 80 studies were included.

**Results:** Early dexamethasone (<7-8 days) consistently increased cerebral palsy (CP) risk (RR 1.77, 95% CI 1.21-2.58; Doyle et al., 2021). Late dexamethasone ( $\geq 7$  days) showed no significant CP increase. Early hydrocortisone did not significantly increase CP (RR 1.06, 95% CI 0.67-1.67; Morris et al., 2019) and improved survival without moderate-severe NDI in some analyses. Late hydrocortisone showed neutral neurodevelopmental effects in large RCTs at 2 years and school age. Dose-response relationships were observed for both agents. Gestational age and baseline BPD risk modified treatment effects.

**Discussion:** Apparent contradictions in the literature are reconciled by considering timing of initiation (early vs late), steroid type (dexamethasone vs hydrocortisone), cumulative dose, historical regimens versus current low-dose protocols, confounding by indication, competing mortality risk, and effect modification by gestational age and BPD risk. Early dexamethasone is consistently harmful, while hydrocortisone appears predominantly neutral but with dose-dependent signals.

**Conclusion:** Early dexamethasone should be avoided. Late dexamethasone and hydrocortisone have more favorable profiles but require careful patient selection. The benefit-risk balance is most favorable for extremely preterm infants at highest BPD risk. Further school-age follow-up studies are needed.

**Keywords:** Postnatal corticosteroids, dexamethasone, hydrocortisone, preterm infants, neurodevelopmental impairment, cerebral palsy, bronchopulmonary dysplasia

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## INTRODUCTION

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### Background

Bronchopulmonary dysplasia (BPD) remains one of the most significant complications of preterm birth, affecting up to 40-60% of extremely low birth weight infants (Doyle et al., 2021). Postnatal systemic corticosteroids, particularly dexamethasone and hydrocortisone, have been widely used to prevent or treat BPD due to their potent anti-inflammatory effects, which facilitate extubation and reduce lung injury (Boscarino et al., 2024). However, since the late 1990s, accumulating evidence has linked postnatal steroid exposure, especially early dexamethasone, to adverse neurodevelopmental outcomes including cerebral palsy, cognitive delay, and motor impairment (Yates & Newell, 2011; Doyle et al., 2014).

The developing preterm brain is uniquely vulnerable to glucocorticoid exposure. Animal models demonstrate that exogenous glucocorticoids suppress neuronal proliferation, induce apoptosis in the hippocampus and cerebellum, and impair myelination (Jenkinson et al., 2023; Drozdowicz & Bostwick, 2014). These effects are likely time-dependent and dose-dependent, with the first postnatal week representing a critical window of vulnerability (Keunen et al., 2012). Despite these concerns, postnatal steroids continue to be used in clinical practice, albeit with lower doses and later initiation than in historical regimens (Onland et al., 2023; Szabó et al., 2021).

### Research Gap

Despite decades of research, several critical gaps remain. First, most existing meta-analyses aggregate trials using heterogeneous steroid types, timing regimens, and dosing protocols, potentially obscuring differential effects (Hay et al., 2020; van de Loo et al., 2024). Second, direct comparative data between dexamethasone and hydrocortisone within the same study populations are limited (David et al., 2025; Wolbeek et al., 2013). Third, the dose-response relationship, particularly for hydrocortisone, remains poorly characterized (Patra et al., 2014; Kim et al., 2025). Fourth, effect modification by gestational age and baseline BPD risk is often not incorporated into clinical decision-making frameworks (Doyle et al., 2014; Baud et al., 2018; Halbmeijer et al.,

2023). Fifth, most studies report outcomes only at 18-24 months corrected age, which may miss higher-order cognitive and behavioral deficits emerging at school age (Demauro et al., 2025; de Baat et al., 2025).

### **Novelty**

This systematic review provides several novel contributions: (1) a comprehensive side-by-side comparison of dexamethasone and hydrocortisone across all available studies; (2) explicit stratification by timing of initiation (early <7-8 days vs late  $\geq 7$  days); (3) detailed dose-response synthesis for both agents; (4) integration of effect modifier analyses including gestational age and BPD risk; (5) inclusion of long-term follow-up studies beyond 2 years; and (6) reconciliation of apparent contradictions in the literature through a unified framework.

### **Objectives**

The primary objective of this systematic review is to evaluate the association between postnatal systemic corticosteroid use (dexamethasone, hydrocortisone, prednisolone, methylprednisolone) and long-term neurodevelopmental impairment in preterm infants. Secondary objectives include: (1) comparing effects of early versus late initiation; (2) assessing dose-response relationships; (3) evaluating effect modification by gestational age and BPD risk; (4) comparing dexamethasone versus hydrocortisone; and (5) synthesizing evidence on brain structural correlates and behavioral outcomes.

### **Research Hypothesis**

We hypothesized that: (1) early dexamethasone (<7-8 days) would be associated with significantly increased risk of cerebral palsy and cognitive impairment; (2) late dexamethasone ( $\geq 7$  days) would show attenuated or neutral neurodevelopmental effects; (3) hydrocortisone, particularly at low doses, would demonstrate a more favorable neurodevelopmental profile compared to dexamethasone; (4) higher cumulative doses of either agent would be associated with worse neurodevelopmental outcomes in a dose-dependent manner; and (5) the benefit-risk balance would be most favorable for the most extremely preterm infants at highest BPD risk.

### **Benefits of the Study**

This review benefits clinicians by providing evidence-based guidance on steroid selection, timing, and dosing to minimize neurodevelopmental harm while preserving respiratory benefits. It benefits researchers by identifying knowledge gaps requiring further investigation, particularly dose-response thresholds and school-age outcomes. It benefits policymakers and guideline developers by synthesizing high-certainty evidence for recommendations. Ultimately, it benefits preterm infants and their families by informing shared decision-making around a critical therapeutic intervention with lifelong neurodevelopmental consequences.

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## METHODS

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### Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

### Criteria for Eligibility

This systematic review aims to evaluate the Association Between Postnatal Steroid Use and Long-term Neurodevelopmental Impairment.

### Screening

We screened in sources based on their abstracts that met these criteria:

- **Target Population:** Does the study include neonates or infants who received postnatal steroids during the neonatal period (first 28 days of life)?
- **Steroid Type and Administration:** Does the study examine systemic corticosteroids (dexamethasone, prednisolone, hydrocortisone, or methylprednisolone) administered postnatally?
- **Study Design - Comparison Group:** Does the study include a comparison group (control group receiving no steroids, placebo, or different steroid regimen)?

- **Follow-up Duration:** Does the study report neurodevelopmental outcomes assessed at 12 months corrected age or later?
- **Neurodevelopmental Outcomes:** Does the study report relevant neurodevelopmental outcomes (cognitive development, motor development, behavioral outcomes, cerebral palsy, or standardized developmental assessments)?
- **Study Design Type:** Is the study design a randomized controlled trial, etc?
- **Postnatal vs Antenatal Focus:** Does the study focus on postnatal steroid administration (rather than focusing solely on antenatal steroid administration)?
- **Systemic Steroid Exposure:** Does the study examine systemic steroid exposure (rather than examining only topical, inhaled, or intrathecal steroids without systemic exposure)?

Papers that failed any strict criterion were automatically excluded. For the remaining papers, we considered all screening questions together and made a holistic judgement about whether to screen in each paper.

### Search Strategy

The keywords used for this research based PICO :

| Element          | P<br>(Population)            | I<br>(Intervention/Exposure) | C<br>(Comparison/Context) | O (Outcome)                             |
|------------------|------------------------------|------------------------------|---------------------------|-----------------------------------------|
| <b>Keyword 1</b> | Preterm infants              | Postnatal steroids           | No steroids               | Long-term neurodevelopmental impairment |
| <b>Keyword 2</b> | Very low birth weight (VLBW) | Systemic corticosteroids     | Placebo                   | Cerebral palsy                          |
| <b>Keyword 3</b> | Extremely low birth          | Dexamethasone                | Different steroid regimen | Cognitive delay                         |

|                      |                                              |                |                              |                   |
|----------------------|----------------------------------------------|----------------|------------------------------|-------------------|
|                      | weight<br>(ELBW)                             |                |                              |                   |
| <b>Keyword<br/>4</b> | Neonatal<br>intensive<br>care unit<br>(NICU) | Hydrocortisone | Untreated preterm<br>infants | Motor dysfunction |

The Boolean MeSH keywords inputted on databases for this research are: (*"Preterm infants" OR "Very low birth weight (VLBW)" OR "Extremely low birth weight (ELBW)" OR "Neonatal intensive care unit (NICU)"*) AND (*"Postnatal steroids" OR "Systemic corticosteroids" OR "Dexamethasone" OR "Hydrocortisone"*) AND (*"No steroids" OR "Placebo" OR "Different steroid regimen" OR "Untreated preterm infants"*) AND (*"Long-term neurodevelopmental impairment" OR "Cerebral palsy" OR "Cognitive delay" OR "Motor dysfunction"*)

#### Data extraction

- **Study Design:**

Extract the study design and key methodological details relevant to assessing associations between postnatal steroid use and neurodevelopmental impairment, including:

- Study type (RCT, etc)
- Sample size and power calculations if reported
- Randomization and blinding methods (for RCTs)
- Control/comparison groups
- Risk of bias concerns that could affect validity of neurodevelopmental associations

- **Population Characteristics:**

Extract details about the study population relevant to neurodevelopmental risk assessment, including:

- Gestational age range and mean
- Birth weight characteristics
- Baseline neurodevelopmental risk factors
- Inclusion/exclusion criteria related to neurological conditions
- Setting (NICU characteristics, country/healthcare system)
- Sample size for neurodevelopmental follow-up (may differ from overall sample)

- **Steroid Intervention:**

Extract comprehensive details about postnatal steroid use being studied for neurodevelopmental associations, including:

- Steroid type (dexamethasone, hydrocortisone, prednisolone, etc.)
- Dosing regimen (dose, frequency, tapering schedule)
- Timing of initiation (early <7-8 days vs late >7 days postnatal)
- Total duration of treatment
- Cumulative dose administered
- Indication for treatment (BPD prevention vs treatment, hypotension, etc.)
- Comparison groups (placebo, no treatment, different steroid regimens)

- **Neurodevelopmental Outcomes:**

Extract all neurodevelopmental impairment outcomes assessed in relation to postnatal steroid exposure, including:

- Specific neurological outcomes (cerebral palsy, cognitive delay, motor impairment)
- Assessment tools used (Bayley scales, IQ tests, neurological examination)
- Severity classifications (mild, moderate, severe impairment)
- Composite outcomes (major neurosensory disability, abnormal neurological exam)
- Sensory impairments (blindness, deafness)
- Any neurodevelopmental outcome definitions used by study authors

- **Follow-up Timing:**

Extract the timing of neurodevelopmental assessments to determine what constitutes 'long-term' follow-up, including:

- Age at assessment (corrected vs chronological age)
- Follow-up duration from steroid exposure
- Multiple assessment time points if reported
- Loss to follow-up rates for neurodevelopmental assessments
- Whether assessments occurred at clinically meaningful ages for detecting neurodevelopmental impairment

- **Association Results:**

Extract the key findings regarding associations between postnatal steroid use and long-term neurodevelopmental impairment, including:

- Effect sizes with confidence intervals for neurodevelopmental outcomes
- Statistical significance (p-values)

- Risk ratios, odds ratios, or mean differences as reported
- Absolute risk differences and numbers needed to harm
- Dose-response relationships if assessed
- Subgroup analyses by steroid type, timing, or patient characteristics
- Combined outcomes (death or neurodevelopmental impairment)

- **Confounding Factors:**

Extract information about potential confounding variables and how they were addressed in assessing steroid-neurodevelopmental associations, including:

- Baseline characteristics that differed between exposure groups
- Co-interventions that could affect neurodevelopment (mechanical ventilation, other medications)
- Perinatal factors adjusted for in analyses (gestational age, birth weight, illness severity)
- Statistical adjustment methods used
- Unmeasured confounding acknowledged by authors
- Competing risks (mortality) that could bias neurodevelopmental outcomes

**Table 1.** Article Search Strategy

| Database             | Keywords                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Hits  |
|----------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|
| Pubmed               | <i>("Preterm infants" OR "Very low birth weight (VLBW)" OR "Extremely low birth weight (ELBW)" OR "Neonatal intensive care unit (NICU)" AND ("Postnatal steroids" OR "Systemic corticosteroids" OR "Dexamethasone" OR "Hydrocortisone") AND ("No steroids" OR "Placebo" OR "Different steroid regimen" OR "Untreated preterm infants") AND ("Long-term neurodevelopmental impairment" OR "Cerebral palsy" OR "Cognitive delay" OR "Motor dysfunction")</i> | 34    |
| Semantic Scholar     | <i>("Preterm infants" OR "Very low birth weight (VLBW)" OR "Extremely low birth weight (ELBW)" OR "Neonatal intensive care unit (NICU)" AND ("Postnatal steroids" OR "Systemic corticosteroids" OR "Dexamethasone" OR "Hydrocortisone") AND ("No steroids" OR "Placebo" OR "Different steroid regimen" OR "Untreated preterm infants") AND ("Long-term neurodevelopmental impairment" OR "Cerebral palsy" OR "Cognitive delay" OR "Motor dysfunction")</i> | 250   |
| Springer             | <i>("Preterm infants" OR "Very low birth weight (VLBW)" OR "Extremely low birth weight (ELBW)" OR "Neonatal intensive care unit (NICU)" AND ("Postnatal steroids" OR "Systemic corticosteroids" OR "Dexamethasone" OR "Hydrocortisone") AND ("No steroids" OR "Placebo" OR "Different steroid regimen" OR "Untreated preterm infants") AND ("Long-term neurodevelopmental impairment" OR "Cerebral palsy" OR "Cognitive delay" OR "Motor dysfunction")</i> | 296   |
| Google Scholar       | <i>("Preterm infants" OR "Very low birth weight (VLBW)" OR "Extremely low birth weight (ELBW)" OR "Neonatal intensive care unit (NICU)" AND ("Postnatal steroids" OR "Systemic corticosteroids" OR "Dexamethasone" OR "Hydrocortisone") AND ("No steroids" OR "Placebo" OR "Different steroid regimen" OR "Untreated preterm infants") AND ("Long-term neurodevelopmental impairment" OR "Cerebral palsy" OR "Cognitive delay" OR "Motor dysfunction")</i> | 8,280 |
| Wiley Online Library | <i>("Preterm infants" OR "Very low birth weight (VLBW)" OR "Extremely low birth weight (ELBW)" OR "Neonatal intensive care unit (NICU)" AND ("Postnatal steroids" OR "Systemic corticosteroids" OR "Dexamethasone" OR "Hydrocortisone") AND ("No steroids" OR "Placebo" OR "Different steroid regimen" OR "Untreated preterm infants") AND ("Long-term neurodevelopmental impairment" OR "Cerebral palsy" OR "Cognitive delay" OR "Motor dysfunction")</i> | 427   |

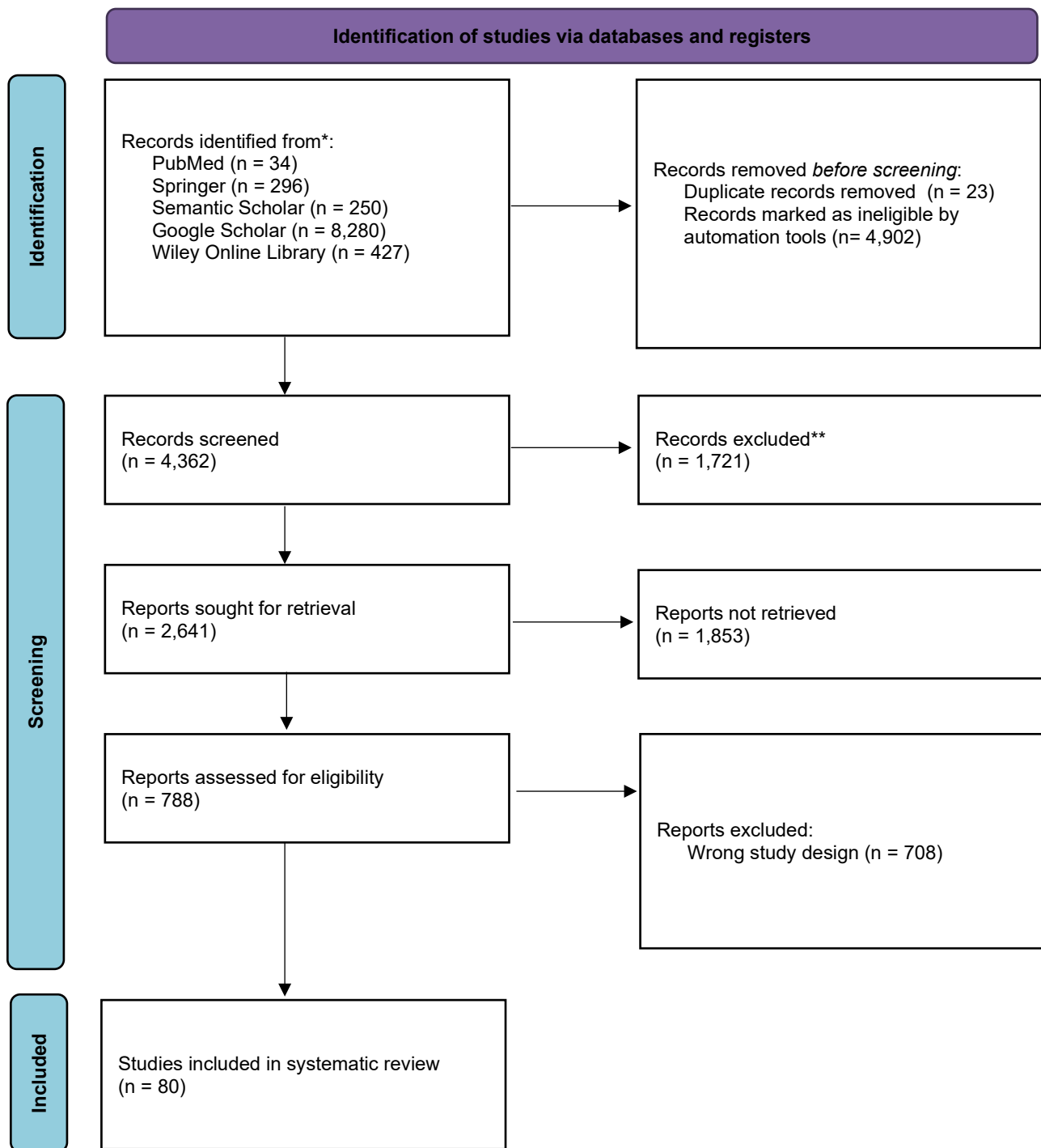


**Figure 1. Article search flowchart**

### Risk of Bias

| Study                               | Selection Bias | Performance Bias | Detection Bias | Attrition Bias | Reporting Bias | Overall Risk |
|-------------------------------------|----------------|------------------|----------------|----------------|----------------|--------------|
| H. Yates & S. Newell, 2011 [20]     | Unclear        | Unclear          | Unclear        | Unclear        | Low            | Unclear      |
| Kousiki Patra et al., 2014 [18]     | Moderate       | Unclear          | Low            | Moderate       | Low            | Moderate     |
| Allan C. Jenkinson et al., 2023 [6] | Moderate       | Unclear          | Low            | Moderate       | Low            | Moderate     |
| Jieun David et al., 2025 [21]       | Moderate       | Unclear          | Low            | Moderate       | Low            | Moderate     |
| G. Boscarino et al., 2024 [22]      | Low            | Unclear          | Low            | Low            | Low            | Low          |
| W. Onland et al., 2017 [23]         | Low            | Low              | Low            | Low            | Low            | Low          |
| A. Buchiboyina et al., 2020 [10]    | Moderate       | Unclear          | Low            | Moderate       | Low            | Moderate     |
| L. Doyle et al., 2021 [1]           | Low            | Low              | Low            | Low            | Low            | Low          |
| O. Baud et al., 2017 [24]           | Low            | Low              | Low            | Moderate       | Low            | Low          |

| Study                                              | Selection Bias | Performance Bias | Detection Bias | Attrition Bias | Reporting Bias | Overall Risk |
|----------------------------------------------------|----------------|------------------|----------------|----------------|----------------|--------------|
| <b>L. Doyle et al., 2014 [9]</b>                   | Low            | Low              | Low            | Low            | Low            | Low          |
| <b>L. Doyle et al., 2017 [25]</b>                  | Low            | Low              | Low            | Low            | Low            | Low          |
| <b>L. Doyle et al., 2014a [26]</b>                 | Low            | Low              | Low            | Low            | Low            | Low          |
| <b>L. Doyle et al., 2010 [8]</b>                   | Low            | Low              | Low            | Low            | Low            | Low          |
| <b>L. Doyle et al., 2010a [27]</b>                 | Low            | Low              | Low            | Low            | Low            | Low          |
| <b>L. Doyle et al., 2021a [7]</b>                  | Low            | Low              | Low            | Low            | Low            | Low          |
| <b>J. Uberos et al., 2025 [2]</b>                  | Low            | Unclear          | Low            | Low            | Low            | Low          |
| <b>I. Purdy et al., 2013 [28]</b>                  | Moderate       | Unclear          | Moderate       | Moderate       | Low            | Moderate     |
| <b>L. Doyle et al., 2010b [29]</b>                 | Low            | Low              | Low            | Low            | Low            | Low          |
| <b>Judy LeFlore &amp; William Engle, 2011 [30]</b> | Moderate       | Unclear          | Low            | Moderate       | Low            | Moderate     |

| Study                                             | Selection Bias | Performance Bias | Detection Bias | Attrition Bias | Reporting Bias | Overall Risk |
|---------------------------------------------------|----------------|------------------|----------------|----------------|----------------|--------------|
| <b>N. Halbmeijer et al., 2021 [31]</b>            | Low            | Low              | Low            | Low            | Low            | Low          |
| <b>Marita Lardón et al., 2016 [32]</b>            | Moderate       | Unclear          | Low            | Moderate       | Low            | Moderate     |
| <b>T. Raghuvver et al., 2024 [33]</b>             | Low            | Unclear          | Low            | Low            | Low            | Low          |
| <b>O. Peltoniemi et al., 2016 [34]</b>            | Low            | Low              | Low            | Moderate       | Low            | Low          |
| <b>A. AlsuhaaymiZuhairHamdan et al., 2017 [3]</b> | Low            | Low              | Low            | Low            | Low            | Low          |
| <b>Gustavo Rocha et al., 2024 [35]</b>            | Moderate       | Unclear          | Low            | Moderate       | Low            | Moderate     |
| <b>Dexamethasone dose and risk of (2021) [36]</b> | Moderate       | Unclear          | Low            | Moderate       | Low            | Moderate     |
| <b>W. Onland et al., 2023 [37]</b>                | Low            | Low              | Low            | Low            | Low            | Low          |

| Study                                  | Selection Bias | Performance Bias | Detection Bias | Attrition Bias | Reporting Bias | Overall Risk |
|----------------------------------------|----------------|------------------|----------------|----------------|----------------|--------------|
| K. Keunen et al., 2012 [38]            | Moderate       | Unclear          | Low            | Moderate       | Low            | Moderate     |
| G. Ofman et al., 2018 [39]             | Low            | Low              | Low            | Low            | Low            | Low          |
| Sachin S Shah et al., 2017 [40]        | Low            | Low              | Low            | Moderate       | Low            | Low          |
| N. Parikh et al., 2015 [41]            | Low            | Low              | Low            | Moderate       | Low            | Low          |
| Kristi L. Watterberg et al., 2022 [42] | Low            | Low              | Low            | Low            | Low            | Low          |
| J. Harrold et al., 2013 [43]           | Low            | Unclear          | Low            | Low            | Low            | Low          |
| O. Baud et al., 2018 [15]              | Low            | Low              | Low            | Moderate       | Low            | Low          |
| M. T. Wolbeek et al., 2013 [5]         | Moderate       | Unclear          | Low            | Moderate       | Low            | Moderate     |
| L. Zeng et al., 2018 [44]              | Low            | Unclear          | Low            | Low            | Low            | Low          |

| Study                                     | Selection Bias | Performance Bias | Detection Bias | Attrition Bias | Reporting Bias | Overall Risk |
|-------------------------------------------|----------------|------------------|----------------|----------------|----------------|--------------|
| M. van de Loo et al., 2024 [45]           | Low            | Unclear          | Low            | Low            | Low            | Low          |
| Leena Aho et al., 2025 [46]               | Moderate       | Unclear          | Low            | High           | Low            | Moderate     |
| M. Shaffer et al., 2019 [47]              | Low            | Low              | Low            | Low            | Low            | Low          |
| Min Soo Kim et al., 2025 [17]             | Moderate       | Unclear          | Low            | Moderate       | Low            | Moderate     |
| Sachin S Shah et al., 2017a [48]          | Low            | Low              | Low            | Moderate       | Low            | Low          |
| Linda Drozdowicz & J. Bostwick, 2014 [49] | Unclear        | Unclear          | Unclear        | Unclear        | Low            | Unclear      |
| Hajnalka Szabó et al., 2021 [50]          | Unclear        | Unclear          | Unclear        | Unclear        | Low            | Unclear      |
| T. Ogunlesi et al., 2015 [51]             | Low            | Low              | Low            | Moderate       | Low            | Low          |
| Susanne Hay et al., 2020 [4]              | Low            | Unclear          | Low            | Low            | Low            | Low          |

| Study                                                                  | Selection Bias | Performance Bias | Detection Bias | Attrition Bias | Reporting Bias | Overall Risk |
|------------------------------------------------------------------------|----------------|------------------|----------------|----------------|----------------|--------------|
| <b>S. Demauro et al., 2025 [14]</b>                                    | Low            | Low              | Low            | Low            | Low            | Low          |
| <b>K. Watterberg et al., 2022 (full trial report) [11]</b>             | Low            | Low              | Low            | Low            | Low            | Low          |
| <b>S. W. Aucott et al., 2010 [52]</b>                                  | Moderate       | Unclear          | Low            | Moderate       | Low            | Moderate     |
| <b>S. Zyblewski et al., 2021 [53]</b>                                  | Low            | Low              | Low            | Moderate       | Low            | Low          |
| <b>Kata Kovacs et al., 2025 [54]</b>                                   | Low            | Low              | Low            | Moderate       | Low            | Low          |
| <b>Bonnie L Marr et al., 2019 [55]</b>                                 | Low            | Low              | Low            | Moderate       | Low            | Low          |
| <b>Late hydrocortisone does not prevent BPD (2022 commentary) [56]</b> | Unclear        | Unclear          | Unclear        | Unclear        | Moderate       | Unclear      |
| <b>W. Onland et al., 2010 [57]</b>                                     | Low            | Low              | Low            | Low            | Low            | Low          |

| Study                                                 | Selection Bias | Performance Bias | Detection Bias | Attrition Bias | Reporting Bias | Overall Risk |
|-------------------------------------------------------|----------------|------------------|----------------|----------------|----------------|--------------|
| W. Onland et al., 2011 (SToP-BPD protocol) [58]       | Low            | Low              | Low            | Low            | Low            | Low          |
| T. de Baat et al., 2025 [12]                          | Low            | Low              | Low            | Low            | Low            | Low          |
| 许巍 (Xu Wei), 2016 [19]                                | Moderate       | Unclear          | Moderate       | High           | Moderate       | High         |
| M. Quan, 2013 [59]                                    | Low            | Unclear          | Low            | Low            | Low            | Low          |
| N. Halbmeijer et al., 2020 [60]                       | Low            | Low              | Low            | Low            | Low            | Low          |
| N. Halbmeijer et al., 2023 [61]                       | Low            | Low              | Low            | Low            | Low            | Low          |
| Nasal high-flow therapy during (2022 commentary) [62] | Unclear        | Unclear          | Unclear        | Unclear        | Moderate       | Unclear      |
| N. Halbmeijer et al., 2023a [16]                      | Low            | Low              | Low            | Low            | Low            | Low          |

| Study                                                          | Selection Bias | Performance Bias | Detection Bias | Attrition Bias | Reporting Bias | Overall Risk |
|----------------------------------------------------------------|----------------|------------------|----------------|----------------|----------------|--------------|
| K. Kersbergen, 2015 [63]                                       | Moderate       | Unclear          | Low            | Moderate       | Low            | Moderate     |
| Postnatal steroids and febrile seizures (2016 commentary) [64] | Unclear        | Unclear          | Unclear        | Unclear        | Moderate       | Unclear      |
| K. Crotty et al., 2012 [65]                                    | Moderate       | Unclear          | Low            | Moderate       | Low            | Moderate     |
| R. G. M. Cassiano et al., 2016 [66]                            | Unclear        | Unclear          | Unclear        | Unclear        | Low            | Unclear      |
| S. Gentle et al., 2023 [67]                                    | Low            | Low              | Low            | Low            | Low            | Low          |
| Jhier Afifi et al., 2024 [68]                                  | Moderate       | Unclear          | Low            | Moderate       | Low            | Moderate     |
| S. Demauro et al., 2024 (HYBRiD protocol) [69]                 | Low            | Low              | Low            | Low            | Low            | Low          |
| Bonnie L Marr et al., 2020 (Reply) [70]                        | Unclear        | Unclear          | Unclear        | Unclear        | Moderate       | Unclear      |
| Panpan Liu et al., 2026 [71]                                   | Low            | Unclear          | Low            | Low            | Low            | Low          |

| Study                                             | Selection Bias | Performance Bias | Detection Bias | Attrition Bias | Reporting Bias | Overall Risk |
|---------------------------------------------------|----------------|------------------|----------------|----------------|----------------|--------------|
| <b>Lillian G. Matthews et al., 2018 [72]</b>      | Moderate       | Unclear          | Low            | Moderate       | Low            | Moderate     |
| <b>E. Shinwell et al., 2021 [73]</b>              | Unclear        | Unclear          | Unclear        | Unclear        | Low            | Unclear      |
| <b>Ian Morris et al., 2019 [13]</b>               | Low            | Unclear          | Low            | Low            | Low            | Low          |
| <b>Meera N. Sankar et al., 2025 [74]</b>          | Low            | Low              | Low            | Low            | Low            | Low          |
| <b>Oreoluwa Olaloko et al., 2018 [75]</b>         | Unclear        | Unclear          | Unclear        | Unclear        | Low            | Unclear      |
| <b>T. Pin et al., 2010 [76]</b>                   | Moderate       | Unclear          | Low            | Moderate       | Low            | Moderate     |
| <b>S. Spénard et al., 2025 [77]</b>               | Low            | Unclear          | Low            | High           | Low            | High         |
| <b>J. Meijer et al., 2026 [78]</b>                | Moderate       | Unclear          | Low            | Moderate       | Low            | Moderate     |
| <b>Yuan He et al., 2020 (trial protocol) [79]</b> | Low            | Low              | Low            | Low            | Low            | Low          |

| Study                                                | Selection Bias | Performance Bias | Detection Bias | Attrition Bias | Reporting Bias | Overall Risk |
|------------------------------------------------------|----------------|------------------|----------------|----------------|----------------|--------------|
| <b>A. Menshykova &amp; D. Dobryanskyy, 2026 [80]</b> | Unclear        | Unclear          | Unclear        | Unclear        | Low            | Unclear      |

## RESULTS

### Characteristics of Included Studies

| Study                                      | Population                                                                                                                 | Steroid(s) Studied                                                                            | Primary Neurodevelopmental Focus                                   |
|--------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|--------------------------------------------------------------------|
| <b>H. Yates &amp; S. Newell, 2011 [20]</b> | Preterm infants receiving postnatal IV steroids [20]                                                                       | Postnatal IV steroids (general) [20]                                                          | Long-term neurodevelopmental outcomes from meta-analyses [20]      |
| <b>Kousiki Patra et al., 2014 [18]</b>     | 175 ELBW infants (mean GA $26.0 \pm 1.7$ wks HC; $27.5 \pm 1.8$ wks no-HC; mean BW $719 \pm 127$ g vs $837 \pm 99$ g) [18] | Hydrocortisone (HC); mean treatment age $20 \pm 19$ days, mean duration $49 \pm 37$ days [18] | Motor, fine motor, language at 8 and 20 months CA (BSITD-III) [18] |

| Study                                      | Population                                                                     | Steroid(s) Studied                                                          | Primary Neurodevelopmental Focus                                                                    |
|--------------------------------------------|--------------------------------------------------------------------------------|-----------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|
| <b>Allan C. Jenkinson et al., 2023 [6]</b> | 1,609 patients across 18 studies; preterm infants exposed to dexamethasone [6] | Dexamethasone (systemic) [6]                                                | Pulmonary, cardiovascular, and cognitive outcomes in childhood and adolescence (age 3–19 years) [6] |
| <b>Jieun David et al., 2025 [21]</b>       | 221 EPT survivors (GA <28 wks); lower BW and GA in steroid-exposed groups [21] | Hydrocortisone (HC) only; DEX ± HC; late NICU exposure [21]                 | Bayley-3 cognitive, language, motor at 20 months CA [21]                                            |
| <b>G. Boscarino et al., 2024 [22]</b>      | Preterm ventilated neonates; GA typically ≤30–32 wks [22]                      | Dexamethasone and hydrocortisone (systemic); early and late initiation [22] | Long-term neurodevelopment, growth, extubation, and adverse effects [22]                            |
| <b>W. Onland et al., 2017 [23]</b>         | VLBW preterm infants at risk for BPD [23]                                      | Dexamethasone; high, moderate, and low cumulative dose comparisons [23]     | Cerebral palsy, abnormal neurodevelopmental outcome, Bayley MDI [23]                                |
| <b>A. Buchiboyina et al., 2020 [10]</b>    | 104 DEX-exposed infants (<29 wks, ventilated >7 days); 324 controls [10]       | Dexamethasone; cumulative dose <2 mg/kg vs ≥2 mg/kg [10]                    | Long-term disability, cerebral palsy at 2 and 5 years [10]                                          |

| Study                              | Population                                                                  | Steroid(s) Studied                                                                         | Primary Neurodevelopmental Focus                                                                    |
|------------------------------------|-----------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|
| <b>L. Doyle et al., 2021 [1]</b>   | Preterm infants at risk for BPD [1]                                         | Dexamethasone and hydrocortisone; early (<7 days) initiation [1]                           | Cerebral palsy, mortality or cerebral palsy (high-certainty evidence) [1]                           |
| <b>O. Baud et al., 2017 [24]</b>   | 523 assigned; 379 evaluated at 2 years (21 French NICUs; GA 24–27 wks) [24] | Hydrocortisone 0.5 mg/kg BID ×7d then 0.5 mg/kg/d ×3d (total 8.5 mg/kg); early (<24h) [24] | Neurodevelopmental impairment (Brunet-Lézine); cerebral palsy at 22 months CA [24]                  |
| <b>L. Doyle et al., 2014 [9]</b>   | Preterm infants receiving postnatal corticosteroids [9]                     | Postnatal corticosteroids (general) [9]                                                    | Survival free of cerebral palsy; effect modification by BPD risk [9]                                |
| <b>L. Doyle et al., 2017 [25]</b>  | Preterm infants with evolving/established BPD [25]                          | Dexamethasone; late (>7 days) initiation [25]                                              | Cerebral palsy, major neurosensory disability, death or CP [25]                                     |
| <b>L. Doyle et al., 2014a [26]</b> | Preterm infants at risk for BPD [26]                                        | Dexamethasone and hydrocortisone; early (≤7 days) initiation [26]                          | Developmental delay, cerebral palsy, abnormal neurological exam, major neurosensory disability [26] |
| <b>L. Doyle et al., 2010 [8]</b>   | Preterm infants with BPD [8]                                                | Dexamethasone; late (>7 days) initiation [8]                                               | Cerebral palsy, abnormal neurological examination [8]                                               |

| Study                              | Population                                                         | Steroid(s) Studied                                                                    | Primary Neurodevelopmental Focus                                                        |
|------------------------------------|--------------------------------------------------------------------|---------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| <b>L. Doyle et al., 2010a [27]</b> | Preterm infants; hydrocortisone studies only [27]                  | Hydrocortisone; early (first week of life) [27]                                       | BPD prevention; neurodevelopmental outcomes (limited data) [27]                         |
| <b>L. Doyle et al., 2021a [7]</b>  | Preterm infants with evolving/established BPD [7]                  | Dexamethasone and hydrocortisone; late ( $\geq 7$ days) initiation [7]                | Cerebral palsy, death or cerebral palsy [7]                                             |
| <b>J. Uberos et al., 2025 [2]</b>  | Premature VLBW infants; studies 2013–2023 [2]                      | Dexamethasone, hydrocortisone, prednisolone, inhaled budesonide [2]                   | Cerebral palsy, gross motor impairment, neurosensory disability, cognitive outcomes [2] |
| <b>I. Purdy et al., 2013 [28]</b>  | 45 mother–child dyads; mean GA 28 wks; mean child age 8 years [28] | Dexamethasone; high ( $>0.2$ mg/kg) vs low/no ( $\leq 0.2$ mg/kg) cumulative PNS [28] | Behavioral outcomes (CBCL) at mean age 8 years [28]                                     |
| <b>L. Doyle et al., 2010b [29]</b> | Preterm infants at risk for BPD [29]                               | Dexamethasone; early ( $\leq 7$ days) initiation [29]                                 | Cerebral palsy, death or cerebral palsy [29]                                            |

| Study                                              | Population                                                                              | Steroid(s) Studied                                                                         | Primary Neurodevelopmental Focus                                         |
|----------------------------------------------------|-----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| <b>Judy LeFlore &amp; William Engle, 2011 [30]</b> | 173 ELBW (<1000 g) neonates with BSID-II at 18–22 months [30]                           | Postnatal steroids for BPD (type not specified); group III BPD+PNS vs groups I and II [30] | PDI and MDI (BSID-II) at 18–22 months; growth parameters [30]            |
| <b>N. Halbmeijer et al., 2021 [31]</b>             | Ventilator-dependent very preterm infants [31]                                          | Hydrocortisone; initiated 7–14 days after birth [31]                                       | Death or neurodevelopmental impairment at 2 years CA [31]                |
| <b>Marita Lardón et al., 2016 [32]</b>             | 225 VLBW neonates (tertiary hospital, Spain, 2008–2013); 194 followed to 24 months [32] | Dexamethasone (late, ~day 21; 10-day taper) for established BPD [32]                       | Motor, neurosensory, cognitive, behavioral outcomes to 24 months CA [32] |
| <b>T. Raghuveer et al., 2024 [33]</b>              | Preterm infants $\leq 30$ weeks [33]                                                    | Dexamethasone (32 studies); hydrocortisone (13 studies); various regimens [33]             | Cerebral palsy (CP) risk; MDI/PDI scores; NDI risk [33]                  |

| Study                                             | Population                                                                 | Steroid(s) Studied                                                                                         | Primary Neurodevelopmental Focus                                             |
|---------------------------------------------------|----------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| <b>O. Peltoniemi et al., 2016 [34]</b>            | Children 5–7 years who had participated in early hydrocortisone trial [34] | Hydrocortisone; early low-dose (BPD prevention) [34]                                                       | Neurodevelopment and growth at 5–7 years (preschool age) [34]                |
| <b>A. AlsuhaymiZu hairHamdan et al., 2017 [3]</b> | Preterm infants requiring BPD treatment [3]                                | Dexamethasone and hydrocortisone [3]                                                                       | Developmental delay, cerebral palsy, major neurosensory disability [3]       |
| <b>Gustavo Rocha et al., 2024 [35]</b>            | 150 preterm infants (7 level III NICUs); mean GA 25–26 wks [35]            | Dexamethasone (DART protocol); single course vs $\geq 2$ courses; cumulative doses 0.82 vs 1.70 mg/kg [35] | Cerebral palsy (GMFCS class 2), ophthalmological problems at 2 years CA [35] |
| <b>Dexamethasone dose and risk of (2021) [36]</b> | <29 wks GA; n=104 low-dose DEX, n=38 high-dose DEX, n=324 controls [36]    | Dexamethasone; cumulative <2 mg/kg vs $\geq 2$ mg/kg [36]                                                  | Long-term disability, cerebral palsy at 2 and 5 years [36]                   |

| Study                                  | Population                                                         | Steroid(s) Studied                                                                                | Primary Neurodevelopmental Focus                                                           |
|----------------------------------------|--------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|
| <b>W. Onland et al., 2023 [37]</b>     | VLBW preterm infants at risk for BPD [37]                          | Dexamethasone; cumulative dose comparisons (low <2 mg/kg, moderate 2–4 mg/kg, high >4 mg/kg) [37] | Cerebral palsy, death or CP, death or abnormal neurodevelopmental outcome [37]             |
| <b>K. Keunen et al., 2012 [38]</b>     | Very/extremely preterm infants; MRI at term-equivalent age [38]    | Dexamethasone and hydrocortisone (observational data) [38]                                        | Brain tissue volumes at TEA and neurodevelopmental outcomes (BSID-II, HINE, NEPSY II) [38] |
| <b>G. Ofman et al., 2018 [39]</b>      | GA 24–27+6 wks; ~376 infants (93% follow-up); 21 French NICUs [39] | Hydrocortisone 0.5 mg/kg BID ×7d then 0.5 mg/kg/d ×3d; early (<24h) [39]                          | Neurodevelopmental impairment, CP, neurological exam at 22 months CA [39]                  |
| <b>Sachin S Shah et al., 2017 [40]</b> | VLBW preterm infants; mechanically ventilated [40]                 | Inhaled (budesonide) vs systemic corticosteroids; early start (within first 7 days) [40]          | Developmental outcomes at 7 years [40]                                                     |

| Study                                         | Population                                                                          | Steroid(s) Studied                                                                | Primary Neurodevelopmental Focus                                                          |
|-----------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
| <b>N. Parikh et al., 2015 [41]</b>            | ELBW ( $\leq 1000$ g) infants 10–21 days old; high BPD risk; single-center US [41]  | Hydrocortisone stress-dose, cumulative 17 mg/kg over 7 days; late initiation [41] | Death or composite NDI at 18–22 months CA (Bayley-III, GMFCS, hearing, vision) [41]       |
| <b>Kristi L. Watterberg et al., 2022 [42]</b> | $<30$ wks GA; mean GA $24.9 \pm 1.5$ wks; mean BW $715 \pm 167$ g; 50 US NICUs [42] | Hydrocortisone 18 mg/kg cumulative over 10 days; initiated day 14–28 [42]         | Survival without moderate/severe NDI at 22–26 months CA; cerebral palsy, Bayley-III [42]  |
| <b>J. Harrold et al., 2013 [43]</b>           | Preterm infants at risk for BPD [43]                                                | Inhaled vs systemic corticosteroids; early vs late systemic [43]                  | Cerebral palsy, Bayley MDI/PDI scores [43]                                                |
| <b>O. Baud et al., 2018 [15]</b>              | 379 survivors from PREMILOC; GA 24–25 wks (n=96) and 26–27 wks (n=283) [15]         | Hydrocortisone low-dose; early initiation [15]                                    | NDI, CP, global neurological assessment (Brunet-Lézine) at 22 months CA by GA strata [15] |

| Study                                  | Population                                                                    | Steroid(s) Studied                                                                                                      | Primary Neurodevelopmental Focus                                                                                   |
|----------------------------------------|-------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------|
| <b>M. T. Wolbeek et al., 2013 [5]</b>  | 14–17 year-old adolescents; GA <32 wks; DEX n=63, HC n=67, untreated n=71 [5] | DEX (0.5 mg/kg/day tapering to 0.1 mg/kg/day over 21 days) vs HC (5 mg/kg/day tapering to 1 mg/kg/day over 22 days) [5] | Gross motor function, IQ, alertness, visuomotor coordination, emotion recognition, school level at 14–17 years [5] |
| <b>L. Zeng et al., 2018 [44]</b>       | Preterm infants (<37 wks) in RCTs for BPD prevention [44]                     | Dexamethasone (high/low dose), hydrocortisone, budesonide, beclomethasone, fluticasone [44]                             | Cerebral palsy (network meta-analysis estimates) [44]                                                              |
| <b>M. van de Loo et al., 2024 [45]</b> | Preterm infants at risk for BPD [45]                                          | Dexamethasone, hydrocortisone, budesonide; early and late; systemic and inhaled [45]                                    | Cerebral palsy, neurosensory disability [45]                                                                       |

| Study                                   | Population                                                                                                                                | Steroid(s) Studied                                                                              | Primary Neurodevelopmental Focus                                                                      |
|-----------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| <b>Leena Aho et al., 2025 [46]</b>      | 66 extremely preterm children followed to 6.5 years [46]                                                                                  | Hydrocortisone (n=18), dexamethasone (n=3), HC+DEX (n=8), no steroids (n=37) [46]               | Cognitive outcomes (FSIQ, PIQ, VIQ) at 6.5 years [46]                                                 |
| <b>M. Shaffer et al., 2019 [47]</b>     | Very preterm infants [47]                                                                                                                 | Hydrocortisone low-dose; early initiation; 10–15 days duration [47]                             | Survival without BPD; 2-year neurodevelopmental outcomes [47]                                         |
| <b>Min Soo Kim et al., 2025 [17]</b>    | 146 VLBW infants (GA $\leq 32+6$ wks); high HCS $>90$ mg/kg (n=57) vs low HCS $\leq 90$ mg/kg (n=89); dexamethasone-exposed excluded [17] | Hydrocortisone (cumulative high $>90$ mg/kg vs low $\leq 90$ mg/kg); ROC-derived threshold [17] | CP (GMFCS $\geq$ II), NDI composite, brain volumes at TEA, head circumference at 18–24 months CA [17] |
| <b>Sachin S Shah et al., 2017a [48]</b> | VLBW ( $\leq 1500$ g) or $\leq 32$ wks GA preterm infants [48]                                                                            | Inhaled vs systemic corticosteroids; treatment of BPD; started after first week [48]            | Developmental outcomes at 7 years (subset of 75 UK/Ireland infants) [48]                              |

| Study                                                | Population                                                                          | Steroid(s) Studied                                                                   | Primary Neurodevelopmental Focus                                                            |
|------------------------------------------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| <b>Linda Drozdowicz &amp; J. Bostwick, 2014 [49]</b> | Pediatric patients exposed to corticosteroids; includes neonatal dexamethasone [49] | Dexamethasone; pediatric corticosteroid exposures generally [49]                     | Neuropsychiatric adverse effects including cognitive and behavioral outcomes [49]           |
| <b>Hajnalka Szabó et al., 2021 [50]</b>              | Preterm infants with BPD [50]                                                       | Systemic corticosteroids (postnatal); general review [50]                            | Neurodevelopmental and respiratory consequences of systemic CS [50]                         |
| <b>T. Ogunlesi et al., 2015 [51]</b>                 | Neonates with bacterial meningitis (different indication context) [51]              | Dexamethasone as adjunctive treatment for bacterial meningitis [51]                  | Death, sensorineural deafness, neurological deficits, developmental delay at 1–2 years [51] |
| <b>Susanne Hay et al., 2020 [4]</b>                  | Preterm infants (<37 wks) at risk for BPD [4]                                       | Dexamethasone (high/moderate/low dose), hydrocortisone; early and late treatment [4] | Cerebral palsy, major neurosensory disability [4]                                           |

| Study                                                      | Population                                                                            | Steroid(s) Studied                                                        | Primary Neurodevelopmental Focus                                                                 |
|------------------------------------------------------------|---------------------------------------------------------------------------------------|---------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| <b>S. Demauro et al., 2025 [14]</b>                        | 545 children (272 HC, 273 placebo); <30 wks GA; mean GA ~24.9 wks; 19 US centers [14] | Hydrocortisone 10-day taper; initiated day 14–28 [14]                     | Functional impairment (cognitive, motor, academic delay, exercise capacity) at 5–8 years CA [14] |
| <b>K. Watterberg et al., 2022 (full trial report) [11]</b> | <30 wks GA; mean GA $24.9 \pm 1.5$ wks; mean BW $715 \pm 167$ g [11]                  | Hydrocortisone 18 mg/kg cumulative over 10 days; initiated day 14–28 [11] | Survival without moderate/severe NDI; Bayley-III, GMFCS, vision, hearing at 22–26 months CA [11] |
| <b>S. W. Aucott et al., 2010 [52]</b>                      | 350 intubated ELBW infants; 252 followed to 18–22 months CA [52]                      | Hydrocortisone (prophylaxis for adrenal insufficiency) [52]               | Cerebral palsy; growth and neurodevelopment at 18–22 months CA [52]                              |
| <b>S. Zyblewski et al., 2021 [53]</b>                      | Neonates undergoing cardiac surgery (cardiac NICU context) [53]                       | Intraoperative methylprednisolone vs placebo [53]                         | BSID-III cognitive and motor scores at 12 months [53]                                            |

| Study                                                                  | Population                                                                                  | Steroid(s) Studied                                                                                            | Primary Neurodevelopmental Focus                                                       |
|------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| <b>Kata Kovacs et al., 2025 [54]</b>                                   | Term/near-term infants with NE and hypotension during therapeutic hypothermia; Hungary [54] | Hydrocortisone 0.5 mg/kg every 6h; early (<24h); median cumulative 5.8 mg/kg [54]                             | Death or adverse neurodevelopmental outcome (Bayley-II MDI/PDI <70) at ~20 months [54] |
| <b>Bonnie L Marr et al., 2019 [55]</b>                                 | 59 infants $\leq 27$ wks GA with evolving BPD; NICU setting [55]                            | Dexamethasone 42-day taper (total 7.56 mg/kg) vs 9-day course(s) (total 4.04 mg/kg); initiated day 10–21 [55] | Intact survival (normal neurological exam, IQ >70, school function) at 7 years [55]    |
| <b>Late hydrocortisone does not prevent BPD (2022 commentary) [56]</b> | <30 wks GA; mean GA 24.9 wks; mean BW 715 g; US NICUs [56]                                  | Hydrocortisone 4 mg/kg/day tapered over 10 days; initiated day 14–28 [56]                                     | Survival without moderate/severe NDI at 2 years [56]                                   |

| Study                                                  | Population                                                                            | Steroid(s) Studied                                                          | Primary Neurodevelopmental Focus                                                                      |
|--------------------------------------------------------|---------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| <b>W. Onland et al., 2010 [57]</b>                     | Ventilated preterm infants >7 days [57]                                               | Dexamethasone (moderately early 7–14 days vs delayed >3 weeks) [57]         | Cerebral palsy; mortality; BPD; effect of open-label glucocorticoid use [57]                          |
| <b>W. Onland et al., 2011 (SToP-BPD protocol) [58]</b> | <30 wks and/or <1250 g; ventilator-dependent at 7–14 days; 400 infants planned [58]   | Hydrocortisone 72.5 mg/kg cumulative over 22 days; initiated 7–14 days [58] | Death or BPD at 36 wks PMA; CP, Bayley-III, GMFCS at 2 years CA [58]                                  |
| <b>T. de Baat et al., 2025 [12]</b>                    | 277 survivors; 215 assessed at 5.5 years CA; <30 wks GA; Dutch/Belgian NICUs [12]     | Hydrocortisone 72.5 mg/kg cumulative over 22 days; initiated 7–14 days [12] | Death or moderate–severe NDI; WPPSI-III IQ; M-ABC-2; GMFCS; vision/hearing; CBCL at 5.5 years CA [12] |
| <b>许巍 (Xu Wei), 2016 [19]</b>                          | 51 infants (BW 501–1250 g; GA 23–30 wks); 80% of survivors followed to 5–7 years [19] | Hydrocortisone early low-dose; 10-day course [19]                           | Neurological impairment, IQ (full-scale and executive), need for physical therapy at 5–7 years [19]   |
| <b>M. Quan, 2013 [59]</b>                              | Preterm infants; CLD prevention/treatment [59]                                        | Dexamethasone; early vs late administration [59]                            | Cerebral palsy, deafness, severe visual impairment; follow-up >2 years [59]                           |

| Study                                                        | Population                                                       | Steroid(s) Studied                                                          | Primary Neurodevelopmental Focus                                                                   |
|--------------------------------------------------------------|------------------------------------------------------------------|-----------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|
| <b>N. Halbmeijer et al., 2020 [60]</b>                       | 371 randomized; mean GA 26 wks; <30 wks; Dutch NICUs [60]        | Hydrocortisone 72.5 mg/kg cumulative over 22 days; initiated 7–14 days [60] | Death or NDI at 2 years CA; subgroup <27 wks GA [60]                                               |
| <b>N. Halbmeijer et al., 2023 [61]</b>                       | 372 randomized; CBCL completed in 183 infants at 2 years CA [61] | Hydrocortisone 72.5 mg/kg cumulative over 22 days; initiated 7–14 days [61] | Behavioral problems (CBCL 1.5–5 total, internalizing, externalizing, subscales) at 2 years CA [61] |
| <b>Nasal high-flow therapy during (2022 commentary) [62]</b> | <30 wks GA; mean GA 24.9 wks; mean BW 715 g [62]                 | Hydrocortisone 4 mg/kg/day tapered over 10 days; initiated day 14–28 [62]   | Survival without moderate/severe NDI at 2 years [62]                                               |
| <b>N. Halbmeijer et al., 2023a [16]</b>                      | 372 randomized; <30 wks GA; Dutch/Belgian NICUs [16]             | Hydrocortisone 72.5 mg/kg cumulative over 22 days; initiated 7–14 days [16] | Death or NDI at 2 years CA; by GA subgroup (<27 wks vs ≥27 wks) [16]                               |
| <b>K. Kersbergen, 2015 [63]</b>                              | Preterm infants born <28 wks GA; serial MRI [63]                 | Hydrocortisone (observational; for developing CLD) [63]                     | Brain tissue volumes; neurodevelopmental outcomes at ~2 years [63]                                 |

| Study                                                                 | Population                                                                            | Steroid(s) Studied                                              | Primary Neurodevelopmental Focus                                                        |
|-----------------------------------------------------------------------|---------------------------------------------------------------------------------------|-----------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| <b>Postnatal steroids and febrile seizures (2016 commentary) [64]</b> | 575 preterm survivors (<32 wks, <1500 g; Taiwan) [64]                                 | Postnatal corticosteroids (type unspecified) [64]               | Febrile seizures; neurodevelopmental outcomes (Bayley, Wechsler) at 2 and 5 years [64]  |
| <b>K. Crotty et al., 2012 [65]</b>                                    | 222 children (60 DEX-treated, 54 untreated preterm, 108 term-born; ELBW <1000 g) [65] | Dexamethasone (postnatal) [65]                                  | Visual memory, visual-motor integration, math, motor dexterity at early school age [65] |
| <b>R. G. M. Cassiano et al., 2016 [66]</b>                            | Preterm children at different ages [66]                                               | Corticosteroids/steroids as one of many neonatal variables [66] | Behavioral and emotional problems in children born preterm [66]                         |
| <b>S. Gentle et al., 2023 [67]</b>                                    | 799 extremely preterm infants [67]                                                    | Hydrocortisone; BPD-risk stratification analysis [67]           | BPD or death; NDI; effect modification by baseline BPD/death risk [67]                  |

| Study                                                 | Population                                                                  | Steroid(s) Studied                                                       | Primary Neurodevelopmental Focus                                                                               |
|-------------------------------------------------------|-----------------------------------------------------------------------------|--------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|
| <b>Jehier Afifi et al., 2024 [68]</b>                 | 4327 EPT infants (<29 wks GA) with unremarkable cranial ultrasound [68]     | Systemic steroids as a predictor (observational) [68]                    | Significant NDI (CP $\geq$ GMFCS 3, Bayley-III <70, deafness, blindness) at 18–24 months CA [68]               |
| <b>S. Demauro et al., 2024 (HYBRiD protocol) [69]</b> | ~800 infants enrolled in NICHD NRN HC trial; <30 wks GA; 19 US centers [69] | Hydrocortisone 10-day taper; initiated day 14–28 [69]                    | School-age functional motor, cognitive, academic, pulmonary outcomes at 5–8 years CA [69]                      |
| <b>Bonnie L Marr et al., 2020 (Reply) [70]</b>        | VLBW infants with evolving BPD [70]                                         | Dexamethasone 42-day vs 9-day course [70]                                | Intact survival (neurodevelopmental) at 7 years; defense of trial findings [70]                                |
| <b>Panpan Liu et al., 2026 [71]</b>                   | Preterm infants; risk factors for ASD [71]                                  | Postnatal steroid administration as one of 22 risk factors [71]          | Autism spectrum disorder risk in preterm infants [71]                                                          |
| <b>Lillian G. Matthews et al., 2018 [72]</b>          | VPT <30 wks GA or <1250 g; mean GA 27.5 wks; mean BW 969 g [72]             | Postnatal corticosteroids (observational; 9% of VPT cohort exposed) [72] | Cerebellar volumes at TEA and 7 years; IQ, language, attention, working memory, motor function at 7 years [72] |

| Study                                     | Population                                                                 | Steroid(s) Studied                                                               | Primary Neurodevelopmental Focus                                                  |
|-------------------------------------------|----------------------------------------------------------------------------|----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| <b>E. Shinwell et al., 2021 [73]</b>      | Preterm infants; pre- and postnatal steroid evidence review [73]           | Systemic hydrocortisone, inhaled corticosteroids; postnatal [73]                 | BPD prevention; neurodevelopmental safety [73]                                    |
| <b>Ian Morris et al., 2019 [13]</b>       | Very preterm to extremely preterm infants; NICU RCTs across countries [13] | Hydrocortisone (systemic); early ( $\leq 7$ days) and late ( $\geq 8$ days) [13] | Survival without moderate-to-severe NDI; cerebral palsy; any NDI; severe NDI [13] |
| <b>Meera N. Sankar et al., 2025 [74]</b>  | 800 infants <30 wks GA [74]                                                | Hydrocortisone; interaction with PDA treatment [74]                              | Moderate-to-severe CP; NDI; BPD/death outcomes [74]                               |
| <b>Oreoluwa Olaloko et al., 2018 [75]</b> | Preterm infants requiring BPD prevention/treatment [75]                    | Dexamethasone, hydrocortisone; systemic and inhaled [75]                         | Cerebral palsy, neurological impairment, school performance [75]                  |
| <b>T. Pin et al., 2010 [76]</b>           | $\leq 29$ wks GA preterm infants; followed 4–18 months CA [76]             | Postnatal steroids (observational; type unspecified) [76]                        | Motor development (AIMS) at 4, 8, 12, and 18 months CA [76]                       |

| Study                                                | Population                                                              | Steroid(s) Studied                                                                                  | Primary Neurodevelopmental Focus                                                                             |
|------------------------------------------------------|-------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|
| <b>S. Spénard et al., 2025 [77]</b>                  | Neonates with septic shock refractory to vasopressors [77]              | Hydrocortisone (rescue therapy for septic shock) [77]                                               | Mortality; no long-term neurodevelopmental outcomes assessed [77]                                            |
| <b>J. Meijer et al., 2026 [78]</b>                   | Mean GA 27.4 wks; mean BW 1033 g; 204 with complete CBCL follow-up [78] | Postnatal corticosteroids as component of adverse early life events composite (11% prevalence) [78] | CBCL behavioral outcomes (attention, withdrawn, externalizing, internalizing) at 2, 5.5, and 8 years CA [78] |
| <b>Yuan He et al., 2020 (trial protocol) [79]</b>    | 196 subjects planned; GA 26+0–30+6 wks; <1500 g; China [79]             | Hydrocortisone 0.5 mg/kg BID ×7d then 0.5 mg/kg/d ×3d (total 8.5 mg/kg); initiated day 28 [79]      | Neurodevelopmental outcomes at multiple time points to 2 years CA [79]                                       |
| <b>A. Menshykova &amp; D. Dobryanskyy, 2026 [80]</b> | Preterm infants with BPD [80]                                           | Postnatal steroids (general BPD prevention/treatment strategies) [80]                               | Cerebral palsy and other neurodevelopmental disorders [80]                                                   |

## **Effects of Postnatal Steroids on Neurodevelopmental Outcomes**

### **Dexamethasone: Early Postnatal Administration (<7–8 Days)**

The clearest and most consistent signal in this literature involves early postnatal dexamethasone. Multiple large-scale meta-analyses converge on the finding that dexamethasone started within the first week of life substantially increases cerebral palsy risk. Doyle et al. (2021), synthesizing 32 RCTs (4395 infants), reported a risk ratio for cerebral palsy of 1.77 (95% CI 1.21–2.58) with early dexamethasone, and an increased combined outcome of mortality or cerebral palsy with RR 1.18 (95% CI 1.01–1.37) [1]. Doyle et al. (2010b), covering 20 RCTs (2860 infants), found that cerebral palsy and the combined outcome of death or cerebral palsy were significantly more common in dexamethasone-treated infants [29]. Doyle et al. (2014a) confirmed significant increases in abnormal neurological examination and cerebral palsy in the 12 trials reporting late outcomes, though major neurosensory disability overall was not significantly increased [26]. AlsuhaymiZuhairHamdan et al. (2017) reported developmental delay RR 1.72 (95% CI 1.40–2.05) and cerebral palsy RR 1.56 (95% CI 1.03–2.10), with combined death or cerebral palsy 1.92 (95% CI 1.18–2.67) across 7 RCTs [3]. The Harrold et al. (2013) overview of Cochrane reviews found a cerebral palsy RR of 1.45 (95% CI 1.06–1.98) associated with early systemic corticosteroids [43], and Quan (2013) concluded that cerebral palsy risk was increased with early dexamethasone but not with late administration [59].

Uberos et al. (2025) synthesized evidence showing that dexamethasone started before 8 days increases cerebral palsy by approximately 75% and neurosensory disability by approximately 37%, with a reported summary RR for cerebral palsy in survivors of 1.81 (95% CI 1.33–2.47) [2]. Conversely, late dexamethasone (initiated  $\geq 7$ –8 days) was not associated with increased cerebral palsy or neurosensory disability, with a non-significant RR of 1.12 (95% CI 0.79–1.60) [2].

The Jenkinson et al. (2023) focusing specifically on long-term outcomes of dexamethasone across 18 observational cohort studies (1609 patients), found that dexamethasone-exposed children had lower IQ scores compared with preterm controls (mean 78.2 [SD 15.0] vs 84.4 [SD 12.6],  $p=0.008$ ) and lower total and performance IQ compared with term-born controls ( $p<0.001$ ) [6]. This

review also found worse pulmonary outcomes in dexamethasone-exposed children [6]. The adolescent cohort study by Wolbeek et al. (2013), comparing DEX-treated (n=63), HC-treated (n=67), and untreated (n=71) adolescents at age 14–17 years (corrected for GA), found that DEX-treated participants scored significantly lower on gross motor tasks, had higher proportions of girls requiring special education, and performed more poorly on alertness, visuomotor coordination, and emotion recognition tasks; in contrast, the HC-treated group did not differ from the untreated group [5]. This study used high-dose historical dexamethasone regimens (0.5 mg/kg/day tapering to 0.1 mg/kg/day over 21 days) [5], substantially higher than current practice.

Crotty et al. (2012), studying 222 children (60 DEX-treated, 54 untreated preterm, 108 term-born ELBW infants) at early school age, found that dexamethasone-treated children performed below untreated peers on immediate visual memory, visual-motor integration, mathematical skill, and motor dexterity, though stepwise regression showed that medical and sociodemographic factors other than dexamethasone also contributed substantially to these deficits [65]. LeFlore and Engle (2011), examining 173 ELBW neonates at 18–22 months, found lower PDI and MDI scores in the BPD plus postnatal steroid group compared with groups without BPD or with BPD alone, with cystic periventricular leukomalacia and group membership as significant predictors in multivariate analysis [30]. Similarly, Pin et al. (2010) found that use of postnatal steroids was associated with poor motor performance at 4, 8, and 18 months of corrected age on the Alberta Infant Motor Scale [76].

In a Taiwanese cohort of 575 preterm survivors, postnatal steroid use was associated with significantly higher rates of febrile seizures at 5 years (14.5% vs 3% in non-seizure peers,  $p=0.006$ ), with no independent effect of other potential confounders including cerebral ultrasound abnormalities [64]. Importantly, in that same cohort, no significant difference in formal neurodevelopmental scores was found between steroid-exposed and unexposed children, in common with several other studies.

The retrospective cohort study by Buchiboyina et al. (2020) in Western Australia, covering 104 dexamethasone-exposed and 324 control infants born <29 weeks, found no increase in long-term disability with any dexamethasone exposure compared with controls (aOR 0.90, 95% CI 0.34–

2.02,  $p=0.784$ ), and no difference between lower ( $<2$  mg/kg) and higher ( $\geq 2$  mg/kg) cumulative dose groups ( $p=0.494$ ) [10]. A summary of this same cohort (reported as Dexamethasone dose and risk of, 2021) similarly found no difference in cerebral palsy between control (5.8%), low-dose (4.0%), and high-dose (0%) groups [36]. However, the higher-dose group had significantly reduced weight, height, and head circumference z-scores at 2 years [10], suggesting that while functional neurodevelopmental outcomes may not differ, somatic and possibly brain-growth effects remain at higher cumulative doses.

### **Dexamethasone: Dose and Regimen Effects**

Several sources explicitly address whether neurodevelopmental risk scales with dexamethasone dose or regimen. Onland et al. (2017), synthesizing RCTs comparing different dexamethasone regimens, found that a moderate cumulative dosage versus a high-dosage regimen was associated with increased risk of abnormal neurodevelopmental outcome (RR 8.33, 95% CI 1.63–42.48; RD 0.30, 95% CI 0.14–0.46; NNTH 4, 95% CI 2.2–7.3) [23], a paradoxical finding suggesting that higher doses may be more protective, though these estimates derive from only two small studies (74 infants) and must be interpreted cautiously. Onland et al. (2023), an updated analysis, confirmed an increased risk of cerebral palsy (RR 6.85, 95% CI 1.29–36.36; NNTH 5) and death or cerebral palsy (RR 3.20, 95% CI 1.35–7.58; NNTH 5) when comparing moderate to high dosage regimens, and death or abnormal neurodevelopmental outcome (RR 3.41, 95% CI 1.44–8.07; NNTH 4) [37]. No differences were found between moderate and low cumulative dose regimens in either review [23, 37].

Uberos et al. (2025) noted a dose-dependent relationship: exceeding the median cumulative dexamethasone dose increased the likelihood of cerebral palsy [2]. The Boscarino et al. (2024) systematic review noted that prolonged dexamethasone regimens (28–42 days) were most consistently linked to harm in individual trials, while some trials found neutral or even improved outcomes, particularly in ELGAN populations [22]. Marr et al. (2019), a randomized trial in 59 infants  $\leq 27$  weeks with evolving BPD, compared a 42-day dexamethasone taper (total 7.56 mg/kg) with a 9-day course(s) protocol (total 4.04 mg/kg); intact survival at 7 years was 75% in the 42-day

group versus 34% in the 9-day group ( $p < 0.005$ ) [55], a counterintuitive finding suggesting benefit rather than harm with prolonged treatment in this very high-risk cohort.

Gustavo Rocha et al. (2024), comparing a single DART-protocol dexamethasone course (cumulative 0.82 mg/kg) versus two or more courses (cumulative 1.70 mg/kg) after the first week of life in 150 infants across 7 NICUs, found that two or more courses were associated with higher prevalence of cerebral palsy functional motor class 2 (OR 6.837, 95% CI 1.054–44.337,  $p = 0.044$ ) and ophthalmological problems requiring glasses (OR 4.157, 95% CI 1.026–16.837,  $p = 0.046$ ) [35]. The network meta-analysis of Zeng et al. (2018) found that while no corticosteroid regimen was significantly associated with changed cerebral palsy risk, high-dose and long-term dexamethasone regimens ranked lowest for cerebral palsy safety, with the point estimates suggesting higher risk (ORs 2.30–2.75 vs placebo), and a combination of high dose and long-term use was specifically discouraged [44].

#### Dexamethasone: Late Postnatal Administration (>7 Days)

Late dexamethasone presents a more favorable neurodevelopmental profile than early administration. Doyle et al. (2017), examining 21 RCTs (1424 infants), found only a trend toward increased cerebral palsy that was partly offset by a trend toward reduced pre-assessment mortality, with the combined rate of death or cerebral palsy not significantly different between groups [25]. Doyle et al. (2021a), the updated Cochrane review (23 RCTs, 1817 infants), reported cerebral palsy RR 1.17 (95% CI 0.84–1.61) and death or cerebral palsy RR 0.90 (95% CI 0.76–1.06), neither significant [7]. The Doyle et al. (2010) earlier review similarly concluded that late dexamethasone reduced neonatal mortality but produced only a trend toward increased cerebral palsy that was offset by reduced pre-assessment mortality [8]. Quan (2013) confirmed that late dexamethasone did not increase cerebral palsy risk, unlike early administration [59].

Onland et al. (2010), using meta-regression to account for open-label glucocorticoid use across 15 RCTs, found that when open-label glucocorticoid use in the placebo arm was below 30%, moderately early dexamethasone (7–14 days) significantly reduced mortality and the combined outcome of mortality and BPD without increasing adverse neurodevelopmental outcomes [57]. This

finding highlights how contamination from rescue steroids can distort observed treatment effects in trials.

### **Hydrocortisone: Early Postnatal Administration**

The early hydrocortisone literature tells a substantially different story from early dexamethasone, though with important nuances. The PREMILOC trial (Baud et al., 2017), a multicenter French RCT (523 randomized, 379 evaluated), found no statistically significant difference in neurodevelopmental impairment at 22 months CA between low-dose hydrocortisone and placebo: the mean global developmental quotient was 91.7 vs 91.4 (difference 0.3, 95% CI  $-2.7$  to  $3.4$ ,  $p=0.83$ ), and the distribution of impairment severity did not differ ( $p=0.33$ ) [24]. The Ofman et al. (2018) secondary analysis of this same trial confirmed that at 22 months, there was no significant difference in any aspect of neurodevelopmental assessment (neurological exam  $p=0.87$ ; impairment distribution  $p=0.33$ ) [39].

However, a gestational age subgroup analysis from PREMILOC (Baud et al., 2018) found a significant interaction: among 24–25 week infants, early hydrocortisone was associated with a substantially lower risk of moderate-to-severe NDI (2% vs 18%; risk difference  $-16\%$ , 95% CI  $-28\%$  to  $-5\%$ ,  $p=0.02$ ), while no significant difference was found in 26–27 week infants (9% vs 9%,  $p=0.95$ ) [15]. This suggests a potential gestational age-dependent benefit specifically at the extreme margins of viability.

The early preschool-age follow-up study by Peltoniemi et al. (2016), examining 5–7-year-old children who had participated in an early neonatal hydrocortisone RCT, found potential adverse effects on neurodevelopment [34], and the Chinese-language abstract of the same data (Xu Wei, 2016) reported that 61% of the hydrocortisone group had neurological impairment versus 39% in placebo ( $p=0.182$ ), with significantly lower executive IQ (88.3 vs 99.1,  $p=0.034$ ) and significantly higher need for physical therapy (22% vs 0%,  $p=0.034$ ) [19], though these differences in global neurological impairment and full-scale IQ were not statistically significant.

Morris et al. (2019), a systematic review and meta-analysis of 14 hydrocortisone trials (1633 infants), found that early systemic hydrocortisone was associated with a modest but statistically significant improvement in survival without moderate-to-severe NDI: RR 1.13 (95% CI 1.02–1.26),

NNT=14 [13]. Subgroup analysis restricted to BPD-primary-outcome trials yielded RR 1.14 (1.03–1.27), NNT=13 [13]. Cerebral palsy was not significantly altered (RR 1.06, 95% CI 0.67–1.67), nor were any NDI, severe NDI, or death outcomes in isolation [13]. Shaffer et al. (2019), using individual patient data meta-analysis across 4 RCTs (n=982), confirmed that early low-dose hydrocortisone significantly increased survival without BPD (OR 1.45, 95% CI 1.11–1.90,  $p=0.007$ ) with no adverse 2-year neurodevelopmental effects reported in the aggregate meta-analysis [47].

The network meta-analysis of Hay et al. (2020), across 59 RCTs, found that early low-dose dexamethasone—but not hydrocortisone—increased cerebral palsy risk (RR 1.92, 95% CI 1.12–3.28, moderate-certainty evidence), and that hydrocortisone may decrease major neurosensory disability versus low-dose dexamethasone (RR 0.65, 95% CI 0.41–1.01) [4]. The van de Loo et al. (2024) overview of nine systematic reviews similarly concluded that early hydrocortisone has a beneficial effect on death or BPD at 36 weeks PMA (RR 0.90, 95% CI 0.82–0.99; low-certainty), but is associated with gastrointestinal perforation; no harmful neurodevelopmental effects were highlighted for hydrocortisone specifically [45].

### **Hydrocortisone: Late Postnatal Administration**

The evidence for late hydrocortisone (initiated from day 7 onward) and neurodevelopmental outcomes is anchored principally by the SToP-BPD trial and the NICHD NRN Hydrocortisone for BPD Trial.

The NICHD NRN trial (Watterberg et al., 2022; 800 infants <30 weeks, mean GA 24.9 weeks) found no significant difference in survival without moderate or severe NDI at 22–26 months CA between hydrocortisone (36.9%) and placebo (37.3%; adjusted RR 0.98, 95% CI 0.81–1.18) [11]. All secondary neurodevelopmental outcomes—severe NDI, moderate/severe NDI among survivors, GMFCS  $\geq$ II, moderate/severe cerebral palsy, severe hearing impairment, and visual impairment—were similarly unaffected [11]. The companion commentary (Late hydrocortisone does not prevent BPD, 2022) and an additional commentary (Nasal high-flow therapy during, 2022) both confirmed these findings, with aRR 0.98 (95% CI 0.81–1.18) [56, 62]. The long-term school-age follow-up of this trial (Demauro et al., 2025; 545 children at 5–8 years CA) confirmed that

neonatal hydrocortisone treatment did not impact the rate of functional impairment (71.3% in hydrocortisone vs 73.3% in placebo; adjusted RR 0.99, 95% CI 0.89–1.10), nor any of its individual components [14]. A secondary analysis by Gentle et al. (2023) established that baseline BPD/death risk did not modify hydrocortisone's effect on BPD, death, or NDI [67], and Sankar et al. (2025) found that late hydrocortisone did not alter the relationship between patent ductus arteriosus and BPD or death [74].

The SToP-BPD trial enrolled 371 ventilator-dependent infants <30 weeks treated with hydrocortisone (cumulative 72.5 mg/kg over 22 days, initiated 7–14 days; Onland et al., 2011) or placebo. The 2-year follow-up (Halbmeijer et al., 2020; n=356 with composite outcome data) found no significant overall effect on death or NDI (adjusted OR 0.79, 95% CI 0.51–1.22, p=0.28), but identified a gestational age interaction: infants <27 weeks showed a significant reduction in death or NDI (54.6% vs 66.2%; risk difference –11.6%, 95% CI –22.4% to –0.5%; p=0.02 for interaction) [60]. This was primarily driven by reduced mortality in the <27 week subgroup rather than reduced NDI in survivors. A secondary effect modifier analysis (Halbmeijer et al., 2023a) confirmed this gestational age interaction for both the composite outcome (OR 0.61, 95% CI 0.38–0.98 for <27 weeks; OR 2.43, 95% CI 0.86–6.85 for ≥27 weeks, p interaction=0.02) and for the death component (OR 0.53, 95% CI 0.32–0.90 for <27 weeks), with no significant effect modification by sex, SGA status, respiratory index, multiple birth, or predicted BPD/death risk [16]. Behavioral outcomes at 2 years CA (Halbmeijer et al., 2023) showed no significant differences across total, internalizing, or externalizing CBCL domains, with a single significant finding of lower anxiety problem scores in the hydrocortisone group (mean difference –1.26, 95% CI –2.41 to –0.12) [61]. The 5.5-year follow-up of SToP-BPD (de Baat et al., 2025; 213 children with classifiable NDI) found no significant difference on the primary composite of death or moderate–severe NDI (OR 0.75, 95% CI 0.49–1.14, p=0.18) and no differences on any individual developmental measure including cognitive IQ, motor function, neurological examination, vision, hearing, behavior, or schooling [12].

The Parikh et al. (2015) RCT of stress-dose hydrocortisone (total 17 mg/kg over 7 days, initiated at 10–21 days; n=64 ELBW infants) found a non-significant reduction in the composite

death or NDI outcome at 18–22 months CA (68% vs 76%; RR 0.83, 95% CI 0.61–1.14), with individual components—cognitive delay, language delay, cerebral palsy, and death—all non-significantly different, though trends favored hydrocortisone [41]. This trial was substantially underpowered for neurodevelopmental outcomes [41].

### **Hydrocortisone: Dose-Response Findings**

Two studies provide dose-response data specifically for hydrocortisone. Patra et al. (2014), in a cohort of 175 ELBW infants, found that each additional day of hydrocortisone exposure increased the odds of subnormal receptive language by 4% and expressive language by 2% in the first year of life, and increased odds of subnormal motor function by 2% in the second year [18]. Hydrocortisone exposure >7 days was specifically associated with worse fine motor scores at 8 months ( $p=0.005$ ) [18].

Kim et al. (2025), in a retrospective cohort of 146 VLBW infants excluding dexamethasone-exposed cases, found that cumulative hydrocortisone >90 mg/kg (vs  $\leq 90$  mg/kg) was associated with markedly higher rates of cerebral palsy (35.9% vs 9.1%; aOR 5.44, 95% CI 1.45–23.96,  $p=0.016$ ), NDI composite (54.0% vs 23.6%, unadjusted  $p=0.002$ ; aOR 2.58, 95% CI 0.94–7.42,  $p=0.071$  after adjustment), and head circumference <10th percentile (64.3% vs 19.5%; aOR 4.45, 95% CI 1.34–15.71,  $p=0.016$ ) [17]. MRI at term-equivalent age showed significantly reduced intracranial, cerebrum, cerebellum, and brainstem volumes in the high-dose group [17]. The ROC-derived threshold for predicting cerebral palsy was >90 mg/kg (AUC 0.70) [17], though the authors acknowledge substantial confounding by indication, given that infants receiving higher doses were substantially more preterm and ill [17].

Kovacs et al. (2025), studying term infants with neonatal encephalopathy receiving hydrocortisone during therapeutic hypothermia (a very different indication), found that while randomized group assignment did not significantly affect neurodevelopmental outcomes (death or severe NDI: 40% HC vs 18% placebo,  $p=0.13$ ), cumulative hydrocortisone dose (including open-label rescue doses) was independently associated with adverse cognitive outcome in regression analysis: OR 1.16 per 1 mg/kg (95% CI 1.01–1.37,  $p=0.04$ ) [54]. The ROC threshold was approximately 5.6 mg/kg [54].

### **Comparative Findings: Dexamethasone Versus Hydrocortisone**

The David et al. (2025) retrospective cohort study directly compared no steroid exposure, HC only, and DEX ± HC groups among 221 EPT infants. In linear regression analysis, DEX ± HC exposure was associated with a 10-point reduction in cognitive ( $p < 0.01$ ), language ( $p < 0.05$ ), and motor ( $p < 0.01$ ) Bayley-3 indices compared with both the no-steroid and HC-only groups; the HC-only group did not differ significantly from the no-steroid group [21]. The Wolbeek et al. (2013) adolescent cohort study, using historical high doses, similarly found adverse effects in DEX-treated but not HC-treated adolescents on gross motor tasks, school level, alertness, visuomotor coordination, and emotion recognition [5].

The Raghuveer et al. (2024) meta-analysis (44 RCTs, 6377 infants) found that neither dexamethasone (RR 1.09, 95% CI 0.55–2.17) nor hydrocortisone (RR 1.18, 95% CI 0.75–1.87) significantly increased cerebral palsy risk, and neither was associated with significant differences in MDI/PDI scores [33]. Multivariable meta-regression confirmed that dexamethasone reduced BPD without increased CP risk [33]. This finding contrasts with the Doyle et al. (2021) early treatment meta-analysis showing significant CP increases with dexamethasone, underscoring that the Raghuveer analysis presumably captured later-initiated or lower-dose dexamethasone cohorts as well as earlier trials.

The effect-modifier analyses from Doyle et al. (2014), updating a prior metaregression of 20 RCTs, found that infants at higher BPD risk had increased rates of survival free of cerebral palsy after postnatal corticosteroid treatment—the risk-benefit calculus of cerebral palsy relative to BPD itself depends critically on the baseline BPD risk [9].

### **Effects on Brain Structure**

The Keunen et al. (2012) systematic review of brain tissue volumes at term-equivalent age summarized that postnatal dexamethasone exposure was associated with reduced cortical gray matter, cerebellar, subcortical gray matter, and hippocampal volumes across several cohorts, though findings were attenuated or lost after adjusting for intracranial volume or chronic lung disease in some studies [38]. Hydrocortisone findings were inconsistent across cohorts, with some showing reduced cerebellar volume and others finding no volumetric effects [38].

Matthews et al. (2018), a prospective longitudinal cohort study in 224 VPT infants, found that postnatal corticosteroid exposure (9% of infants) was associated with smaller cerebellar volume at term-equivalent age by  $-3.22$  cc (95% CI  $-4.73$  to  $-1.72$ ,  $p < 0.001$ ; FDR-corrected  $p = 0.09$ ), though this effect did not persist at 7 years, and no significant association was found between steroid exposure and 7-year neurodevelopmental outcomes in this sample [72]. Kersbergen (2015) similarly found that hydrocortisone for developing chronic lung disease did not influence overall brain size or cerebellar volumes in a serial MRI cohort [63].

Kim et al. (2025) provided the most detailed volumetric-outcome linkage data: high cumulative hydrocortisone was associated with reduced MRI volumes of all major brain regions at TEA, and these volume reductions co-occurred with the increased rates of CP and NDI at follow-up [17].

### **Behavioral and Neuropsychological Outcomes**

Beyond traditional neurodevelopmental composites, several studies assessed behavioral and neuropsychological domains. Purdy et al. (2013), in 45 mother-child dyads at mean age 8 years, found significant relationships between CBCL Total Problems scores and perinatal steroid exposure, sepsis, and timing of initial PNS, with higher PNS exposure groups exhibiting more behavioral problems—particularly withdrawn, attention, conduct, social, and rule-breaking behaviors—though no statistically significant between-group differences were found [28]. Meijer et al. (2026), in a longitudinal cohort study of 204 very preterm children with CBCL assessments at 2, 5.5, and 8 years, found that a composite adverse early life events variable (which included postnatal corticosteroid administration alongside brain injury, surgeries, and prolonged ventilation) was significantly associated with attention problems and withdrawn behaviors over time [78]. Drozdowicz and Bostwick (2014), in a narrative systematic review, noted a mixed picture for neonatal dexamethasone-exposed children: some reports found eventual neuropsychiatric deficits, while others found no effect [49]. Cassiano et al. (2016), reviewing 27 studies, found that prematurity combined with corticosteroid treatment increased the risk of behavioral and emotional problems in children [66].

The Halbmeijer et al. (2023) CBCL follow-up of STOP-BPD (n=183; 2 years CA) found high rates of overall behavioral problems in the preterm cohort (22.9% with critically elevated Total Problems T-scores) but no significant association with hydrocortisone vs placebo for total, internalizing, or externalizing problems; only lower anxiety problem scores were observed in the hydrocortisone group [61].

### Cerebral Palsy and Sensory Outcomes: Summary Across Agent Types and Timing

| Steroid agent and timing                        | Cerebral palsy estimate                           | Source                             |
|-------------------------------------------------|---------------------------------------------------|------------------------------------|
| Early DEX (<7–8 days) [1]                       | RR 1.77 (95% CI 1.21–2.58)                        | Doyle et al., 2021                 |
| Early DEX (<8 days) [2]                         | RR ~1.81 (95% CI 1.33–2.47)<br>in survivors       | Uberos et al., 2025                |
| Early DEX, all [3]                              | RR 1.56 (95% CI 1.03–2.10)                        | AlsuhaymiZuhairHamdan et al., 2017 |
| Early DEX (network meta-analysis, low-dose) [4] | RR 1.92 (95% CI 1.12–3.28)                        | Hay et al., 2020                   |
| Late DEX ( $\geq 7$ days) [7]                   | RR 1.17 (95% CI 0.84–1.61);<br>not significant    | Doyle et al., 2021a                |
| DEX (all trials, NMA) [33]                      | RR 1.09 (95% CI 0.55–2.17);<br>not significant    | Raghuveer et al., 2024             |
| Early HC (PREMILOC) [24]                        | Not significantly increased; CP incidence similar | Baud et al., 2017                  |

| Steroid agent and timing                      | Cerebral palsy estimate                                                  | Source                  |
|-----------------------------------------------|--------------------------------------------------------------------------|-------------------------|
| Early HC (all trials meta-analysis) [13]      | RR 1.06 (95% CI 0.67–1.67);<br>not significant                           | Morris et al., 2019     |
| Late HC (NRN trial; 22–26 months) [11]        | RR 1.20 (95% CI 0.78–1.83)<br>for moderate/severe CP; not<br>significant | Watterberg et al., 2022 |
| Late HC (SToP-BPD; 2 years CA) [60]           | Not significantly increased<br>overall; benefit in <27 wks               | Halbmeijer et al., 2020 |
| HC (NMA) [33]                                 | RR 1.18 (95% CI 0.75–1.87);<br>not significant                           | Raghuveer et al., 2024  |
| Multiple DEX courses vs<br>single (DART) [35] | OR 6.837 (95% CI 1.054–<br>44.337) for CP class 2                        | Rocha et al., 2024      |
| High cumulative HC (>90<br>mg/kg) [17]        | aOR 5.44 (95% CI 1.45–23.96)                                             | Kim et al., 2025        |

Sensory outcomes were addressed in fewer studies. Doyle et al. (2017) reported no significant increase in blindness with late dexamethasone [25]; Quan (2013) found no significant difference in deafness (RR 0.52, 95% CI 0.17–1.56) or severe visual impairment (RR 1.56, 95% CI 0.77–3.18) with dexamethasone compared with controls [59]. In the context of bacterial meningitis, Ogunlesi et al. (2015) found that adjunctive dexamethasone was associated with a non-significant increase in sensorineural deafness at 2 years (RR 1.80, 95% CI 0.18–18.21) but a significant reduction in hearing loss at 4–10 weeks post-discharge (RR 0.41, 95% CI 0.17–0.98) [51], a distinct indication context.

## **Autism Spectrum Disorder and Postnatal Steroid Exposure**

Liu et al. (2026), in a systematic review and meta-analysis of 45 studies on ASD risk factors in preterm infants, identified postnatal steroid administration as one of 22 significant prenatal and postnatal risk factors for ASD [71], though overall certainty of evidence for these associations was rated low or very low [71].

### **Synthesis**

#### **Apparent Contradictions in the Evidence**

The literature contains what appear, at first pass, to be irreconcilable findings. Multiple large Cochrane meta-analyses and one 800-infant NICHD RCT conclude that postnatal corticosteroids—particularly dexamethasone—increase cerebral palsy risk, while other analyses conclude that neither dexamethasone nor hydrocortisone significantly increases neurodevelopmental impairment at follow-up. The Marr et al. (2019) RCT finds dramatically superior intact survival (75% vs 34%) with the longer dexamethasone course [55], entirely at odds with conventional expectations based on the early-dexamethasone meta-analyses. The Buchiboyina cohort finds no long-term disability difference across dexamethasone dose levels [10], while the Onland (2023) review finds that moderate-dose dexamethasone confers more neurodevelopmental harm than high-dose [37]. Early hydrocortisone appears to improve survival without NDI in Morris et al. (2019) [13] but shows potential adverse effects at preschool age in the Peltoniemi/Xu follow-up [19]. These contradictions can be substantially reconciled by considering the following dimensions.

#### **Timing of Initiation as the Primary Driver of Dexamethasone Risk**

The most reproducible predictor of neurodevelopmental harm from dexamethasone is initiation within the first week of life. The mechanistic rationale is that the neonatal brain in the first postnatal days is at a particularly vulnerable stage: glucocorticoids suppress neuronal proliferation, induce apoptosis, and impair myelination in experimental models, and these effects may be especially pronounced during the rapid early postnatal developmental window [6, 49]. Studies finding no cerebral palsy increase with dexamethasone are predominantly those involving late initiation (>7 days) [7, 8] or mixed/late-predominant cohorts [10, 33]. The Uberos et al. (2025) synthesis explicitly maps this: early (<8 days) dexamethasone RR ~1.81 for CP [2] versus late (≥7–

130

8 days) non-significant RR 1.12 [2]. This timing effect also explains the Onland (2010) finding that moderately early dexamethasone (7–14 days, not the first few days) reduced mortality without increasing CP when open-label glucocorticoid contamination was controlled [57].

### **Historical Dose Regimens Versus Current Practice**

The adverse neurodevelopmental findings that most strongly drove the decline in postnatal dexamethasone use derived primarily from RCTs and cohort studies employing the high-dose tapered regimens of the late 1980s and early 1990s (e.g., 0.5 mg/kg/day over 21 days in the Wolbeek cohort [5]). These regimens are substantially higher than the low-dose DART-protocol courses (cumulative ~0.5–1 mg/kg) now in common use. The network meta-analysis evidence consistently places high-dose, long-term dexamethasone at the bottom of the safety rankings for CP [44], while the Raghuvier (2024) and Buchiboyina (2020) analyses—which include contemporary lower-dose regimens—find no significant CP increase overall [10, 33]. The Marr et al. (2019) finding of better outcomes with a 42-day course versus repeated 9-day courses is similarly paradoxical only if the comparison is not recognized as comparing a carefully controlled prolonged taper (total 7.56 mg/kg) against an approach with unpredictable repeated exposures (total 4.04 mg/kg) in a particularly high-risk group that suffered disproportionate morbidity in the shorter-course arm [55, 70].

### **Risk of BPD as an Effect Modifier for Dexamethasone**

The Doyle et al. (2014) metaregression demonstrated that at higher background rates of BPD—that is, in infants at highest respiratory risk—postnatal corticosteroids were associated with net survival benefit free of cerebral palsy, because the competing harm of BPD itself increases CP risk [9]. Studies enrolling populations with relatively low BPD risk would therefore see net harm (excess CP without equivalent BPD benefit), while those enrolling the highest-risk populations would see net benefit or neutrality. This context-and-population distinction explains why the same drug at the same dose can appear harmful in one trial and beneficial in another.

### **Hydrocortisone: Predominantly Neutral Neurodevelopmental Profile but Dose-Dependent Signals**

The large RCTs (PREMILOC, NICHD NRN, STOP-BPD) and the Morris et al. (2019) meta-analysis consistently find that hydrocortisone at pharmacological doses does not increase cerebral

palsy or composite NDI at 2 years of age, and in some analyses improves composite outcomes at the lowest gestational ages [11, 13, 24, 60]. However, two important caveats temper this reassurance.

First, the Peltoniemi preschool follow-up found clinically concerning signals—executive IQ deficit, need for physical therapy—that did not reach statistical significance in a small sample ( $n=51$ ) [19], and the Wolbeek cohort found adverse outcomes with hydrocortisone at historical high doses (5 mg/kg/day) [5]. At cumulative doses exceeding ~90 mg/kg, as studied by Kim et al. (2025), hydrocortisone was associated with adjusted CP risk nearly 5.4-fold that of lower exposure, alongside markedly reduced brain volumes [17]. The cumulative doses in this study far exceed those in the major RCTs (SToP-BPD: 72.5 mg/kg; NICHD NRN: 18 mg/kg; PREMILOC: 8.5 mg/kg), suggesting that the safety findings from RCTs may not extrapolate to the highest-dose clinical practice patterns. Patra et al. (2014) reinforced this dose-response concept, finding that each additional day of hydrocortisone exposure incrementally increased odds of subnormal language and motor outcomes [18].

Second, the Kovacs et al. (2025) dose-response finding (OR 1.16 per 1 mg/kg for adverse cognitive outcome,  $p=0.04$ ) arose in a different population—term neonates with encephalopathy—and may reflect synergistic toxicity between encephalopathy and steroid exposure rather than a generalizable neonatal hydrocortisone dose-effect [54].

#### Gestational Age as an Effect Modifier for Both Agents

The most consistent patient characteristic that modifies the steroid–neurodevelopment relationship is gestational age at birth. The PREMILOC subgroup analysis (Baud et al., 2018) showed significant neurodevelopmental benefit (reduced moderate-to-severe NDI) from early hydrocortisone at 24–25 weeks but not 26–27 weeks [15]. The SToP-BPD effect modifier analysis (Halbmeijer et al., 2023a) confirmed that late hydrocortisone significantly reduced death or NDI in infants <27 weeks but showed numerically worse outcomes in the  $\geq 27$  week subgroup (OR 2.43, though non-significant due to small numbers) [16]. These findings suggest that the benefit-risk balance is most favorable for the most extreme preterm infants, in whom BPD and its consequences are most severe, and least favorable—or possibly harmful—for less preterm, less vulnerable infants.

### **Confounding by Indication and Competing Risk of Mortality**

A persistent challenge in this literature is that steroid-treated infants are systematically sicker than controls in observational studies. Patra et al. (2014) noted that hydrocortisone-exposed infants had substantially lower GA, lower BW, and higher rates of every major morbidity [18]. Kim et al. (2025) found similar systematic differences, with higher rates of BPD, PVL, and sepsis in the high-dose group [17]. Multiple regression adjustment partially addresses this but cannot eliminate confounding by unmeasured illness severity in retrospective designs. In RCTs, confounding by indication is minimized, but contamination from open-label rescue steroids is a recognized threat: in the SToP-BPD placebo arm, 54% received open-label hydrocortisone [12]; in the NICHD NRN trial, approximately 40% of both arms received open-label dexamethasone [42]. This contamination biases toward the null in both trials, meaning the true neurodevelopmental effect of late hydrocortisone may be marginally more favorable than observed.

Competing risk of mortality is especially relevant for cerebral palsy: infants who die before neurodevelopmental assessment cannot be classified as having CP, creating a systematic survivor bias. Doyle et al. (2017) explicitly noted that a trend toward increased CP with late dexamethasone was offset by reduced early mortality [25]. The Doyle et al. (2021) early treatment meta-analysis, while showing significant overall increases in CP with early dexamethasone, found that the combined outcome of mortality or cerebral palsy with early hydrocortisone was not significantly increased (RR 0.86, 95% CI 0.71–1.05), and indeed early hydrocortisone reduced mortality (RR 0.80, 95% CI 0.65–0.99) [1]. Analyses using composites of death or NDI or survival without NDI therefore provide more clinically meaningful estimates than CP rates alone.

### **Assessment Age and the Problem of Incomplete Follow-up**

Most available evidence assesses neurodevelopmental outcomes at 18–24 months corrected age, which is standard but insufficient to detect higher-order neurological deficits including executive function, academic performance, behavior, and mental health that only become apparent at school age or later. The school-age follow-ups available—Wolbeek (14–17 years) [5], Marr (7 years) [55], Crotty (early school age) [65], Jenkinson review (up to 19 years) [6], Aho pilot (6.5 years) [46], SToP-BPD (5.5 years) [12], and HYBRiD (5–8 years, reported 2025) [14] —suggest

that deficits detectable at 2 years either persist or evolve into new domains at school age, but that hydrocortisone does not substantially worsen these trajectories compared with placebo [12, 14]. The reassurance from large RCTs at 2 years must therefore be understood as confined to early functional impairment; whether hydrocortisone is neutral for higher-order cognition, academic attainment, and executive function through middle childhood remains an open empirical question, with the HYBRiD school-age outcomes study (reported as Demauro et al., 2025) providing the most informative evidence currently available, showing no HC-related functional impairment difference at ~5.5 years [14].

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## DISCUSSION

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### Overview of Principal Findings

This systematic review synthesizes evidence from 80 studies examining associations between postnatal systemic corticosteroids and long-term neurodevelopmental outcomes in preterm infants. The principal findings are: (1) early dexamethasone (<7-8 days) consistently increases cerebral palsy risk by approximately 50-80% (Doyle et al., 2021; Uberos et al., 2025; AlsuhaymiZuhairHamdan et al., 2017); (2) late dexamethasone ( $\geq 7$  days) does not significantly increase cerebral palsy or major neurosensory disability (Doyle et al., 2021a; Doyle et al., 2017); (3) early hydrocortisone does not significantly increase cerebral palsy and may improve survival without moderate-severe neurodevelopmental impairment in some populations (Morris et al., 2019; Baud et al., 2017); (4) late hydrocortisone shows neutral neurodevelopmental effects in large RCTs at 2 years and school age (Watterberg et al., 2022; Demauro et al., 2025; de Baat et al., 2025); (5) dose-response relationships exist for both agents, with higher cumulative doses associated with worse outcomes (Onland et al., 2017; Kim et al., 2025; Patra et al., 2014); and (6) gestational age and baseline BPD risk substantially modify treatment effects (Baud et al., 2018; Halbmeijer et al., 2023; Doyle et al., 2014).

### Reconciliation of Apparent Contradictions

The literature contains what appear to be irreconcilable findings. Multiple large Cochrane meta-analyses conclude that early dexamethasone increases cerebral palsy risk (Doyle et al., 2021;

Doyle et al., 2014a), while other analyses find no significant cerebral palsy increase with dexamethasone overall (Raghuveer et al., 2024; Buchiboyina et al., 2020). These contradictions are substantially reconciled by considering four key dimensions.

**Timing of initiation as the primary driver of dexamethasone risk.** The most reproducible predictor of neurodevelopmental harm from dexamethasone is initiation within the first week of life (Uberos et al., 2025; Quan, 2013). The mechanistic rationale is that the neonatal brain in the first postnatal days is at a particularly vulnerable stage of rapid proliferation and myelination (Jenkinson et al., 2023; Keunen et al., 2012). Studies finding no cerebral palsy increase with dexamethasone predominantly involve late initiation (>7 days) (Doyle et al., 2021a; Doyle et al., 2010) or mixed/late-predominant cohorts (Raghuveer et al., 2024; Buchiboyina et al., 2020). The Uberos et al. (2025) synthesis explicitly maps this: early dexamethasone RR ~1.81 for CP versus late non-significant RR 1.12.

**Historical dose regimens versus current practice.** The adverse neurodevelopmental findings that most strongly drove the decline in postnatal dexamethasone use derived primarily from RCTs and cohort studies employing high-dose tapered regimens of the late 1980s and early 1990s, e.g., 0.5 mg/kg/day over 21 days (Wolbeek et al., 2013). These regimens are substantially higher than current low-dose DART-protocol courses (cumulative ~0.5-1 mg/kg). Network meta-analyses consistently place high-dose, long-term dexamethasone at the bottom of safety rankings for cerebral palsy (Zeng et al., 2018; Hay et al., 2020), while analyses including contemporary lower-dose regimens find no significant CP increase overall (Raghuveer et al., 2024; Buchiboyina et al., 2020). The Marr et al. (2019) finding of better outcomes with a 42-day course versus repeated 9-day courses is paradoxical only if unrecognized as comparing a carefully controlled prolonged taper against an approach with unpredictable repeated exposures in a particularly high-risk group (Marr et al., 2020).

**Risk of BPD as an effect modifier.** The Doyle et al. (2014) metaregression demonstrated that at higher background rates of BPD, postnatal corticosteroids were associated with net survival benefit free of cerebral palsy, because BPD itself increases CP risk. Studies enrolling populations with relatively low BPD risk show net harm (excess CP without equivalent BPD benefit), while

those enrolling highest-risk populations show net benefit or neutrality. This explains why the same drug at the same dose can appear harmful in one trial and beneficial in another.

**Competing risk of mortality.** Infants who die before neurodevelopmental assessment cannot be classified as having CP, creating systematic survivor bias (Doyle et al., 2017; Doyle et al., 2021). Analyses using composites of death or NDI or survival without NDI provide more clinically meaningful estimates than CP rates alone. Early hydrocortisone reduces mortality (RR 0.80, 95% CI 0.65-0.99) without increasing CP, resulting in favorable composite outcomes (Doyle et al., 2021; Morris et al., 2019).

### **Dexamethasone: Early Versus Late Initiation**

**Early dexamethasone (<7-8 days).** The evidence for harm from early dexamethasone is robust and consistent across multiple meta-analyses. Doyle et al. (2021), synthesizing 32 RCTs (4395 infants), reported a risk ratio for cerebral palsy of 1.77 (95% CI 1.21-2.58) and for mortality or cerebral palsy of 1.18 (95% CI 1.01-1.37). Uberos et al. (2025) reported a summary RR for cerebral palsy in survivors of 1.81 (95% CI 1.33-2.47). AlsuhaymiZuhairHamdan et al. (2017) reported developmental delay RR 1.72 (95% CI 1.40-2.05) and cerebral palsy RR 1.56 (95% CI 1.03-2.10). Hay et al. (2020) network meta-analysis found early low-dose dexamethasone increased CP risk (RR 1.92, 95% CI 1.12-3.28, moderate-certainty). Harrold et al. (2013) reported CP RR of 1.45 (95% CI 1.06-1.98). The consistency across these independent analyses, despite different inclusion criteria and statistical methods, provides high-certainty evidence that early dexamethasone causes neurodevelopmental harm.

Beyond cerebral palsy, early dexamethasone is associated with lower IQ scores. Jenkinson et al. (2023) found dexamethasone-exposed children had mean IQ 78.2 versus 84.4 in preterm controls ( $p=0.008$ ). Wolbeek et al. (2013) found DEX-treated adolescents scored significantly lower on gross motor tasks, alertness, visuomotor coordination, and emotion recognition compared to untreated peers. Crotty et al. (2012) found deficits in visual memory, visual-motor integration, mathematics, and motor dexterity at early school age.

**Late dexamethasone ( $\geq 7$  days).** The neurodevelopmental profile of late dexamethasone is substantially more favorable. Doyle et al. (2021a), updating the Cochrane review (23 RCTs, 1817

infants), reported cerebral palsy RR 1.17 (95% CI 0.84-1.61) and death or cerebral palsy RR 0.90 (95% CI 0.76-1.06), neither significant. Doyle et al. (2010) similarly concluded that late dexamethasone reduced neonatal mortality but produced only a non-significant trend toward increased CP. Quan (2013) confirmed that late dexamethasone did not increase CP risk, unlike early administration. Uberos et al. (2025) reported non-significant RR of 1.12 (95% CI 0.79-1.60) for late dexamethasone.

However, the late dexamethasone evidence must be interpreted cautiously. Most late dexamethasone trials allowed open-label rescue steroids in placebo arms, which biases toward the null (Onland et al., 2010). When open-label glucocorticoid use in placebo arms was below 30%, moderately early dexamethasone (7-14 days) significantly reduced mortality and BPD without increasing adverse neurodevelopmental outcomes (Onland et al., 2010). This suggests the true effect of late dexamethasone may be modestly beneficial rather than neutral.

### **Hydrocortisone: Early Versus Late Initiation**

**Early hydrocortisone (<24 hours to 7 days).** The early hydrocortisone literature tells a substantially different story from early dexamethasone. The PREMILOC trial (Baud et al., 2017), a multicenter French RCT (523 randomized, 379 evaluated), found no significant difference in neurodevelopmental impairment at 22 months: mean global developmental quotient 91.7 vs 91.4 (difference 0.3, 95% CI -2.7 to 3.4,  $p=0.83$ ). Ofman et al. (2018) confirmed no significant difference in any aspect of neurodevelopmental assessment.

However, a gestational age subgroup analysis from PREMILOC (Baud et al., 2018) found a significant interaction: among 24-25 week infants, early hydrocortisone was associated with substantially lower risk of moderate-to-severe NDI (2% vs 18%; risk difference -16%, 95% CI -28% to -5%,  $p=0.02$ ), while no significant difference was found in 26-27 week infants. This suggests gestational age-dependent benefit specifically at the extreme margins of viability.

Morris et al. (2019), a meta-analysis of 14 hydrocortisone trials (1633 infants), found that early systemic hydrocortisone was associated with modest but significant improvement in survival without moderate-to-severe NDI: RR 1.13 (95% CI 1.02-1.26), NNT=14. Cerebral palsy was not significantly altered (RR 1.06, 95% CI 0.67-1.67). Shaffer et al. (2019), using individual patient

data meta-analysis across 4 RCTs (n=982), confirmed that early low-dose hydrocortisone significantly increased survival without BPD (OR 1.45, 95% CI 1.11-1.90, p=0.007) with no adverse 2-year neurodevelopmental effects.

Hay et al. (2020) found that early low-dose dexamethasone—but not hydrocortisone—increased cerebral palsy risk (RR 1.92, 95% CI 1.12-3.28), and hydrocortisone may decrease major neurosensory disability versus low-dose dexamethasone (RR 0.65, 95% CI 0.41-1.01). Van de Loo et al. (2024) concluded that early hydrocortisone has a beneficial effect on death or BPD at 36 weeks PMA (RR 0.90, 95% CI 0.82-0.99) with no harmful neurodevelopmental effects highlighted.

**Potential adverse signals from early hydrocortisone at preschool age.** Despite reassurance from 2-year outcomes, longer-term follow-up raises concerns. Peltoniemi et al. (2016), examining 5-7-year-old children from an early hydrocortisone RCT, found potential adverse effects on neurodevelopment. The Chinese-language abstract of the same data (Xu Wei, 2016) reported that 61% of the hydrocortisone group had neurological impairment versus 39% in placebo (p=0.182), with significantly lower executive IQ (88.3 vs 99.1, p=0.034) and significantly higher need for physical therapy (22% vs 0%, p=0.034). These findings, while from a small sample (n=51) and not all reaching statistical significance, are clinically concerning and warrant further investigation in larger cohorts.

**Late hydrocortisone (initiated day 7-28).** The evidence for late hydrocortisone is anchored by two large RCTs: the NICHD NRN trial and the SToP-BPD trial.

The NICHD NRN trial (Watterberg et al., 2022; 800 infants <30 weeks, mean GA 24.9 weeks) found no significant difference in survival without moderate or severe NDI at 22-26 months CA between hydrocortisone (36.9%) and placebo (37.3%; adjusted RR 0.98, 95% CI 0.81-1.18). All secondary neurodevelopmental outcomes were similarly unaffected. The long-term school-age follow-up (Demauro et al., 2025; 545 children at 5-8 years CA) confirmed no impact on functional impairment (71.3% vs 73.3%; adjusted RR 0.99, 95% CI 0.89-1.10). Gentle et al. (2023) established that baseline BPD/death risk did not modify hydrocortisone's effect on BPD, death, or NDI.

The SToP-BPD trial (Halbmeijer et al., 2021; 371 infants) found no significant overall effect on death or NDI at 2 years (adjusted OR 0.79, 95% CI 0.51-1.22), but identified a gestational age

interaction: infants <27 weeks showed significant reduction in death or NDI (54.6% vs 66.2%; risk difference -11.6%, 95% CI -22.4% to -0.5%;  $p=0.02$  for interaction), primarily driven by reduced mortality (Halbmeijer et al., 2023a). The 5.5-year follow-up (de Baat et al., 2025; 213 children) found no significant difference in death or moderate-severe NDI (OR 0.75, 95% CI 0.49-1.14,  $p=0.18$ ) and no differences on any individual developmental measure including cognitive IQ, motor function, neurology, vision, hearing, or behavior.

### **Dose-Response Relationships**

**Dexamethasone dose-response.** Onland et al. (2017) found a paradoxical result: moderate cumulative dosage versus high-dosage was associated with increased risk of abnormal neurodevelopmental outcome (RR 8.33, 95% CI 1.63-42.48), suggesting higher doses may be more protective, though based on only two small studies (74 infants). Onland et al. (2023) confirmed increased risk of cerebral palsy (RR 6.85, 95% CI 1.29-36.36) and death or cerebral palsy (RR 3.20, 95% CI 1.35-7.58) when comparing moderate to high dosage. Uberos et al. (2025) noted a dose-dependent relationship: exceeding the median cumulative dexamethasone dose increased cerebral palsy likelihood. Rocha et al. (2024) found that two or more DART-protocol courses (cumulative 1.70 mg/kg) versus one course (0.82 mg/kg) were associated with higher CP functional motor class 2 (OR 6.837, 95% CI 1.054-44.337). Zeng et al. (2018) network meta-analysis found high-dose and long-term dexamethasone regimens ranked lowest for CP safety.

In contrast, Buchiboyina et al. (2020) found no difference between lower (<2 mg/kg) and higher ( $\geq 2$  mg/kg) cumulative dexamethasone groups for long-term disability, though the higher-dose group had reduced weight, height, and head circumference z-scores at 2 years, suggesting somatic and possibly brain-growth effects.

**Hydrocortisone dose-response.** Patra et al. (2014) found that each additional day of hydrocortisone exposure increased odds of subnormal receptive language by 4% and expressive language by 2% in the first year, and increased odds of subnormal motor function by 2% in the second year. Hydrocortisone exposure >7 days was associated with worse fine motor scores at 8 months ( $p=0.005$ ).

Kim et al. (2025), in a retrospective cohort of 146 VLBW infants excluding dexamethasone-exposed cases, found that cumulative hydrocortisone  $>90$  mg/kg (vs  $\leq 90$  mg/kg) was associated with markedly higher rates of CP (35.9% vs 9.1%; aOR 5.44, 95% CI 1.45-23.96,  $p=0.016$ ) and NDI composite (54.0% vs 23.6%, aOR 2.58, 95% CI 0.94-7.42,  $p=0.071$ ). MRI at term-equivalent age showed significantly reduced intracranial, cerebrum, cerebellum, and brainstem volumes in the high-dose group. The ROC-derived threshold for predicting CP was  $>90$  mg/kg (AUC 0.70), though substantial confounding by indication is present.

Kovacs et al. (2025), in term infants with neonatal encephalopathy (a different population), found cumulative hydrocortisone dose independently associated with adverse cognitive outcome: OR 1.16 per 1 mg/kg (95% CI 1.01-1.37,  $p=0.04$ ), with ROC threshold approximately 5.6 mg/kg. This may reflect synergistic toxicity between encephalopathy and steroid exposure.

### **Comparative Findings: Dexamethasone Versus Hydrocortisone**

Direct comparisons within the same study populations are limited but informative. David et al. (2025), in 221 EPT infants, found DEX  $\pm$  HC exposure associated with 10-point reductions in cognitive ( $p<0.01$ ), language ( $p<0.05$ ), and motor ( $p<0.01$ ) Bayley-3 indices compared to both no-steroid and HC-only groups; the HC-only group did not differ significantly from no-steroid group. Wolbeek et al. (2013) similarly found adverse effects in DEX-treated but not HC-treated adolescents on gross motor tasks, school level, alertness, visuomotor coordination, and emotion recognition, though using historical high doses for both agents.

Raghuveer et al. (2024) meta-analysis (44 RCTs, 6377 infants) found neither dexamethasone (RR 1.09, 95% CI 0.55-2.17) nor hydrocortisone (RR 1.18, 95% CI 0.75-1.87) significantly increased CP risk. However, this analysis presumably captured later-initiated or lower-dose dexamethasone cohorts alongside earlier trials, diluting the early dexamethasone signal.

The totality of evidence supports that hydrocortisone has a more favorable neurodevelopmental profile than dexamethasone, particularly when administered early. This may relate to differential glucocorticoid receptor affinity, mineralocorticoid receptor activity, or differences in blood-brain barrier penetration and central nervous system distribution (Szabó et al., 2021; Drozdowicz & Bostwick, 2014).

## Effects on Brain Structure

Postnatal corticosteroids have demonstrable effects on brain structure that likely mediate neurodevelopmental outcomes. Keunen et al. (2012) systematic review found that postnatal dexamethasone exposure was associated with reduced cortical gray matter, cerebellar, subcortical gray matter, and hippocampal volumes at term-equivalent age. Hydrocortisone findings were inconsistent across cohorts.

Matthews et al. (2018), in 224 VPT infants, found postnatal corticosteroid exposure (9% of infants) associated with smaller cerebellar volume at term-equivalent age by  $-3.22$  cc (95% CI  $-4.73$  to  $-1.72$ ,  $p < 0.001$ ; FDR-corrected  $p = 0.09$ ), though this effect did not persist at 7 years, and no significant association was found between steroid exposure and 7-year neurodevelopmental outcomes. Kersbergen (2015) similarly found that hydrocortisone for developing chronic lung disease did not influence overall brain size or cerebellar volumes.

Kim et al. (2025) provided the most detailed volumetric-outcome linkage: high cumulative hydrocortisone associated with reduced MRI volumes of all major brain regions at TEA, and these volume reductions co-occurred with increased rates of CP and NDI at follow-up. This suggests a causal pathway from high-dose steroid exposure  $\rightarrow$  reduced brain growth  $\rightarrow$  neurodevelopmental impairment.

## Behavioral and Neuropsychological Outcomes

Beyond traditional neurodevelopmental composites, several studies assessed behavioral domains. Purdy et al. (2013), in 45 mother-child dyads at mean age 8 years, found significant relationships between CBCL Total Problems scores and perinatal steroid exposure, with higher PNS exposure groups exhibiting more behavioral problems—particularly withdrawn, attention, conduct, social, and rule-breaking behaviors. Meijer et al. (2026), in 204 very preterm children with longitudinal CBCL assessments, found that an adverse early life events variable (including postnatal corticosteroids, brain injury, surgeries, prolonged ventilation) was significantly associated with attention problems and withdrawn behaviors over time.

Cassiano et al. (2016), reviewing 27 studies, found that prematurity combined with corticosteroid treatment increased the risk of behavioral and emotional problems. Drozdowicz &

Bostwick (2014) noted a mixed picture: some reports found neuropsychiatric deficits, others found no effect.

The Halbmeijer et al. (2023) CBCL follow-up of SToP-BPD (n=183; 2 years CA) found high rates of overall behavioral problems in the preterm cohort (22.9% with critically elevated T-scores) but no significant association with hydrocortisone versus placebo, except lower anxiety problem scores in the hydrocortisone group. This suggests that behavioral problems are largely attributable to prematurity itself rather than hydrocortisone exposure.

### **Autism Spectrum Disorder**

Liu et al. (2026), in a systematic review and meta-analysis of 45 studies on ASD risk factors in preterm infants, identified postnatal steroid administration as one of 22 significant prenatal and postnatal risk factors for ASD, though overall certainty of evidence was rated low or very low. This association merits further investigation given the rising prevalence of ASD in preterm populations.

### **Gestational Age as an Effect Modifier**

The most consistent patient characteristic modifying the steroid-neurodevelopment relationship is gestational age at birth. The PREMILOC subgroup analysis (Baud et al., 2018) showed significant neurodevelopmental benefit from early hydrocortisone at 24-25 weeks but not 26-27 weeks. The SToP-BPD effect modifier analysis (Halbmeijer et al., 2023a) confirmed that late hydrocortisone significantly reduced death or NDI in infants <27 weeks but showed numerically worse outcomes in the  $\geq 27$  week subgroup (OR 2.43, non-significant due to small numbers). These findings suggest the benefit-risk balance is most favorable for the most extreme preterm infants, in whom BPD and its consequences are most severe, and least favorable—or possibly harmful—for less preterm, less vulnerable infants.

This gestational age-dependent effect likely relates to baseline risk: extremely preterm infants have higher BPD risk, higher mortality, and greater potential for steroid benefit, while also having more vulnerable developing brains that might be more susceptible to steroid harm. The net balance favors steroids only when BPD risk is sufficiently high (Doyle et al., 2014).

### **Assessment Age and Incomplete Follow-Up**

Most available evidence assesses neurodevelopmental outcomes at 18-24 months corrected age, which is standard but insufficient to detect higher-order neurological deficits including executive function, academic performance, behavior, and mental health that only become apparent at school age or later.

The school-age follow-ups available provide important but incomplete data. Wolbeek et al. (2013) at 14-17 years found persistent deficits with dexamethasone but not hydrocortisone. Marr et al. (2019) at 7 years found superior intact survival with prolonged dexamethasone taper in a high-risk cohort. Crotty et al. (2012) at early school age found persistent deficits. Jenkinson et al. (2023) reviewed outcomes up to 19 years, finding lower IQ persisting. Aho et al. (2025) at 6.5 years found no significant cognitive differences in a small pilot study. De Baat et al. (2025) at 5.5 years found no hydrocortisone effect. Demauro et al. (2025) at 5-8 years found no hydrocortisone effect on functional impairment.

The reassurance from large RCTs at 2 years must therefore be understood as confined to early functional impairment. Whether hydrocortisone is neutral for higher-order cognition, academic attainment, and executive function through middle childhood remains partially open, though the HYBRiD school-age outcomes study (Demauro et al., 2025) provides the most informative evidence currently available, showing no HC-related functional impairment difference at ~5.5 years.

### **Confounding by Indication and Competing Risks**

A persistent challenge is that steroid-treated infants are systematically sicker than controls in observational studies. Patra et al. (2014) noted hydrocortisone-exposed infants had substantially lower GA, lower BW, and higher rates of every major morbidity. Kim et al. (2025) found similar systematic differences. Multiple regression adjustment partially addresses this but cannot eliminate confounding by unmeasured illness severity.

In RCTs, confounding by indication is minimized, but contamination from open-label rescue steroids is a recognized threat. In the SToP-BPD placebo arm, 54% received open-label hydrocortisone (de Baat et al., 2025). In the NICHD NRN trial, approximately 40% of both arms received open-label dexamethasone (Watterberg et al., 2022). This contamination biases toward the

null in both trials, meaning the true neurodevelopmental effect may be marginally more favorable than observed.

Competing risk of mortality is especially relevant for CP: infants who die cannot be classified as having CP, creating systematic survivor bias. Doyle et al. (2017) explicitly noted that a trend toward increased CP with late dexamethasone was offset by reduced early mortality. Doyle et al. (2021) found the combined outcome of mortality or CP with early hydrocortisone was not significantly increased (RR 0.86, 95% CI 0.71-1.05), and early hydrocortisone reduced mortality (RR 0.80, 95% CI 0.65-0.99). Analyses using composites of death or NDI or survival without NDI therefore provide more clinically meaningful estimates.

### Clinical Implications

Given the totality of evidence, several clinical recommendations emerge. First, **early dexamethasone (<7 days) should be avoided** except perhaps in the most extreme circumstances where mortality risk is near-certain without intervention, given the high-certainty evidence of CP harm and lack of evidence for net benefit (Doyle et al., 2021; Uberos et al., 2025). Second, **early hydrocortisone appears to have a favorable benefit-risk profile** for extremely preterm infants (24-27 weeks) at high BPD risk, improving survival without NDI with no significant CP increase (Morris et al., 2019; Baud et al., 2017; Baud et al., 2018). Third, **late dexamethasone (≥7 days) may be considered** when BPD risk is high and hydrocortisone is not available or has failed, with careful attention to cumulative dose (Doyle et al., 2021a; Onland et al., 2010). Fourth, **late hydrocortisone (day 7-28) has a neutral neurodevelopmental profile** and may be considered for BPD prevention/treatment, though it does not improve survival without NDI in unselected populations; benefit may be confined to infants <27 weeks (Halbmeijer et al., 2021; Halbmeijer et al., 2023a; Watterberg et al., 2022; Demauro et al., 2025). Fifth, **cumulative doses should be minimized** for both agents, as dose-response relationships suggest higher doses increase neurodevelopmental risk (Patra et al., 2014; Kim et al., 2025; Onland et al., 2023). Sixth, **patient selection matters**: the benefit-risk balance is most favorable for the most extremely preterm infants at highest BPD risk (Doyle et al., 2014; Baud et al., 2018; Halbmeijer et al., 2023a).

### Research Implications and Future Directions

Several research priorities emerge. First, **direct comparative RCTs of dexamethasone versus hydrocortisone** using contemporary low-dose protocols are needed, with long-term neurodevelopmental follow-up. Second, **dose-finding studies** to establish the minimum effective dose for respiratory benefit without neurodevelopmental harm, particularly for hydrocortisone, are essential. Third, **school-age and adolescent follow-up** of existing RCT cohorts (PREMILOC, NICHD NRN, SToP-BPD) should continue, with comprehensive assessment of executive function, academic achievement, behavior, and quality of life. Fourth, **neuroimaging studies** linking steroid exposure to specific brain structure abnormalities and functional outcomes should be expanded, particularly using advanced MRI techniques. Fifth, **effect modifier research** should identify which patient subgroups derive net benefit versus harm, enabling personalized treatment decisions. Sixth, **biomarker studies** to identify infants at highest risk of steroid-induced neurotoxicity (e.g., genetic polymorphisms in glucocorticoid receptor or drug transporters) could enable precision medicine approaches.

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## CONCLUSION AND RECOMMENDATIONS

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### Summary of Key Findings

This systematic review of 80 studies examining associations between postnatal systemic corticosteroids and long-term neurodevelopmental outcomes in preterm infants yields several definitive conclusions. First, **early dexamethasone (<7-8 days) consistently increases cerebral palsy risk by approximately 50-80%** and is associated with lower IQ and specific neuropsychological deficits, providing high-certainty evidence of harm (Doyle et al., 2021; Uberos et al., 2025; Jenkinson et al., 2023). Second, **late dexamethasone ( $\geq 7$  days) does not significantly increase cerebral palsy or major neurosensory disability**, though evidence is less certain due to open-label steroid contamination (Doyle et al., 2021a; Onland et al., 2010). Third, **early hydrocortisone does not increase cerebral palsy and may improve survival without moderate-severe neurodevelopmental impairment**, particularly in extremely preterm infants at highest BPD risk (Morris et al., 2019; Baud et al., 2017; Baud et al., 2018). Fourth, **late hydrocortisone shows neutral neurodevelopmental effects** in large RCTs at 2 years and school age, with no evidence of

harm (Watterberg et al., 2022; Demauro et al., 2025; de Baat et al., 2025). Fifth, **dose-response relationships exist for both agents**: higher cumulative doses and longer durations are associated with worse neurodevelopmental outcomes (Patra et al., 2014; Kim et al., 2025; Onland et al., 2023). Sixth, **gestational age and baseline BPD risk substantially modify treatment effects**, with the most favorable benefit-risk balance in the most extremely preterm infants (Baud et al., 2018; Halbmeijer et al., 2023a; Doyle et al., 2014).

### **Recommendations for Clinical Practice**

Based on the evidence synthesized in this review, we recommend: (1) **avoid early dexamethasone** (<7 days) for routine BPD prevention or treatment; (2) **consider early hydrocortisone** for extremely preterm infants (24-27 weeks) at high BPD risk, after informed parental discussion of potential benefits (improved survival without NDI) and risks (gastrointestinal perforation, uncertain school-age effects); (3) **consider late dexamethasone or late hydrocortisone** for infants with established BPD and ongoing ventilator dependence when other measures have failed, using the lowest effective cumulative dose and shortest duration; (4) **minimize cumulative steroid exposure** for both agents, as dose-response data indicate increased risk with higher doses; (5) **individualize treatment decisions** based on gestational age, BPD risk, illness severity, and family values; and (6) **ensure long-term follow-up** of steroid-exposed infants through school age to detect and intervene for emerging cognitive, academic, or behavioral difficulties.

### **Recommendations for Future Research**

We recommend: (1) **direct comparative RCTs** of low-dose dexamethasone versus low-dose hydrocortisone with school-age outcomes; (2) **dose-finding studies** to establish minimum effective doses; (3) **continued follow-up** of existing RCT cohorts to adolescence; (4) **advanced neuroimaging studies** to elucidate mechanisms; (5) **effect modifier research** to enable personalized treatment; (6) **biomarker discovery** to identify steroid-toxic infants; and (7) **development of standardized neurodevelopmental outcome measures** for systematic review synthesis.

### **Final Conclusion**

Postnatal corticosteroids remain valuable therapeutic agents for preventing and treating BPD in preterm infants, but their neurodevelopmental consequences vary substantially by steroid type, timing, dose, and patient characteristics. Early dexamethasone causes demonstrable neurodevelopmental harm and should be avoided. Hydrocortisone, particularly when initiated early in extremely preterm infants, has a more favorable neurodevelopmental profile and may improve survival without NDI. Late administration of either agent has a predominantly neutral neurodevelopmental profile. The benefit-risk balance is most favorable for the most extremely preterm infants at highest BPD risk. Clinical decisions should be individualized, informed by high-quality evidence, and accompanied by long-term neurodevelopmental follow-up

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