Intervenciones neonatales para mejorar outcomes neonatales.

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Contenidos

Users' Guides to the Medical Literature

How to Read a Systematic Review and Meta-analysis and Apply the Results to Patient Care
Users' Guides to the Medical Literature

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Clinical decisions should be based on the totality of the best evidence and not the results of individual studies. When clinicians apply the results of a systematic review or meta-analysis to patient care, they should start by evaluating the credibility of the methods of the systematic review, ie, the extent to which these methods have likely protected against misleading results. Credibility depends on whether the review addressed a sensible clinical question; included an exhaustive literature search; demonstrated reproducibility of the selection and assessment of studies; and presented results in a useful manner. For reviews that are sufficiently credible, clinicians must decide on the degree of confidence in the estimates that the evidence warrants (quality of evidence). Confidence depends on the risk of bias in the body of evidence; the precision and consistency of the results; whether the results directly apply to the patient of interest; and the likelihood of reporting bias. Shared decision making requires understanding of the estimates of magnitude of beneficial and harmful effects, and confidence in those estimates.

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Clinical Scenario

You are consulted regarding the perioperative management of a 66-year-old man undergoing hip replacement. He is a smoker and has a history of type 2 diabetes and hypertension. Because he has multiple cardiovascular risk factors, you consider using perioperative β-blockers to reduce the risk of postoperative cardiovascular complications. You identify a recently published systematic review and meta-analysis evaluating the effect of perioperative β-blockers on death, nonfatal myocardial infarction, and stroke.[1] How should you use this meta-analysis to help guide your clinical decision making?

Introduction and Definitions

Traditional, unstructured review articles are useful for obtaining a broad overview of a clinical condition but may not provide a reliable and unbiased answer to a focused clinical question. A systematic review is a research summary that addresses a focused clinical question in a structured, reproducible manner. It is often, but not always, accompanied by a meta-analysis, which is a statistical pooling or aggregation of results from different studies providing a single estimate of effect. **Box 1** summarizes the typical process of a systematic review and meta-analysis including the safeguards against misleading results.

In 1994, a Users' Guide on how to use an "overview article"[2] was published in *JAMA* and presented a framework for critical appraisal of systematic reviews. In retrospect, this framework did not distinguish between 2 very different issues: the rigor of the review methods and the confidence in estimates (quality of evidence) that the results warrant. The current Users' Guide reflects the evolution of thinking since that time and presents a contemporary conceptualization.

We refer to the first judgment as the credibility[3] of the review: the extent to which its design and conduct are likely to have protected against misleading results.[4] Credibility may be undermined by inappropriate eligibility criteria, inadequate literature search, or failure to optimally summarize results. A review with credible methods, however, may leave clinicians with low confidence in effect estimates. Therefore, the second judgment addresses the confidence in estimates.[5] Common reasons for lower confidence include high risk of bias of the individual studies; inconsistent results; and small sample size of the body of evidence, leading to imprecise estimates. This Users' Guide presents criteria for judging both credibility and confidence in the estimates (**Box 2**).

This guide focuses on a question of therapy and is intended for clinicians applying the results to patient care. It does not provide comprehensive advice to researchers on how to conduct[6] or report[7] reviews. We also provide a rationale for seeking systematic reviews and meta-analyses and explaining the summary estimate of a meta-analysis.

Box 1. The Process of Conducting a Systematic Review and Meta-analysis

1. Formulate the question
2. Define the eligibility criteria for studies to be included in terms of Patient, Intervention, Comparison, Outcome (PICO), and study design
3. Develop a priori hypotheses to explain heterogeneity
4. Conduct search
5. Screen titles and abstracts for inclusion
6. Review full text of possibly eligible studies
7. Assess the risk of bias
8. Abstract data
9. When meta-analysis is performed:
   - Generate summary estimates and confidence intervals
   - Look for explanations of heterogeneity
   - Rate confidence in estimates of effect

Box 2. Guide for Appraising and Applying the Results of a Systematic Review and Meta-analysis[a]

First Judgment: Evaluate the Credibility of the Methods of Systematic Review

Did the review explicitly address a sensible clinical question?

Was the search for relevant studies exhaustive?

Were selection and assessments of studies reproducible?

Did the review present results that are ready for clinical application?

Did the review address confidence in estimates of effect?

Second Judgment: Rate the Confidence in the Effect Estimates

How serious is the risk of bias in the body of evidence?

Are the results consistent across studies?

How precise are the results?

Do the results directly apply to my patient?

Is there concern about reporting bias?

Are there reasons to increase the confidence rating?

[a] Systematic reviews can address multiple questions. This guide is applied to aspects of the systematic review that answer the clinical question at hand—ideally the effect of the intervention vs the comparator of interest on all outcomes of importance to patients.

Why Seek Systematic Reviews and Meta-analysis?

When searching for evidence to answer a clinical question, it is preferable to seek a systematic review, especially one that includes a meta-analysis. Single studies are liable to be unrepresentative of the total evidence and be misleading.[8] Collecting and appraising multiple studies require time and expertise that practitioners may not have. Systematic reviews include a greater range of patients than any single study, potentially enhancing confidence in applying the results to the patient at hand.

Meta-analysis of a body of evidence includes a larger sample size and more events than any individual study, leading to greater precision of estimates, facilitating confident decision making. Meta-analysis also provides an opportunity to explore reasons for inconsistency among studies.

A key limitation of systematic reviews and meta-analyses is that they produce estimates that are as reliable as the studies summarized. A pooled estimate derived from meta-analysis of randomized trials at low risk of bias will always be more reliable than that derived from a meta-analysis of observational studies or of randomized trials with less protection against bias.

First Judgment: Was the Methodology of the Systematic Review Credible?

Did the Review Explicitly Address a Sensible Clinical Question?

Systematic reviews of therapeutic questions should have a clear focus and address questions defined by particular patients, interventions, comparisons, and outcomes (PICO). When a meta-analysis is conducted, the issue of how narrow or wide the scope of the question becomes particularly important. Consider 4 hypothetical examples of meta-analyses with varying scope: (1) the effect of all cancer treatments on mortality or disease progression; (2) the effect of chemotherapy on prostate cancer–specific mortality; (3) the effect of docetaxel in castration-resistant prostate cancer on cancer-specific mortality; (4) the effect of docetaxel in metastatic castration-resistant prostate cancer on cancer-specific mortality

These 4 questions represent a gradually narrowing focus in terms of patients, interventions, and outcomes. Clinicians will be uncomfortable with a meta-analysis of the first question and likely of the second. Combining the results of these studies would yield an estimate of effect that would make little sense or be misleading. Comfort level in combining studies increases in the third and fourth questions, although clinicians may even express concerns about the fourth question because it combines symptomatic and asymptomatic populations.

What makes a meta-analysis too broad or too narrow? Clinicians need to decide whether, across the range of patients, interventions or exposures, and outcomes, it is plausible that the intervention will have a similar effect. This decision will reflect an understanding of the underlying biology and may differ between individuals; it will only be possible, however, when systematic reviewers explicitly present their eligibility criteria.

Was the Search for Relevant Studies Exhaustive?

Systematic reviews are at risk of presenting misleading results if they fail to secure a complete or representative sample of the available eligible studies. For most clinical questions, searching a single database is insufficient. Searching MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials may be a minimal requirement for most clinical questions[6] but for many questions will not uncover all eligible articles. For instance, one study demonstrated that searching MEDLINE and EMBASE separately retrieved, respectively, only 55% and 49% of the eligible trials.[9] Another study found that 42% of published meta-analyses included at least 1 trial not indexed in MEDLINE.[10] Multiple synonyms and search terms to describe each concept are needed.

Additional references are identified through searching trial registries, bibliography of included studies, abstract presentations, contacting experts in the field, or searching databases of pharmaceutical companies and agencies such as the US Food and Drug Administration.

Were Selection and Assessments of Studies Reproducible?

Systematic reviewers must decide which studies to include, the extent of risk of bias, and what data to abstract. Although they

follow an established protocol, some of their decisions will be subjective and prone to error. Having 2 or more reviewers participate in each decision may reduce error and subjectivity. Systematic reviewers often report a measure of agreement on study selection and quality appraisal (eg, κ statistic). If there is good agreement between the reviewers, the clinician can have more confidence in the process.

Did the Review Present Results That Are Ready for Clinical Application?

Meta-analyses provide estimates of effect size (the magnitude of difference between groups).[11] The type of effect size depends on the nature of the outcome (relative risk, odds ratio, differences in risk, hazard ratios, weighted mean difference, and standardized mean difference). Standardized effect sizes are expressed in multiples of the standard deviation. This facilitates comparison of studies, irrespective of units of measure or the measurement scale.

Results of meta-analyses are usually depicted in a forest plot. The point estimate of each study is typically presented as a square with a size proportional to the weight of the study, and the confidence interval (CI) is presented as a horizontal line. The combined summary effect, or pooled estimate, is typically presented as a diamond, with its width representing the confidence or credible interval (the CI indicates the range in which the true effect is likely to lie). Forest plots for the perioperative β-blockers scenario are shown in the **Figure**.

Meta-analysis provides a weighted average of the results of the individual studies in which the weight of the study depends on its precision. Studies that are more precise (ie, have narrower CIs) will have greater weight and thus more influence on the combined estimate. For binary outcomes such as death, the precision depends on the number of events and sample size. In panel B of the Figure, the POISE trial[12] had the largest number of deaths (226) and the largest sample size (8351); therefore, it had the narrowest CI and the largest weight (the effect from the trial is very similar to the combined effect). Smaller trials with smaller numbers of events in that plot have a much wider CI, and their effect size is quite different from the combined effect (ie, had less weight in meta-analysis). The weighting of continuous outcomes is also based on the precision of the study, which in this case depends on the sample size and SD (variability) of each study.

In most meta-analyses such as the one in this clinical scenario, aggregate data from each study are combined (ie, study-level data). When data on every individual enrolled in each of the studies are available, individual-patient data meta-analysis is conducted. This approach facilitates more detailed analysis that can address issues such as true intention-to-treat and subgroup analyses.

Relative association measures and continuous outcomes pose challenges to risk communication and trading off benefits and harms. Patients at high baseline risk can expect more benefit than those at lower baseline risk from the same intervention (the same relative effect). Meta-analysis authors can facilitate decision making by providing absolute effects in populations with various risk levels.[13,14] For example, given 2 individuals, one with low Framingham risk of cardiovascular events (2%) and the other with a high risk (28%), we can multiply each of these baseline risks with the 25% relative risk reduction obtained from a meta-analysis of statin therapy trials.[15] The resulting absolute risk reduction (ie, risk difference) attributable to statin therapy would be 0.5% for the low-risk individual and 7% for the high-risk individual.

Continuous outcomes can also be presented in more useful ways. Improvement of a dyspnea score by 1.06 scale points can be better understood by informing readers that the minimal amount considered by patients to be important on that scale is 0.5 points.[16] A standardized effect size (eg, paroxetine reduced depression severity by 0.31 SD units) can be better understood if (1) referenced to cutoffs of 0.2, 0.5, and 0.8 that represent small, moderate, and large effect, respectively; (2) translated back to natural units with which clinicians have more familiarity (eg, converted to a change of 2.47 on the Hamilton Rating Scale for Depression); or (3) dichotomized (for every 100 patients treated with paroxetine, 11 will achieve important improvement).[17]

Did the Review Address Confidence in Estimates of Effect?

A well-conducted (ie, credible) systematic review should present readers with information needed to make their second judgement: the confidence in the effect estimates. For example, if systematic reviewers do not evaluate the risk of bias in the individual studies or attempt to explain heterogeneity, this second judgement will not be possible.

In **Box 3**, we return to the clinical scenario to determine credibility of the systematic review identified. Overall, you conclude that the credibility of the methods of this systematic review is high and move on to examine the estimates of effect and the associated confidence in these estimates.

Second Judgment: What Is the Confidence in the Estimates of Effect?

Several systems are used to evaluate the quality of evidence, of which 4 are most commonly used: the Grading of Recommendations Assessment, Development and Evaluation (GRADE) and the systems from the American Heart Association, the US Preventive Services Task Force, and the Oxford Centre for Evidence-Based Medicine.[5,18-20] These systems share the similar features of being used by multiple organizations and providing a confidence rating in the estimates that gives randomized trials a higher rating than nonrandomized studies. The 4 systems are described in eTable 1 in the Supplement.

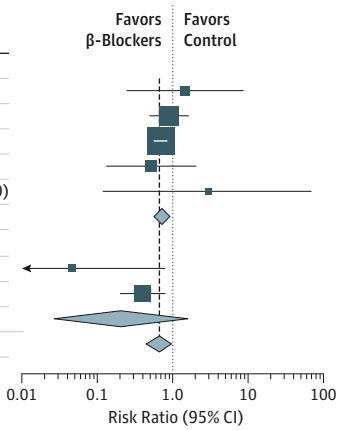
The general framework used in this Users' Guide follows the GRADE approach.[21] GRADE categorizes confidence in 4 categories: high, moderate, low, or very low. The lower the confidence, the more likely the underlying true effect is substantially different from the observed estimate of effect and, thus, the more likely that further research would demonstrate different estimates.[5]

Confidence ratings begin by considering study design. Randomized trials are initially assigned high confidence and observational studies are given low confidence, but a number of factors may modify these initial ratings. Confidence may decrease when there is high risk of bias, inconsistency, imprecision, indirectness, or concern about publication bias. An increase in confidence rating is uncommon and occurs primarily in observational studies when the effect size is large. Readers of a systematic review can consider these factors regardless of whether systematic review authors formally used this approach. Readers do, however, require the necessary information, and thus the need for a final credibility guide: Did the Review Address Confidence in Estimates of Effect?

Figure. Results of a Meta-analysis of the Outcomes of Nonfatal Infarction, Death, and Nonfatal Stroke in Patients Receiving Perioperative β-Blockers

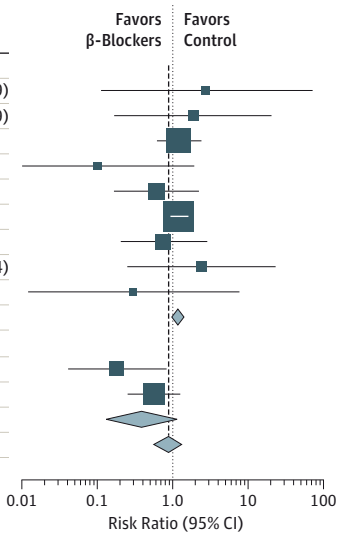
A Nonfatal myocardial infarction

Source	β-Blockers Events, No.	β-Blockers Total, No.	Control Events, No.	Control Total, No.	RR (95% CI)
Low risk of bias					
DIPOM	3	462	2	459	1.49 (0.25-8.88)
MaVS	19	246	21	250	0.92 (0.51-1.67)
POISE	152	4174	215	4177	0.71 (0.58-0.87)
POBBLE	3	55	5	48	0.52 (0.13-2.08)
BBSA	1	110	0	109	2.97 (0.12-72.19)
Subtotal (I^2 = 0%; P = .70)					0.73 (0.61-0.88)
High risk of bias					
Poldermans	0	59	9	53	0.05 (0.00-0.79)
Dunkelgrun	11	533	27	533	0.41 (0.20-0.81)
Subtotal (I^2 = 57%; P = .13)					0.21 (0.03-1.61)
Overall					0.67 (0.47-0.96)
I^2 = 29%; P = .21					
Interaction test between groups, P = .22					



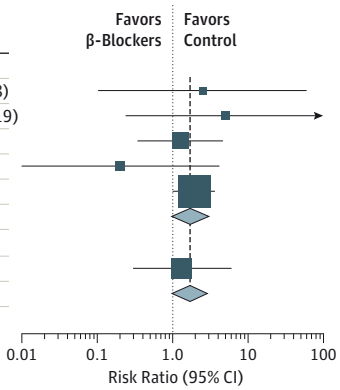
B Death

Source	β-Blockers Events, No.	β-Blockers Total, No.	Control Events, No.	Control Total, No.	RR (95% CI)
Low risk of bias					
BBSA	1	110	0	109	2.97 (0.12-72.19)
Bayliff	2	49	1	50	2.04 (0.19-21.79)
DIPOM	20	462	15	459	1.32 (0.69-2.55)
MaVS	0	246	4	250	0.11 (0.01-2.09)
Neary	3	18	5	20	0.67 (0.19-2.40)
POISE	129	4174	97	4177	1.33 (1.03-1.73)
Mangano	4	99	5	101	0.82 (0.23-2.95)
POBBLE	3	55	1	48	2.62 (0.28-24.34)
Yang	0	51	1	51	0.33 (0.01-8.00)
Subtotal (I^2 = 0%; P = .68)					1.27 (1.01-1.60)
High risk of bias					
Poldermans	2	59	9	53	0.20 (0.05-0.88)
Dunkelgrun	10	533	16	533	0.63 (0.29-1.36)
Subtotal (I^2 = 44%; P = .18)					0.42 (0.15-1.23)
Overall					0.94 (0.63-1.40)
I^2 = 30%; P = .16					
Interaction test between groups, P = .04					



C Nonfatal stroke

Source	β-Blockers Events, No.	β-Blockers Total, No.	Control Events, No.	Control Total, No.	RR (95% CI)
Low risk of bias					
POBBLE	1	53	0	44	2.50 (0.10-59.88)
DIPOM	2	462	0	459	4.97 (0.24-103.19)
MaVS	5	246	4	250	1.27 (0.35-4.67)
Yang	0	51	2	51	0.20 (0.01-4.07)
POISE	27	4174	14	4177	1.93 (1.01-3.68)
Subtotal (I^2 = 0%; P = .60)					1.73 (1.00-2.99)
High risk of bias					
Dunkelgrun	4	533	3	533	1.33 (0.30-5.93)
Overall					1.67 (1.00-2.80)
I^2 = 0%; P = .71					
Interaction test between groups, P = .75					



Abbreviations: BBSA, Beta Blocker in Spinal Anesthesia study; DIPOM, Diabetic Postoperative Mortality and Morbidity trial; MaVS, Metoprolol after Vascular Surgery study; POBBLE, Perioperative β-blockade trial; POISE, Perioperative Ischemic Evaluation trial. Dotted line indicates no effect. Dashed line is centered on meta-analysis pooled estimate.

How Serious Is the Risk of Bias in the Body of Evidence?

A well-conducted systematic review should always provide readers with insight about the risk of bias in each individual study and overall.[6,7] Differences in studies' risk of bias can explain important differences in results.[22] Less rigorous studies sometimes overestimate the effectiveness of therapeutic and preventive interventions.[23] The effects of antioxidants on the risk of prostate cancer[24] and on atherosclerotic plaque formation[25] are 2 of many

Box 3. Using the Guide: Judgment 1, Determining Credibility of the Methods of a Systematic Review (Perioperative β-Blockers in Noncardiac Surgery)[1]

Systematic review authors constructed a sensibly structured clinical question (in patients at higher-than-average cardiovascular risk undergoing noncardiac surgery, what is the effect of β-blockers vs no β-blockers on nonfatal myocardial infarction, death, and stroke)

They conducted a comprehensive search of numerous databases and registries

Two independent reviewers selected eligible trials, although the authors did not report extent of agreement

The authors ultimately presented results in a transparent and understandable way. Although they did not report an absolute effect—an important limitation—the raw data allow readers to easily calculate an absolute effect and a number needed to treat (Box 4 and Table).

The authors provided the information needed to address confidence in study results. They described the risk of bias for each trial, noted substantial heterogeneity in estimates of the effect of β-blockers on death, determined that risk of bias provided a likely explanation for the variability, and therefore focused on the results of the studies with low risk of bias.

examples of observational studies that showed misleading results subsequently contradicted by large randomized clinical trials.

Ideally, systematic reviewers will evaluate and report the risk of bias for each of the important outcomes measured in each individual study. There is no one correct way to assess the risk of bias.[26] Review authors can use detailed checklists or focus on a few key aspects of the study. Different study designs require the use of different instruments (eg, for randomized clinical trials, the Cochrane Risk of Bias Tool[27]). A judgment about the overall risk of bias for all of the included studies may then result in decreasing the confidence in estimates.[5]

Are the Results Consistent Across Studies?

Readers of a meta-analysis that combines results from multiple studies should judge the extent to which results differ from study to study (ie, variability or heterogeneity). They can start by visually inspecting a forest plot,[28] first noting differences in the point estimates and then the extent to which CIs overlap. Large differences in point estimates or CIs that do not overlap suggest that random error is an unlikely explanation of the different results and therefore decreases confidence in the combined estimate.

Authors of a meta-analysis can help readers by conducting statistical evaluation of heterogeneity (eTable 2 in the Supplement). The first test is called the Cochran Q test (a yes-or-no test), in which the null hypothesis is that the underlying effect is the same in each of the studies[29] (eg, the relative risk derived from study 1 is the same as that from studies 2, 3, and 4). A low *P* value of the test means that random error is an unlikely explanation for the differences in results from study to study, thus decreasing confidence in a single summary estimate.

The I^2 statistic focuses on the magnitude of variability rather than its statistical significance.[30] An I^2 of 0% suggests that chance explains variability in the point estimates, and clinicians can be comfortable with a single summary estimate. As the I^2 increases, we become progressively less comfortable with unexplained variability in results.

When substantial heterogeneity exists, clinicians should look for possible explanations. Authors of meta-analyses may conduct subgroup analyses to explain heterogeneity. Such analyses may not reflect true subgroup differences, and a Users' Guide is available to aid readers in evaluating the credibility of these analyses.[7] Authors of meta-analyses can address one important credibility criterion, whether chance can explain differences between subgroups, using what is called a test of interaction.[31] The lower the *P* value of the test of interaction, the less likely chance explains the difference between intervention effects in the subgroups examined, and therefore the greater likelihood that the subgroup effect is real.

Another approach to exploring causes of heterogeneity in meta-analysis is meta-regression. Investigators construct a regression model in which independent variables are individual study characteristics (eg, the population, how the intervention was administered) and the dependent variable is the estimate of effect in each study. Conclusions from meta-regression have the same limitations as those from subgroup analysis, and inferences about explanations of heterogeneity may not be accurate. For example, meta-regression[32] of trials evaluating statin therapy in patients undergoing percutaneous interventions for acute coronary syndrome showed that the earlier statins were given, the lower the risk of cardiac events. Although the trials were randomized (to statin vs no statin or a lower-dose statin), the conclusion about early administration was not based on randomization and should be evaluated using the Users' Guide on subgroup analysis.[7]

It is not uncommon that a large degree of between-study heterogeneity remains unexplained. Clinicians and patients still need, however, a best estimate of the treatment effect to inform their decisions. Pending further research that may explain the observed heterogeneity, the summary estimate remains the best estimate of the treatment effect. Clinicians and patients must use this best available evidence, although this inconsistency between studies appreciably reduces confidence in the summary estimate.[33]

In the β-blocker meta-analysis, the risk of bias explains variability in results in the outcome of death (Figure, panel B). Results are very different for the trials with high and low risk of bias, and the *P* value for the test of interaction (.04) tells us that chance is an unlikely explanation for the difference. Therefore, we use the results from the trials with low risk of bias as our best estimate of the treatment effect.

How Precise Are the Results?

There are 2 fundamental reasons that studies mislead: one is systematic error (otherwise known as bias), and the other is random error. Random error is large when sample sizes, and numbers of events, are small, and decreases as sample size and number of events increase. When sample size and number of events are small, we refer to results as "imprecise"; when they are large, we label results as "precise."

When results are imprecise, we lose confidence in estimates of effect. But how is the clinician to determine if results are sufficiently precise? Meta-analysis generates not only an estimate of the average effect across studies, but also a CI around that estimate. Examination of that CI—the range of values within which the true effect plausibly lies—allows a judgement of whether a meta-analysis yields results that are sufficiently precise.

Clinicians can judge precision by considering the upper and lower boundaries of the CI and then considering how they would advise

Box 4. Using the Guide: Judgment 2, Determining the Confidence in the Estimates (Perioperative β-Blockers in Noncardiac Surgery)[1]

See the Table for the raw data used in this discussion.

How to Calculate Risk Difference (Absolute Risk Reduction or Increase)?

In the Figure, the risk ratio (RR) for nonfatal myocardial infarction is 0.73. The baseline risk (risk without perioperative β-blockers) can be obtained from the trial that is the largest and likely enrolled most representative population[12] (215/4177, approximately 52 per 1000). The risk with intervention would be (52/1000 × 0.73, approximately 38 per 1000). The absolute risk difference would be (52/1000 − 38/1000 = −14, approximately 14 fewer myocardial infarctions per 1000). The same process can be used to calculate the confidence intervals around the risk difference, substituting the boundaries of the confidence interval (CI) of the RR for the point estimate.

The number needed to treat to prevent 1 nonfatal myocardial infarction can also be calculated as the inverse of the absolute risk difference (1/0.014 = 72 patients).

Risk of Bias

Of the 11 trials included in the analysis, 2 were considered to have high risk of bias.[35,36] Limitations included lack of blinding, stopping early because of large apparent benefit,[36] and concerns about the integrity of the data.[1] The remaining 9 trials had adequate bias protection measures and represented a body of evidence that was at low risk of bias.

Inconsistency

Visual inspection of forest plots (Figure) shows that the point estimates, for both nonfatal myocardial infarction and death, substantially differ across studies. For the outcome of stroke, results are extremely consistent. There is minimal overlap of CIs of point estimates for the analysis of death. Confidence intervals in the analysis of nonfatal myocardial infarction do overlap to a great extent and fully overlap in the outcome of stroke. Heterogeneity *P* values were .21 for nonfatal myocardial infarction, .16 for death, and .71 for stroke; I^2 values were 29%, 30%, and 0%, respectively. A test of interaction between the 2 groups of studies (high risk of bias vs low risk of bias) yields a nonsignificant *P* value of .22 for myocardial infarction (suggesting that the difference between these 2 subgroups of studies could be attributable to chance) and a significant *P* value of .04 for the outcome of death. Considering that the observed heterogeneity is at least partially explained by the risk of bias and that the trials with low risk of bias for all outcomes are consistent, you decide to obtain the estimates of effect from the trials with low risk of bias and do not lower the confidence rating because of inconsistency.

Imprecision

For the outcomes of death and nonfatal stroke, clinical decisions would differ if the upper vs the lower boundaries of the CI represented the truth; therefore, imprecision makes us lose confidence in both estimates. No need to lower the confidence rating for nonfatal myocardial infarction.

Indirectness

The age of the majority of patients enrolled across the trials ranged between 50 and 70, similar to the patient in the opening scenario, who is 66 years old. Most of the trials enrolled patients with risk factors for heart disease undergoing surgical procedures classified as intermediate surgical risk, similar to the risk factors and hip surgery of the patient. Although the drug used and the dose varied across trials, the consistent results suggest we can use a modest dose of the β-blocker with which we are most familiar. The outcomes of death, nonfatal stroke, and nonfatal infarction are the key outcomes of importance to patients. Overall, the available evidence presented in the systematic review is direct and applicable to the patient of interest and addresses the key outcomes.

Reporting Bias

The authors of the systematic review and meta-analysis constructed funnel plots that appear to be symmetrical and results of the statistical tests for the symmetry of the plot were nonsignificant, leaving no reason for lowering the confidence rating because of possible reporting or publication bias.

Confidence in the Estimates

Overall, evidence warranting high confidence suggests that individuals with risk factors for heart disease can expect a reduction in risk of a perioperative nonfatal infarction of 14 in 1000 (from approximately 20 per 1000 to 6 per 1000). Unfortunately, they can also expect an increase in their risk of dying or having a nonfatal stroke. Because most people are highly averse to stroke and death, it is likely that the majority of patients faced with this evidence would decline β-blockers as part of their perioperative regimen. Indeed, that is what this patient decides when informed about the evidence.

Table. Evidence Summary of the Perioperative β-Blockers Question

Outcome	No. of Participants (Trials)	Confidence	Relative Effect (95% CI)	Risk Difference per 1000 Patients[a]
Nonfatal myocardial infarction	10 189 (5)	High	0.73 (0.61-0.88)	14 fewer (6 fewer to 20 fewer)
Stroke	10 186 (5)	Moderate	1.73 (1.00- 2.99)	2 more (0 more to 6 more)
Death	10 529 (9)	Moderate	1.27 (1.01-1.60)	6 more (0 more to 13 more)

[a] See Box 4.

their patients were the upper boundary to represent the truth and how they would advise their patients were the lower boundary to represent the truth. If the advice would be the same in either case, then the evidence is sufficiently precise. If decisions would change across the range of the confidence interval, then confidence in the evidence will decrease.[34]

For instance, consider the results of nonfatal myocardial infarction in the β-blocker example (**Box 4** and **Table**). The CI around the absolute effect of β-blockers is a reduction of from 6 (the minimum) to 20 (the maximum) infarctions in 1000 patients given β-blockers. Considering this range of plausible effects, clinicians must ask themselves: Would my patients make different choices about

the use of β-blockers if their risk of infarction decreased by only 6 in 1000 or by as much as 20 in 1000?

One might readily point out that this judgment is subjective—it is a matter of values and preferences. Quite so, but that is the nature of clinical decision making: the trade-off between the desirable and undesirable consequences of the alternative courses of action is a matter of values and preferences and is therefore subjective. To the extent that clinicians are confident that patients would place similar weight on reductions of 6 and 20 in 1000 infarctions, concern about imprecision will be minimal. To the extent that clinicians are confident that patients will view 6 in 1000 as trivial and 20 in 1000 as important, concern about imprecision will be large. To the extent that clinicians are uncertain of their patients' values and preferences on the matter, judgments about imprecision will be similarly insecure.

The judgment regarding myocardial infarction may leave clinicians with doubt about imprecision—much less so for stroke and death (Box 4 and Table). With regard to both, if the boundary most favoring β-blockers (ie, no increase in death and stroke) represented the truth, patients would have no reluctance regarding use of β-blockers. On the other hand, if risk of death and stroke increased by, respectively, 13 and 6, reluctance regarding use of β-blockers would increase substantially. Given uncertainty about which extreme represents the truth, confidence in estimates decreases because of imprecision.

Do the Results Directly Apply to My Patient?

The optimal evidence for decision making comes from research that directly compared the interventions in which we are interested, evaluated in the populations in which we are interested, and measured outcomes important to patients. If populations, interventions, or outcomes in studies differ from those of interest, the evidence can be viewed as indirect.

A common example of indirectness of population is when we treat a very elderly patient using evidence derived from trials that excluded elderly persons. Indirectness of outcomes occurs when trials use surrogate end points (eg, hemoglobin A_{1c} level), whereas patients are most concerned about other outcomes (eg, macrovascular and microvascular disease).[37] Indirectness also occurs when clinicians must choose between interventions that have not been tested in head-to-head comparisons.[38] For instance, many trials have compared osteoporosis drugs with placebo, but very few have compared them directly against one another.[39] Making comparisons between treatments under these circumstances requires extrapolation from existing comparisons and multiple assumptions.[40]

Decisions regarding indirectness of patients and interventions depend on an understanding of whether biologic or social factors are sufficiently different that one might expect substantial differences in the magnitude of effect. Indirectness can lead to lowering confidence in the estimates.[38]

Is There Concern About Reporting Bias?

When researchers base their decision to publish certain material on the magnitude, direction, or statistical significance of the results, a systematic error called reporting bias occurs. This is the most difficult type of bias to address in systematic reviews. When an entire study remains unreported, the standard term is publication bias. It has been shown that the magnitude and direction of results may be more important determinants of publication than study design, relevance, or quality[41] and that positive studies may be as much as 3 times more likely to be published than negative studies.[42] When authors or study sponsors selectively report specific outcomes or analyses, the term selective outcome reporting bias is used.[43]

Empirical evidence suggests that half of the analysis plans of randomized trials are different in protocols than in published reports.[44] Reporting bias can create misleading estimates of effect. A study of the US Food and Drug Administration reports showed that they often included numerous unpublished studies and that the findings of these studies can alter the estimates of effect.[45] Data on 74% of patients enrolled in the trials evaluating the antidepressant reboxetine were unpublished. Published data overestimated the benefit of reboxetine vs placebo by 115% and vs other antidepressants by 23%, and also underestimated harm.[46]

Detecting publication bias in a systematic review is difficult. When it includes a meta-analysis, a common approach is to examine whether the results of small studies differ from those of larger ones. In a figure that relates the precision (as measured by sample size, SE, or variance) of studies included in a meta-analysis to the magnitude of treatment effect, the resulting display should resemble an inverted funnel (eFigure, panel A in the Supplement). Such funnel plots should be symmetric around the combined effect. A gap or empty area in the funnel suggests that studies may have been conducted and not published (eFigure, panel B in the Supplement). Other explanations for asymmetry are, however, possible. Small studies may have a higher risk of bias explaining their larger effects, may have enrolled a more responsive patient group, or may have administered the intervention more meticulously. Last, there is always the possibility of a chance finding.

Several empirical tests have been developed to detect publication bias. Unfortunately, all have serious limitations, require a large number of studies (ideally 30 or more),[47] and none has been validated against a criterion standard of real data in which we know whether bias existed.[47]

More compelling than any of these theoretical exercises is the success of systematic reviewers in obtaining the results of unpublished studies. Prospective study registration with accessible results may be a solution to reporting bias.[48,49] Until complete reporting becomes a reality,[50] clinicians using research reports to guide their practice must remain cognizant of the dangers of reporting biases and, when they suspect bias, should lower their confidence in the estimates.[51]

Are There Reasons to Increase the Confidence Rating?

Some uncommon situations warrant an increase in the confidence rating of effect estimates from observational studies. Consider our confidence in the effect of hip replacement on reducing pain and functional limitations in severe osteoarthritis, epinephrine to prevent mortality in anaphylaxis, insulin to prevent mortality in diabetic ketoacidosis, or dialysis to prolong life in patients with end-stage renal failure.[52] In each of these situations, we observe a large treatment effect achieved over a short period among patients with a condition that would have inevitably worsened in the absence of an intervention. This large effect can increase confidence in a true association.[52]

Box 4 and the Table summarize the effect of β-blockers in patients undergoing noncardiac surgery and addresses our confidence in the apparent effects of the intervention.

Conclusions

Clinical and policy decisions should be based on the totality of the best evidence and not the results of individual studies. Systematic summaries of the best available evidence are required for optimal clinical decision making. Applying the results of a systematic review and meta-analysis includes a first step in which we judge the credibility of the methods of the systematic review and a second step in which we decide how much confidence we have in the estimates of effect.

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Antenatal Corticosteroids
Who Should We Be Treating?

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KEYWORDS

• Antenatal corticosteroids • Prematurity • Preterm birth • Preterm labor
• Respiratory distress syndrome

KEY POINTS

- Antenatal corticosteroids are a crucial treatment in improving neonatal outcomes for those patients at risk for preterm birth.
- Reduction in neonatal morbidities include respiratory distress syndrome, intraventricular hemorrhage, and necrotizing enterocolitis.
- Therapeutic benefits have been demonstrated as early as 23 weeks' gestation, and recent data have supported neonatal benefit through the late preterm period.

INTRODUCTION

One of the most important antenatal therapies to improve outcomes for patients at risk for preterm birth is antenatal corticosteroids.[1,2] As early as 1969, Liggins[2] noted that lambs who received glucocorticoids and then delivered prematurely had lungs that remained partially expanded. This preliminary evidence led to a randomized, controlled trial of betamethasone therapy on 282 mothers who were at risk for preterm delivery, to assess the effect of steroids on neonatal morbidity and mortality. They found that in pregnancies at risk for premature delivery, when treated with corticosteroids, infants demonstrated a decreased risk of respiratory distress syndrome (RDS) compared with those not treated with steroids.[3] Additionally, they found that early neonatal mortality was 3.2% in the antenatal corticosteroid treated group and 15.0% in the controls ($P = .01$). From these early studies, Liggins[3] hypothesized that glucocorticoids caused premature liberation of surfactant into the alveoli, by induction of an enzyme related to the biosynthesis of surfactant.

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Mechanism of Action

Antenatal corticosteroids affect the fetal lungs through multiple processes (**Box 1**). They stimulate development of both type I and type II pneumocytes, which are surface epithelial cells of the lung alveoli. Type II pneumocytes contain phospholipid multilamellar bodies, the precursors to pulmonary surfactant.[4] The saccular stage of lung development begins at 24 to 28 weeks' gestation and is when type II pneumocytes first appear. It is at this phase that steroid administration has the clear capability to induce type II pneumocytes to increase surfactant production.[5] Additionally, glucocorticoids act to increase lung compliance and maximal lung volume, as well as to reduce protein extravasation from the pulmonary vasculature to the airspace, thereby helping to clear lung fluid before delivery. These biochemical and structural effects on the lung are the basis for improved clinical outcomes after glucocorticoid treatment.[4]

Clinical Efficacy

RDS is a syndrome most commonly diagnosed in premature neonates, clinically characterized by tachypnea, tachycardia, chest wall retractions, expiratory grunting, and nasal flaring. It likely occurs owing to insufficient production of pulmonary surfactant and structural immaturity of the lungs. The incidence of RDS increases with earlier gestational ages, and is highest in infants before 28 weeks' gestation.[6] Approximately 1% of newborn infants are affected by RDS and it is the leading cause of death in babies who are born prematurely.[6,7] The introduction of antenatal steroids for the acceleration of fetal lung maturity and the development of exogenous surfactant has demonstrated reduced rates of RDS in randomized trials worldwide.[8] A recent 2017 Cochrane review of all randomized trials comparing treatment with antenatal corticosteroids versus placebo in patients at risk for preterm birth demonstrated a significant

Box 1
Effects of antenatal corticosteroids on fetal lungs

Anatomy and biochemistry
- Thinning of the mesenchyme of the alveolar-capillary structure
- Increased saccular and alveolar gas volumes
- Decreased alveolar septation
- Increased antioxidant volumes
- Increased surfactant

Physiology
- Increase compliance
- Improved gas exchange
- Decreases epithelial permeability
- Protection of the preterm lung from injury during resuscitation

Interactions with exogenous surfactant
- Improved surfactant treatment responses
- Improved surfactant dosage–response curve
- Decreases inactivation of surfactant

Clinical
- Decreases incidence of respiratory distress syndrome
- No effect on the incidence on bronchopulmonary dysplasia
- Decreased mortality

(*From* Jobe AH, Kamath-Rayne BD. Fetal lung development and surfactant. In: Creasy RK, Resnik R, Greene MF, et al, editors. Creasy and Resnik's maternal-fetal medicine: principles and practice. Philadelphia: Elsevier/Saunders; 2014. p. 184; with permission.)

reduction in overall RDS (relative risk [RR], 0.66; 95% confidence interval [CI], 0.56–0.77) as well as moderate to severe RDS (RR, 0.59; 95% CI, 0.38–0.91). Additionally, neonates exposed to antenatal corticosteroids had a reduced need for mechanical ventilation (RR, 0.68; 95% CI, 0.56–0.84).[8]

Additional common complications of prematurity include intraventricular hemorrhage (IVH) and necrotizing enterocolitis. In preterm infants born before 26 weeks' gestation, the frequency of IVH is between 20% and 30%.[9] Bleeding into the central nervous system owing to impaired cerebral blood flood and immature delicate fetal blood vessels in the germinal matrix tissue results in hemorrhage into the ventricular system.[10] Antenatal corticosteroids promote circulatory stability in the vulnerable vascular germinal matrix. The clinical benefit of therapy was demonstrated in a 2017 systematic review with a reduction of neonatal IVH (RR, 0.55; 95% CI, 0.40–0.76).[8] However, the precise molecular mechanism of action of how antenatal corticosteroids reduce IVH is unclear.[11] Vascular endothelial growth factor promotes angiogenesis in the germinal matrix, which in rabbit models has been thought to contribute to increased vascular fragility and hemorrhage.[12] In vitro, the downregulation of vascular endothelial growth factor is accomplished by glucocorticoids, resulting in the suppression of angiogenesis in various disease models.[13,14] Additional growth factors, as upregulated by glucocorticoids, have been found to play a key role in maturation of the vasculature in immature blood vessels.[15] Necrotizing enterocolitis affects almost 10% of preterm infants and carries a mortality rate of up to 35%.[6] The beneficial effects of corticosteroid administration have been demonstrated in both animal[16] and human models,[17,18] and have been shown to accelerate maturation of the intestinal mucosal barrier. A 2017 Cochrane review similarly found necrotizing enterocolitis to be significantly reduced with antenatal steroid therapy (RR, 0.50; 95% CI, 0.32–0.78).[8] Additionally, antenatal corticosteroids have been shown to decrease neonatal mortality (RR, 0.69; 95% CI, 0.59–0.81) and decrease rates of systemic infection in the first 48 hours of life (RR, 0.60; 95% CI, 0.41–0.88; **Table 1**).[8]

GESTATIONAL AGE CONSIDERATIONS TO ANTENATAL CORTICOSTEROID ADMINISTRATION

The recommended gestational age for the administration of antenatal corticosteroids is based on studies that have demonstrated that therapy can result in improved neonatal morbidity and mortality. The American College of Obstetricians and Gynecologists recommends a single course of corticosteroids for women between 24 0/7 weeks' and 33 6/7 weeks' gestation, and recently extended this recommendation to include late preterm pregnancies (34 0/7–36 5/7 weeks' gestation). Antenatal steroids may also be considered for pregnant women as early as 23 0/7 weeks' gestation, who are at risk of preterm delivery within 7 days.[19]

Periviable

The prevalence of periviable birth ranges from 0.03% to 1.9%.[20] These early deliveries account for more than 40% of neonatal deaths.[21] Neonatal morbidity and mortality is affected by many factors, including gestational age and birth weight, as well as a variety of antecedent maternal and fetal medical problems. The *Eunice Kennedy Shriver* National Institute of Child and Human Development (NICHD) Neonatal Research Network developed an easily accessible online calculator to estimate the overall and intact survival for extremely low birth weight neonates.[22] The risk of common neonatal outcomes near the limit of viability are numerous, including moderate or profound neurodevelopmental impairment or death. The group assessed 5 clinical

Table 1
Neonatal clinical outcomes with administration of antenatal corticosteroids: treatment versus no treatment

Outcomes	Anticipated Absolute Effects (95% CI)		Relative Effect (95% CI)	Number of Participants (Studies)
	Risk with Placebo/ No Treatment	Risk with Corticosteroids		
Chorioamniotis	Study population 48 per 1000	40 per 1000 (32–51)	RR 0.83 (0.66–1.06)	5546 (15 RCTs)
Perinatal deaths	Study population 102 per 1000	73 per 1000 (59–91)	Average RR 0.72 (0.58–0.89)	6729 (15 RCTs)
Respiratory distress syndrome	Study population 176 per 1000	116 per 1000 (98–135)	Average RR 0.66 (0.56–0.77)	7764 (28 RCTs)
Intraventricular hemorrhage	Study population 51 per 1000	28 per 1000 (20–39)	Average RR 0.55 (0.40–0.76)	6093 (16 RCTs)
Mean birthweight (g)	Absolute risks not calculated		Mean birthweight was 18.47 g less (40.83 g less to 3.90 g more)	6182 (16 RCTs)

Abbreviations: CI, confidence interval; RCT, randomized, controlled trial; RR, relative risk.
Adapted from Roberts D, Dalziel S. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev 2006. (3):CD00445; with permission.

factors: gestational age between 22 and 25 weeks, birthweight (401–1000 g), plurality, neonatal gender, and if antenatal corticosteroids were administered within 7 days of delivery.[23,24]

The biologic plausibility that corticosteroids will be efficacious in the periviable period is based on data related to perinatal mortality. However, sequential phases of fetal lung development also suggest a role for pulmonary benefit. Alveolar development is detected as early as 22 weeks' gestation.[25] Research studies in both the laboratory setting[5] as well as in clinical observational studies[26,27] support the use of corticosteroid administration in the periviable period. The *Eunice Kennedy Shriver* NICHD Neonatal Research Network published observational data that demonstrated a significant reduction in death or neurodevelopmental impairment at 18 to 22 months for neonates who had been exposed to antenatal corticosteroids and born at 23 weeks' gestation (83.4% steroids vs 90.5% without steroids; adjusted odd ratio [AOR], 0.58; 95% CI, 0.42–0.80), 24 weeks' gestation (68.4% steroids vs 80.3% without steroids; AOR, 0.62; 95% CI, 0.49–0.78), and 25 weeks' gestation (52.7% steroids vs 67.9% without steroids; AOR, 0.61; 95% CI, 0.50–0.74). Of note, at 22 weeks' gestation there was no significant difference in these outcomes (90.2% steroids vs 93.1% without steroids; AOR, 0.81; 95% CI, 0.29–2.21). In infants that were born at 22 weeks' gestation receiving steroids, the only outcome that was significantly less was death or necrotizing enterocolitis (73.5% with steroids vs 84.5% without steroids; AOR, 0.54; 95% CI, 0.30–0.97). They also demonstrated that exposure to antenatal corticosteroids in infants born between 23 and 25 weeks' gestation decreased the incidence of death, IVH, periventricular leukomalacia, and necrotizing enterocolitis.[28]

Additional prospective cohort studies have demonstrated that, among infants born from 23 to 34 weeks' gestation, antenatal exposure to corticosteroids compared with no exposure was associated with lower mortality and morbidity at most gestations.[29] However, despite these improved outcomes in the periviable period, significant neonatal morbidity and mortality still exist. When delivery is anticipated in this gestational age window, health care providers must provide both medical information in parallel with emotional support for families faced with these complex and ethically challenging decisions. The NICHD Neonatal Research Network has compiled outcome data on extremely preterm infants and created an online tool to help providers provide estimated rates of neonatal morbidity and mortality based on delivery characteristics (**Fig. 1**). Each patient and their family must receive informed consent and be provided with options in both declining and accepting interventions based on their values and personal circumstances.

24 0/7 to 33 6/7 Weeks

In 1994, the National Institutes of Health held a consensus conference on the use of antenatal corticosteroids for fetal maturation in all fetuses between 24 and 34 weeks' gestation owing to underuse in the 1980s and early 1990s.[30] Administration in this gestational age window is recommended by the American College of Obstetricians and Gynecologists. Additionally, a recent 2017 Cochrane metaanalysis reinforces the beneficial effects and supports the continued used of antenatal corticosteroids to be considered part of routine therapy for patients at risk for preterm delivery between 24 and 34 weeks' gestation. Steroid treatment at this gestational age was associated with a reduction in perinatal death, neonatal death, RDS, moderate to severe RDS, IVH, necrotizing enterocolitis, need for mechanical ventilation, and systemic infections in the first 48 hours of life.[8] Based on these data, it seems that between 24 and 34 weeks' gestation there is an optimal therapeutic window for steroid-induced reprograming of lung development.

Late Preterm Pregnancies

In women between 34 0/7 weeks and 36 6/7 weeks' gestation at risk of preterm birth within 7 days, and who have not received a previous dose of antenatal corticosteroids, the American College of Obstetricians and Gynecologists recommend a single course of betamethasone.[19] The implementation of steroids in this late preterm birth period is also supported by the Society for Maternal Fetal Medicine.[31] This cohort of patients is particularly important to capture, because 70% of all preterm births occur in the late preterm period.[32] The data to support late preterm steroid administration stem from the Antenatal Late Preterm Steroids trial, which was conducted by the *Eunice Kennedy Shriver* NICHD, Maternal-Fetal Medicine Units (MFMU) Network.[33] This was a double-blinded, placebo-controlled, randomized, controlled trial assessing women with a singleton gestation, who were at high risk for preterm birth between 34 0/7 and 36 6/5 weeks' gestation between 2010 and 2015. To be eligible, women had to present with either preterm labor with a cervix that was at least 3 cm dilated or 75% effaced, preterm premature rupture of membranes, or with an indication for a planned late preterm delivery between 24 hours and 7 days of assessment. In 2831 subjects, the study demonstrated a significant decrease in the primary outcome, the need for respiratory support within the first 72 hours of life (14.4% vs 11.6%; RR, 0.80; 95% CI, 0.66–0.97). Additionally, they demonstrated significant decreases in the rates of severe respiratory morbidity, bronchopulmonary dysplasia, transient tachypnea of the newborn, the need for resuscitation at birth, and the need for postnatal surfactant. Compared with placebo, patients treated with steroids had no

Enter the characteristics below	
Gestational Age *(Best Obstetric Estimate in Completed Weeks)*	*Select Age*
Birth Weight *(401 to 1000 grams)*	*grams*
Sex	*Female/Male*
Singleton Birth	*Yes/No*
Antenatal Corticosteroids *(Within Seven Days Before Delivery)*	*Yes/No*

Estimated outcomes for infants in the NRN sample are as follows:

Outcomes	Outcomes for All Infants	Outcomes for Mechanically Ventilated Infants
Survival	____ %	____ %
Survival Without Profound Neurodevelopmental Impairment	____ %	____ %
Survival Without Moderate to Severe Neurodevelopmental Impairment	____ %	____ %
Death	____ %	____ %
Death or Profound Neurodevelopmental Impairment	____ %	____ %
Death or Moderate to Severe Neurodevelopmental Impairment	____ %	____ %

Fig. 1. Rates of neonatal morbidity and mortality based on delivery characteristics.

increased risk of clinical chorioamniotis, endometritis, or cesarean delivery. Neonates treated with betamethasone did have an increased risk of hypoglycemia (24% vs 14.9%; RR, 1.61; 95% CI, 1.38–1.88), but these rates were similar to those expected in late preterm neonates.[34] This Advanced Paediatric Life Support multicenter study is the largest randomized clinical trial to date assessing the benefits of antenatal corticosteroids in the late preterm period, and their findings are consistent with several other randomized, controlled trials on the benefits of antenatal corticosteroids before 34 weeks' gestation.[8,35] As summarized in a large metaanalysis, including 6 trials, infants of mothers who received antenatal corticosteroids at 34 0/7 to 36 6/7 weeks had a significantly lower incidence of transient tachypnea of the newborn (RR, 0.72; 95% CI, 0.56–0.92), severe RDS (RR, 0.60; 95% CI, 0.33–0.94), and use of surfactant (RR, 0.61; 95% CI, 0.38–0.99).[35]

Early Term

Neonates delivered in the early term period (between 37 0/7 and 38 6/7) are at increased risk for adverse outcomes compared with neonates delivered at and after 39 weeks' gestation.[36] Infants born at 37 0/7 weeks to 37 6/7 weeks are at 1.7 times increased risk for respiratory complications than those born between 38 0/7 and 38 6/7 weeks' gestation; and these neonates are at 2.4 times increased risk than those born between 39 0/7 and 39 6/7 weeks' gestation.[37] Additionally, it is known that infants born by cesarean section are at increased risk for the most significant neonatal morbidity in the early term period, namely, RDS and transient tachypnea of the newborn.[35,38] The administration of antenatal corticosteroids after 37 weeks in this early term cohort has shown to be beneficial in select populations. The Antenatal Steroids for Term Caesarean Section (ASTECS) randomized trial tested whether steroids reduce respiratory distress in neonates born by elective cesarean section at term. The treatment group received betamethasone 48 hours before delivery. They found significantly decreased rates in their primary outcome of RDS requiring admission to the neonatal intensive care unit (0.051 in the control group vs 0.024 in the treatment group; RR, 0.46; 95% CI, 0.23–0.93). These findings imply that babies born by elective cesarean section after 37 weeks' gestation can benefit from antenatal corticosteroids.[39]

Additionally, in a 2016 metaanalysis of 3 randomized trials of antenatal corticosteroids administered 48 hours before a scheduled cesarean section after 37 0/7 weeks, there was an appreciable reduction of transient tachypnea of the newborn (3% vs 7%; RR, 0.38; 95% CI, 0.25–0.57), respiratory distress system (2.7% vs 6.7%; RR, 0.40; 95% CI, 0.27–0.59), and the use of mechanical ventilation (0.7% vs 3.6%; RR, 0.19; 95% CI, 0.08–0.43). Additionally seen were higher APGAR scores at 1 and 5 minutes, reductions in time on oxygen, maximum inspired oxygen, and the duration of stay in the neonatal intensive care unit.[35]

IT IS ALL ABOUT TIMING

The administration of antenatal corticosteroids should include a thoughtful review of timing. The optimal time to administer steroids before delivery cannot be predicted in most cases.[40,41] The ideal therapeutic window after administration is when delivery occurs 24 hours to 7 days after a complete course of treatment.[42–44] The minimal amount of time required between receiving steroids and delivery to define an improved neonatal outcome has not been predicted precisely. Therefore, there are very few cases when delivery is considered imminent where therapy should be withheld. In a 2017 multicenter, population-based prospective cohort study gathering data from 11 European countries, outcomes demonstrated that the administration of

steroids was associated with a decrease in mortality, reaching a plateau with more than 50% risk reduction after an administration-to-birth interval of 18 to 36 hours. A simulation of steroids administered 3 hours before delivery compared with those who did not receive steroids showed an estimated decrease in neonatal mortality would be 26%.[45] Similar benefits were seen in observational studies with a decrease in the need for vasopressors as well as a decreased risk of IVH and neonatal death, even with incomplete courses of steroids.[46]

At the other end of the spectrum, there have been some studies to show a decreasing therapeutic benefit if steroids are administered more than 7 days before delivery.[44,47] The frequency of RDS has been found to be higher in infants delivering more than 1 week after steroid exposure.[43] And in infants delivering more than 14 days after steroid exposure, there is an associated increased risk for ventilator support and surfactant use.[48,49]

In terms of incomplete doses, clinical results are variable. In extreme prematurity, even the receipt of a partial course of antenatal corticosteroids has been shown to have improved neonatal outcomes.[50] However, other studies looking at the time interval from steroid exposure to delivery in very low birth weight infants have demonstrated no statistically significant improvement with respect to RDS treated with surfactant, IVH, necrotizing enterocolitis, or death.[51]

The Choice of Antenatal Corticosteroid

Historically, betamethasone and dexamethasone have both been acceptable options for corticosteroid therapy for effectively accelerating fetal lung maturity, because they differ by only 1 methyl group.[52] In a 2013 Cochrane review, 12 randomized trials were included to assess the superiority of 1 corticosteroid over the other. They found that dexamethasone was associated with a reduced risk of a reduced risk of IVH compared with betamethasone (RR, 0.44; 95% CI, 0.21–0.92). However, no statistically significant differences were noted for the other primary outcomes, including RDS (RR, 1.06; 95% CI, 0.88–1.27) and perinatal death (RR 1.41; 95% CI, 0.54–3.67). Additionally, those infants exposed to dexamethasone had a significantly shorter stay in the neonatal intensive care unit (mean difference, −0.91; 95% CI, −1.71 to −0.05).[53] In comparison, Lee and colleagues[54] found that prenatal betamethasone exposure was associated with a decreased likelihood of impaired neurodevelopmental status and reduced risk of hearing impairment when compared with dexamethasone. In a 2000 Consensus Panel convened by the NICHD, no significant scientific evidence supported the preferential benefit of betamethasone over dexamethasone. The American College of Obstetricians and Gynecologists notes the inconsistency of these data, and that no sufficient evidence supports the recommendation of one corticosteroid regimen over the other.[19]

The standard treatment dose should consist of either (i) two 12-mg doses of betamethasone given intramuscularly 24 hours apart or (ii) four 6-mg doses of dexamethasone administered intramuscularly every 12 hours.[55] Compared with intramuscular dexamethasone, neonates given oral dexamethasone had a significantly increased incidence of neonatal sepsis (RR, 8.48; 95% CI, 1.11–64.93); no statistical differences were seen for other outcomes.[53]

When to Rescue

The American College of Obstetricians and Gynecologists recommend a single repeat course of antenatal corticosteroids should be considered if (i) the patients is less than 34 0/7 weeks' gestation, (ii) she is at imminent risk of delivery within the next 7 days, and (iii) her prior course of antenatal corticosteroids was administered more than

14 days ago.[19] These recommendations are evidenced from a 2015 systematic review of 10 randomized trials, who had already received a single course of corticosteroids 7 or more days previously, and were considered to be still at risk for preterm birth. The authors concluded that, compared with no repeat corticosteroid treatment, repeat administration reduced the risk of primary outcomes, including RDS (RR, 0.83; 95% CI, 0.75–0.91), and composite serious infant outcome (RR, 0.84; 95% CI, 0.75–0.94). When evaluating long-term childhood outcomes, no significant harm or benefit was observed.[56] Given these results, depending on the clinical scenario, rescue corticosteroids could be considered as early as 7 days from the prior dose if the second course will be completed at less than 34 weeks' gestation.

SAFETY SURROUNDING THE USE OF ANTENATAL CORTICOSTEROIDS

Maternal Safety

Maternal therapy is overall well-tolerated and systematic reviews have confirmed no increased risk of maternal death, chorioamnionitis, or endometritis.[8] Betamethasone has low mineralocorticoid activity in comparison with other corticosteroids, so even in patients with severe preeclampsia, no worsening maternal outcomes have been demonstrated, and hypertension is not a contraindication to therapy. A small increased risk of gestational diabetes has been reported.[57] Studies have demonstrated a transient leukocytosis within 7 days of administration.[58] The steroid effect can occur within hours after the first dose and may last up to 1 week. Additionally, a resultant leukocytosis has been observed, with a return to baseline within approximately 3 days.[59,60]

Fetal Safety

Fetal outcomes have been studied to assess for safety profile. Observational studies have noted associated transient decreases in variability on external fetal heart rate monitoring[61,62] and occasionally reduced scores on the biophysical profile for fetal breathing and body movements.[63,64] A prospective study examining betamethasone administration in fetuses between 26 and 32 weeks' gestation observed that body movements were reduced on day 2 by 50% ($P<.01$), and breathing movements were largely absent on day 2 ($P<.01$); all values returned to baseline on day 4.[65] Additionally observed was a transient improvement in umbilical artery end-diastolic flow, lasting up to 3 days.[66,67] Additionally, the NICHD MFMU demonstrated that repeated doses was associated with a decrease in placental growth in a dose-dependent fashion.[68]

Neonatal Safety

The clinical effects on perinatal outcomes have mostly been related to the numbers of courses, and have been predominately studied before 34 weeks' gestation. In terms of single course, a large 2017 Cochrane review demonstrated no increased risk of either neonatal infection or small-for-gestational age infants.[8] However, this neonatal safety profile was not supported with multidose regimens.

Initially in 2006, the Australasian Collaborative Trial of Repeated Doses of Steroids demonstrated a neonatal benefit of weekly courses of antenatal corticosteroids,[69] and these results were supported in a Cochrane systematic review.[70] This dose–response relationship was further explored in 2008 in the Multiple Courses of Antenatal Corticosteroids for Preterm Birth (MACS) randomized, controlled trial. Infants exposed to multiple courses of steroids weighed less at birth than those exposed to placebo (2216 g vs 2330 g; $P = .0026$), were shorter (44.5 vs 45.4 cm; $P<.001$) and had a smaller head

circumference (31.1 cm vs 31.7 cm; $P<.001$).[71] Additionally, in a 2006 study by the NICHD MFMU Network, repeated courses of corticosteroids demonstrated a reduction in multiples of the birth weight median by gestational age (0.88 vs 0.91; $P = .01$), and more neonates weighing less than the 10th percentile (23.7 vs 15.3%; $P = .02$). Significant weight reductions occurred for the group receiving 4 or more courses. From this study, these investigators were able to demonstrate that repeated courses of antenatal corticosteroids do not improve the composite neonatal outcomes, and is also accompanied by a decrease in birth weight and an increase in the number of small-for-gestational age infants.[72] In addition to reduction in birth weight, the administration of multiple courses of steroids in patients with preterm labor before 34 weeks' gestation has been associated with an increased risk of perinatal infection and sepsis-related neonatal death.[73] Long-term follow-up data on multidose regimens are inconclusive. A 2007 study by the NICHD MFMU demonstrated that children who had been exposed to multiple versus single courses did not differ significantly in childhood Bayley scores or anthropometric measurements. However, although not significantly different, they did find a higher rate of cerebral palsy among children who had been exposed to 4 or more doses.[74] Nevertheless, the 2- and 5-year follow-up data on multiple course regimens have not shown to affect pediatric mortality or disability.[75,76] From these studies and concerns for neonatal harm, as well as the balance of risks and benefits, the American College of Obstetricians and Gynecologists do not recommend multiple courses of steroids.[19]

Neonatal outcomes are less well-studied in patients receiving steroids in the late term period. One of the greatest concerns is an increased incidence of neonatal hypoglycemia that, if prolonged or persistent, can be associated with developmental delay and physical growth defects.[77] The ALPS trial did find that in patients receiving treatment between 34 0/7 weeks and 36 5/7 weeks, neonatal hypoglycemia occurred more frequently (24% vs 15%; RR, 1.60; 95% CI, 1.37–1.89); however, this event did not result adverse events related to the hypoglycemia.[33] Additionally, adverse events related to hypoglycemia were similar to those reported in the general population of late preterm infants.[33] In a systematic review and metaanalysis, steroids given after 34 weeks' gestation did not result in any long-term neurologic or cognitive outcomes at ages 8 to 15 years[39]; however, the long-term safety of antenatal corticosteroid administration at term is still not well-studied and not currently recommended in the United States. Further studies are needed to assess the long-term neurodevelopmental outcomes of children exposed to corticosteroids at this gestational age.

CONSIDERATIONS FOR SPECIAL POPULATIONS

Multiple Gestations and Obesity

Previous theoretic concerns that the added maternal plasma volume in multiple gestations could decrease the neonatal benefits of the traditional dosing of antenatal corticosteroids have not been validated.[78] Compared with singletons, maternal and umbilical cord serum betamethasone concentrations have not been shown to be significantly different.[79] Similarly, obesity can affect the volume of distribution. And even though the blood flow per gram of fat in a normal weight individual is more than that of a morbidly obese patient,[80] no differences in betamethasone concentrations were seen in obese versus nonobese women.[79] After preterm steroid prophylaxis, infants of obese women have not been shown to receive more pulmonary surfactant than preterm infants of nonobese women (odds ratio, 0.67; 95% CI, 0.13–1.40).[81] Additionally, maternal body mass index has not been shown to affect neonatal morbidities in those receiving steroids.[82]

The clinical outcomes studies to support the therapeutic benefit of antenatal corticosteroids in twin pregnancy are contradictory. In a secondary analysis of twins delivered between 24 0/7 and 36 6/7 weeks, the primary outcome of RDS was not reduced in those twins receiving steroids.[83] However, other studies have shown that as early as 22 weeks, steroid exposure has proven to be beneficial in multiple gestations. In comparing exposure with nonexposure, twins born between 22 and 28 weeks receiving steroids have been associated with a lower risk of in-hospital mortality (adjusted RR, 0.87; 95% CI, 0.78–0.96).[84] This therapeutic benefit in twins was demonstrated in a recent retrospective cohort study using data on twins born between 24 0/7 and 33 6/7 weeks. Neonatal outcomes were compared in those who received a completed course of antenatal corticosteroids 1 to 7 days before birth and those who did not, and found a clinically significant decrease in neonatal mortality, short-term respiratory morbidity, and severe neurologic injury that is similar in magnitude to that observed among singletons.[85] Additional studies in twins have supported a significant reduction in RDS when the steroid to delivery interval was between 2 and 7 days (aOR, 0.419; 95% CI, 0.181–0.968; $P = .42$).[86] As seen in singletons, optimal therapeutic neonatal benefit is not demonstrated exceeding an interval of 7 days to delivery.[87] Also of note, exposure to rescue steroids has been associated with improved neonatal outcomes.[88]

To date, there has not been a large enough sample size or a randomized, controlled trial to confirm a therapeutic benefit of steroid administration in twin pregnancy. However, the American College of Obstetricians and Gynecologists recommend that twin gestations at risk for preterm birth received the same standard regimen as that recommended for a singleton pregnancy.[19]

Maternal Glycemia Associated with Steroid Administration

Although antenatal corticosteroid therapy has been found to cause a transient hyperglycemia, administration to women with diabetes in pregnancy is still recommended. Because direct evidence on the effectiveness and safety of steroids is lacking for this cohort of patients,[89] close observation is warranted. The glycemic effect of steroids begins about 12 hours after administration of the first dose, and lasts up to 5 days after the second dose.[90] Glucose levels increase in both patients with and without diabetes, although the mean maximum glucose levels have been seen to be higher for those with diabetes than without (205 mg/dL vs 173 mg/dL; $P<.01$).[91] Additionally, studies have supported these findings, seeing glucose levels increase by 33% to 48% in diabetic patients and by 16% to 33% in those without diabetes.[92]

A standardized protocol for preventing hyperglycemia during the treatment of diabetic patients receiving antenatal corticosteroids has not yet been established. Retrospective data have demonstrated that the requirement for insulin is greatest 9 to 10 hours after each dose of betamethasone.[93] Glycemic control and monitoring was dependent on the underlying nature of the diabetes, and how well the patient was controlled at baseline. The National Institute for Health and Clinical Excellence guidelines on the management of diabetes in pregnancy recommend that diabetic women receiving steroids should have additional insulin, although a specific protocol has not been designed. Based on studied patients in the United Kingdom, Kaushal and colleagues[94] have established a protocol. Subcutaneous insulin and diet are continued from the first dose of corticosteroids until 12 hours after the second, and then supplementary intravenous insulin is infused according to hourly blood glucose measurements. Their protocol includes 4 graded sliding scales. The initial scale is selected based on the patient's current subcutaneous insulin dose, and it is advanced if the blood glucose is 10.1 mmol/L or more for 2 consecutive hours. Some protocols

have demonstrated a need for increasing the insulin dose from 20%[95] to 40% shortly after steroid treatment is needed to prevent severe dysregulation of metabolic control.[96] This management decision should individualized to the patient, and a proactive approach is needed to ensure optimal outcomes.

Infection and Preterm Premature Rupture of Membranes

The American College of Obstetricians and Gynecologists recommend that antenatal corticosteroids be administered to patients with preterm premature rupture of membranes, because it has been shown to decrease neonatal mortality, RDS, IVH, and necrotizing enterocolitis.[8,97,98] However, the neonatal benefit of patients with preterm premature rupture of membranes at less than 28 weeks' gestation is less clear.[99] Additionally, owing to insufficient evidence, the American College of Obstetricians and Gynecologists does not recommend for or against a rescue course of corticosteroids at any gestational age.[100]

The use of betamethasone has been found to cause a leukocytosis.[101] In patients with preterm premature rupture of membranes who are treated with steroids, there is no difference in chorioamnionitis or RDS.[102] And even in patients with confirmed histologic chorioamniotis, antenatal steroids have been found to be associated with less neonatal mortality and morbidity.[103,104] Additionally, a second maternal antenatal corticosteroid course has not been associated with an increased rate of chorioamnionitis[105] or neonatal sepsis.[106]

SUMMARY

Antenatal corticosteroids remain one of the most powerful tools in our armamentarium to fight the neonatal complications of prematurity. The rate of preterm birth continues to increase, and we must stay equipped to battle the morbidity and mortality that it brings. Over 40 years ago, Liggins and Howie introduced the beneficial effects on newborn lungs leading to less respiratory disease. Since that time, numerous additional therapeutic benefits have been described, including the reduction of neonatal death, IVH, and necrotizing enterocolitis. With advancing technologies and knowledge, the cusp of viability continues to broaden, and with this comes great responsibility to use our knowledge and tools to improve outcomes for patients. Concurrently, we must commit ourselves to providing patients with a thorough understanding, not only of the benefit, but also the limitations of these interventions in the management of preterm birth.

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Effects of Delayed Cord Clamping on Four-Month Ferritin Levels, Brain Myelin Content, and Neurodevelopment: A Randomized Controlled Trial

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Objective To evaluate whether placental transfusion influences brain myelination at 4 months of age.

Study design A partially blinded, randomized controlled trial was conducted at a level III maternity hospital in the US. Seventy-three healthy term pregnant women and their singleton fetuses were randomized to either delayed umbilical cord clamping (DCC, >5 minutes) or immediate clamping (ICC, <20 seconds). At 4 months of age, blood was drawn for ferritin levels. Neurodevelopmental testing (Mullen Scales of Early Learning) was administered, and brain myelin content was measured with magnetic resonance imaging. Correlations between myelin content and ferritin levels and group-wise DCC vs ICC brain myelin content were completed.

Results In the DCC and ICC groups, clamping time was 172 ± 188 seconds vs 28 ± 76 seconds ($P < .002$), respectively; the 48-hour hematocrit was 57.6% vs 53.1% ($P < .01$). At 4 months, infants with DCC had significantly greater ferritin levels (96.4 vs 65.3 ng/dL, $P = .03$). There was a positive relationship between ferritin and myelin content. Infants randomized to the DCC group had greater myelin content in the internal capsule and other early maturing brain regions associated with motor, visual, and sensory processing/function. No differences were seen between groups in the Mullen testing.

Conclusion At 4 months, infants born at term receiving DCC had greater ferritin levels and increased brain myelin in areas important for early life functional development. Endowment of iron-rich red blood cells obtained through DCC may offer a longitudinal advantage for early white matter development. *(J Pediatr 2018;■■:■■-■■).*

Trial Registration ClinicalTrials.gov: NCT01620008.

See editorial, p •••

Delayed cord clamping (DCC) at birth supports a transfer of blood from the placenta to the newborn infant, resulting in a 30% increase in blood volume and a 50% increase in iron-rich red cell volume.[1,2] Ferritin, the major iron storage protein in the body, is increased after DCC through 6 months of age,[3] whereas immediate cord clamping (ICC) decreases early iron stores[4-11] and may contribute to iron deficiency (ID) in infancy.[12] Infant ID can adversely affect cognitive, motor, social–emotional, and behavioral development.[13-18] Red blood cells from DCC may provide a critical early iron endowment for the oligodendrocytes, the most metabolically active cells in the brain. These myelin-producing cells are sensitive to iron deprivation, as oligodendrocytes require iron for both maturation and function.[19-24] Iron is transported readily across the blood–brain barrier, on demand, through the process of transferrin endocytosis.[20] Studies in animals clearly link hypomyelination with ID and neurodevelopmental impairment,[15] and abnormal myelination is associated with a variety of childhood developmental disorders, including dyslexia and autism spectrum disorders.[25-27]

DCC	Delayed cord clamping
GLM	General linear model
ICC	Immediate cord clamping
ID	Iron deficiency
mcDESPOT	Multicomponent-Driven Equilibrium Single-Pulse Observation of T1 and T2
MRI	Magnetic resonance imaging
RCT	Randomized controlled trial
RPBV	Residual placental blood volume
VFm	Myelin water volume fraction

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Based on the importance of iron availability for oligodendrocytes to form myelin, we investigated the potential effects of timing of umbilical cord clamping (DCC vs ICC) on myelin maturation. We employed a novel, noninvasive neuroimaging technique termed mcDESPOT (multicomponent-Driven Equilibrium Single-Pulse Observation of T1 and T2) to quantify myelin water volume fraction (VFm), a surrogate measure for myelin content[28-30] that has been used previously to characterize normative patterns of myelination in healthy infants,[31,32] and to investigate relationships between myelin content and evolving brain function and cognitive skills.[33,34]

We hypothesized that infants born at term exposed to placental transfusion via DCC (or cord milking) would have greater iron stores and enhanced myelin formation showing increased myelin content at 4 months of age compared with infants who were exposed to ICC.

Methods

Enrollment for this randomized controlled trial (RCT) was conducted from July 2012 to November 2015 (ClinicalTrials.gov: NCT01620008), and corresponding follow-up at 4 months of age occurred from November 2012 to March 2016. The study was conducted at Women and Infants Hospital of Rhode Island and Brown University (Providence, Rhode Island) after approval by the institutional review boards from Women and Infants Hospital, the University of Rhode Island, and Brown University. Results of the birth and 2-day data have been published previously.[35] Assessments at 12 months of age were completed in November 2016 and 24-month assessments in December 2017.

Intervention, Randomization, and Blinding

Methods for enrollment and randomization for this study have been described previously.[35] We obtained informed consent from healthy, term pregnant women and enrolled them prenatally. Just before birth, blocked stratified randomization was used (in sequenced and sealed envelopes) to assign women to either DCC (>5 minutes) or ICC (<20 seconds). Milking of the cord (5 times) was the proxy for DCC at cesarean delivery or if the provider could not delay. Residual placental blood volume (RPBV), the remaining blood in the placenta after birth, was obtained via drainage.[35] Blinding of the research assistants at the infant's birth was not possible due to the nature of the intervention. However, group assignment was not revealed to the pediatric or laboratory staff or the magnetic resonance imaging (MRI) and developmental testing personnel. All study staff except the birth research assistants were unaware of the randomization assignment.

Participant Follow-Up

There were 4 separate data collection points for the subjects at 4 months of age: well-baby visit, blood draw for iron indices (including ferritin), MRI, and neurodevelopmental testing. To support retention, contact with participants was maintained by the research assistants and the lead research nurse. Research assistants attended the infants' 4-month well-baby pediatric visits and collected growth and health data. Within 1 week of the blood draw, MRI scans were completed (limited to 140 days of life for the 4-month analyses). Neurodevelopmental testing was completed within 1 week of a successful MRI.

At 4 months, a heel capillary blood sample was collected for a complete blood count and iron indices including ferritin, transferrin, soluble transferrin receptor, and C-reactive protein. The samples were collected by a pediatric nurse at the child's home or by a laboratory technician at the hospital laboratory. Discussion of the blood sample methods is found in the **Appendix** (available at www.jpeds.com).

Infants underwent MRI during natural, nonsedated sleep at either nap or bedtime on a Siemens Tim Trio 3 Tesla scanner (Siemens Healthineers Headquarters, Erlangen, Germany). Measures of brain myelin content, as measured by VFm, were acquired from 4-month-old participants using the mcDESPOT MRI technique and following previously described guidelines for infant neuroimaging.[36] Further details about the MRI technique can be found in the **Appendix**. Notably, this technique has been used extensively to study myelination patterns in infancy and early childhood.[31-33,37,38]

Within 7 days of a successful MRI, each child was assessed with the Mullen Scales of Early Learning, a standardized and population-normed tool for assessing fine and gross motor control, visual reception, and expressive and receptive language for children up to 5 years, 9 months of age.[39] In addition to individual age-normalized domain scores, there are 3 composite Mullen scores that reflect overall cognitive ability (Early Learning Composite) as well as verbal and nonverbal development quotients. Each of these composite scores is expressed as a standard score with a mean of 100 and an SD of 15. In addition, mothers were asked to complete the Edinburgh Postnatal Depression Scale at the enrollment visit and at 4 months after birth as well as the Parental Stress Index at 4 months of age.

Sample Size

Effect sizes based on data from previous studies of ferritin levels after DCC suggest that without adjustment sample sizes of 30 per group would have more than 80% power at an alpha of 0.05 to detect differences in ferritin levels between the 2 groups.[3,5,6] Substantial variance reduction (at least 50%) can be achieved by controlling for baseline covariates, such as age, gestational age, and birth weight, as planned. No previous data exist for the effects of umbilical cord clamping time on VFm. Deoni et al reported that the SD of VFm estimates in white matter is 5% in healthy children.[40] To reliably measure a 5% VFm difference between the control and experimental groups, using a 2-sample t test (alpha = 0.05, power = 0.80), 16 observations per group were required.

Statistical Analyses

Data analyses included 2-sided Pearson χ^2 tests, 2-sample t tests, and Wilcoxon rank-sum tests for non-normally distributed

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variables. Primary analyses were conducted using intention-to-treat, and sensitivity analyses were conducted using actual treatment to assess the robustness of the findings and to examine results of the biological variables. Log transformation was used for the analysis of the ferritin levels due to non-normal distribution of the ferritin data. The level of significance was .05 (2-tailed) for main effects. Data were analyzed with SAS 9.3 (SAS Institute, Inc, Cary, North Carolina) and SPSS Version 23 (IBM Corp, Armonk, New York).

Image Analysis and Statistical Testing

Associations between VFm and 4-month blood ferritin levels were evaluated at each image voxel using a general linear model (GLM) that included age, gestational age, and birth weight as additional variables of noninterest. Voxel-wise VFm differences between the DCC and ICC groups additionally were investigated by performing an unpaired *t* test. The FMRIB Software Library package (FMRIB Analysis Group, Oxford, United Kingdom) was used to construct the GLM, and both the GLM and group differences were tested nonparametrically using permutation testing (randomize) and 5000 permutations. Significance was defined as $P < .05$, with correction for the multiple comparisons in MRI data using a cluster-based technique.[41,42]

Table I. Maternal and infant demographics and clinical variables at birth (for infants who were successfully scanned at 4 months, intention-to-treat)

Characteristics	DCC (n = 23)	ICC (n = 21)	*P* value
Maternal			
Age, y	29 ± 6	28 ± 6	.76
Race, white	16 (70)	15 (71)	.89
Primipara	12 (52)	10 (48)	.76
Maternal education, y	15 ± 3	14 ± 3	.53
Public insurance	12 (52)	10 (48)	.76
Hemoglobin at admission, g/dL	11.7 ± 1.1	11.9 ± 1.1	.51
Lead level at admission, μg/dL	1.1 ± 0.4	1.0 ± 0.3	.38
Ferritin at admission, ng/mL	25.3 ± 26	18.8 ± 17	.34
Mode of delivery: vaginal	17 (74)	14 (67)	.60
Edinburgh Postnatal Depression Scale total score	3 ± 3	5 ± 5	.12
Parental Stress Index total score	51 ± 14	55 ± 16	.37
Infant			
Gestational age at birth, d, range	279.3 ± 8	277.8 ± 8	.54
Birth weight, g	3589 ± 521	3411 ± 430	.23
Male	12 (52)	12 (57)	.74
Cord-clamping time, s (includes UCM)	172 ± 188*	28 ± 76	.002
Cord-clamping time, s (without UCM) (n = 15, 20)	250 ± 190†	28.1 ± 78	<.001
RPBV, mL/kg	22.1 ± 8.5‡	27.2 ± 7.3	.05
Protocol violations	4 (17)	2 (10)	.45

UCM, umbilical cord milking.
Values are n (%) or mean ± SD.
*$P < .01$.
†$P < .001$.
‡$P < .05$.

Results

Seventy-three healthy term pregnant women were randomized to DCC or ICC. At 4 months, 64 (88%) infants were active participants. Of those, 59 (92%) had blood draws and 58 (91%) underwent MRI scanning. Fifty-six (88%) infants completed the developmental testing. Of the 58 MRIs completed, 48 MRIs were completed before 140 days (83%) and 44 (92%) were usable (**Figure 1**; available at www.jpeds.com). Only data from these 44 infants are reported here and are referred to as the MRI cohort.

Participant demographics and clinical variables for infants with an MRI within 140 days are shown in **Tables I** and **II**. There were no significant group differences with respect to maternal age, education, type of insurance, mode of delivery, gestational age, birth weight, or sex. Consistent with the previous report,[35] infants in the MRI cohort with DCC had longer cord-clamping time (per protocol) ($P = .002$), less RPBV at birth ($P = .05$), and greater hematocrit levels at 2 days of age ($P = .01$). There was no difference in cord ferritin levels between the groups.

Table II shows no differences in hemoglobin, hematocrit, or other blood values at 4 months of age with analysis by intention to treat. However, infants who received DCC exhibited greater ferritin and log ferritin levels, and the absolute (relative) effect size was 31.1 (48%), 95% CI –59.7, –2.5. All ferritin levels were within normal range.[43] Ferritin levels <40 occurred in 22% of the in the ICC group compared with 9% of the DCC group ($P = .23$). The mode of feeding was not different between groups and was not a significant predictor for ferritin. Thus, it was not included in a model for ferritin and VFm. None of the infants in either group received iron supplementation.

There were no significant differences between groups on any of the other blood values examined (**Table II**). We found no significant differences in neurodevelopmental testing in the Mullen verbal and nonverbal developmental quotient composite scores or overall cognitive ability between the DCC and ICC groups (**Table II**). The values highlight that both groups fall within the normal range of Mullen scores and are within 1 SD of the standardized mean.

There were significant positive associations between VFm and 4-month blood ferritin levels (**Figure 2**). In particular, these associations were localized in regions of early developing white matter, including the right hemisphere cerebellar white matter, brain stem, parietal and occipital lobes, as well as the left and right anterior and posterior internal capsules. In all cases, greater levels of ferritin were associated with increased VFm. Controlling for sex did not affect the findings.

Dichotomous comparisons between infants in the DCC and ICC groups revealed infants exposed to DCC had significantly more myelin content in early myelinating areas than infants exposed to ICC. Analysis was completed using both intention to treat and actual treatment. Both analyses demonstrated significant differences, but actual treatment showed more robust differences in the various brain regions (**Figure 3**). Regions with increased myelin included the brain stem and cerebellum, left and right posterior arms of the internal capsule,

Table II. Clinical variables for infants with MRI (intention-to-treat)

Variables	DCC (n = 23)	ICC (n = 21)	*P* value
Neonatal			
Apgar scores, median (range)			
1 min	8 (3-9)	8 (2-9)	.77
5 min	9 (8-9)	9 (5-9)	.67
Cord hematocrit, %	43.7 ± 6	45.8 ± 5	.25
Cord ferritin, ng/dL	145 ± 92	141 ± 93	.89
BiliTool, high-risk zone (bilitool.org)	2 (9)	2 (10)	1.00
Peak total bilirubin, mg/dL	8.5 ± 4	9.1 ± 2	.56
Two-day hematocrit, %	57.6 ± 6*	53.1 ± 6	.01
Two-day hemoglobin, g/dL	19.1 ± 2	18.0 ± 2	.06
4-mo variables			
Hematocrit, %	34 ± 2.3	34 ± 2.4	.76
Hemoglobin, g/dL	11.7 ± 1.0	11.7 ± 0.7	.93
Ferritin, ng/dL	96.4 ± 58*	65.3 ± 32	.03
Log ferritin	4.4 ± 0.5*	4.1 ± 0.5	.03
Mean corpuscular volume, fL	81.4 ± 4.0	81.5 ± 3.7	.94
Transferrin, mg/dL	228 ± 31	239 ± 35	.28
Soluble transferrin receptor, mg/L	3.8 ± 0.9	3.8 ± 0.8	.93
C-reactive protein, mg/L	0.35 ± 0.4	1.0 ± 1.7	.08
Mullen Early Learning composite score	105.1 ± 8.7	103.5 ± 9.2	.55
Nonverbal composite score	120.5 ± 19.8	116.3 ± 21.0	.50
Verbal composite score	111.6 ± 21.5	109.2 ± 19.7	.70

Values are n (%), mean ± SD, or median (full range).
*$P < .05$.

and parietal lobe white matter. Controlling for sex did not yield any differences.

Discussion

Infants who received a placental transfusion had greater ferritin levels at 4 months of age compared with those with ICC, as previously reported.[3] In addition, these greater ferritin levels were associated with increased brain myelination at 4 months of age. Using mcDESPOT-derived VFm, a novel quantitative MRI measure of brain myelin content, we found that infants who received DCC had increased myelination at 4 months of age compared with those who received ICC. We observed significant VFm differences between infants receiving DCC and ICC, with infants receiving DCC having increased VFm in similar brain regions associated with the blood ferritin levels. Collectively, these results suggest a direct neurophysiological link between DCC and early myelin development, reinforcing and strengthening the literature that draws attention to the benefits of DCC in the newborn and supporting the previous finding that an endowment of iron-rich blood cells facilitated by placental transfusion is associated with increased iron storage and blood ferritin levels.[3] This study extends the available evidence to show that increased ferritin levels are associated with greater brain myelin content at 4 months of age.

Beginning in the late second trimester and early third trimester, oligodendrocytes lay the groundwork for the lipid myelin bilayers that sheathe neuronal axons in a carefully orchestrated pattern that extends center-out and from posterior to anterior brain regions.[44,45] This process initiates within the brain stem and cerebellum, progresses to the cerebellum and internal capsules by the first postnatal month, and extends to parietal and occipital white matter between 4 and 6 months of age, before continuing its protracted developmental trajectory across the cortex.[31,36,46] Over the first 2 postnatal years, myelination advances rapidly, with myelin present in nearly all brain areas by 9 months of age, and approximately 80% of adult levels reached by the end of year 2. An activity-driven process,[47] the establishment and maintenance of the myelin sheath requires timed delivery of essential lipids and micronutrients, including iron.[23,30,48] Significant associations between blood ferritin levels and VFm as well as VFm differences between infants with DCC and ICC were localized to these early developing brain regions, including the brain stem, cerebellar, parietal and occipital white matter, and the internal capsules. Our findings suggest that placental transfusion at birth may result in increased iron stores, represented by ferritin, and may help promote myelination in the first few months of life. This is particularly important, as myelinated axons facilitate rapid and efficient brain communication and messaging.[49,50] Future

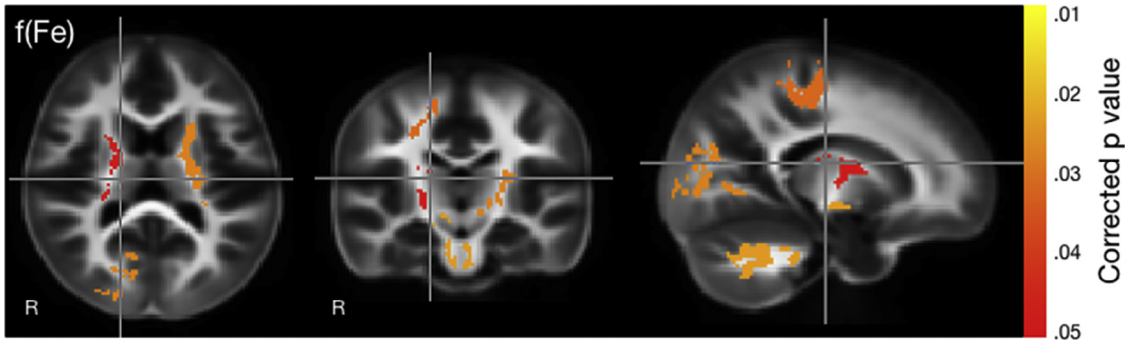

Figure 2. Correlation between myelin and ferritin at 4 months of age. Significance is indicated by the color scale on the *right* with *yellow* at *P* value of .01 and *red* indicating .05.

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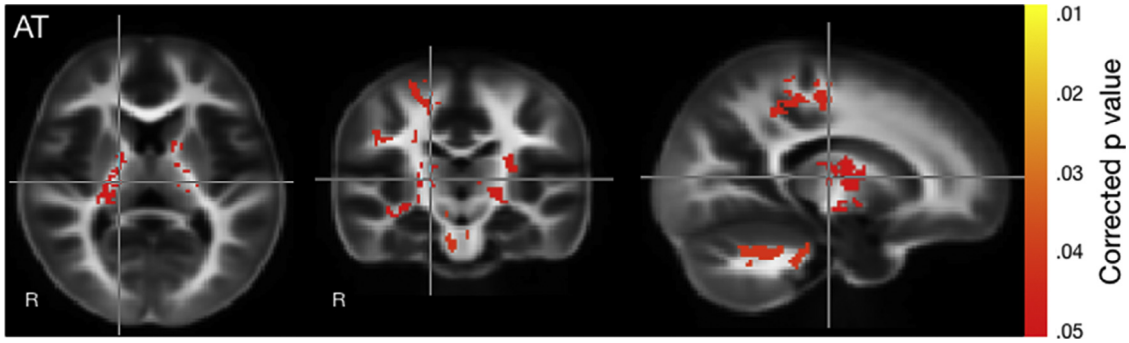

Figure 3. Group differences in myelin content between infants with DCC vs ICC by actual treatment. Significance is indicated by the color scale on the *right* with *yellow* at *P* value of .01 and *red* at a *P* value of .05. These colors represent areas in which myelin is greater in infants who had DCC compared with those who had ICC.

research examining whether these myelination differences between infants with DCC and ICC persist, become more extensive, or normalize over time will be important. Evaluation of the long-term consequences of DCC on infant brain development and other neurodevelopmental outcomes is planned. In this RCT, infants will return for MRI scans and neurodevelopmental testing at 12 and 24 months of age, providing the opportunity to continue to study such outcomes.

The early developing brain regions, ie, the internal capsules, differed between infants with DCC and ICC. These areas of the brain are essential to a wide variety of cognitive functions, including motor and sensory processing.[46] Previous studies investigating neurobehavioral outcomes following DCC using neurodevelopmental testing only demonstrated improved scores in fine motor and the social domains in infants with DCC at 4 years of age, especially in boys,[51] although no differences were seen at 4 and 12 months of age.[3,52] Our findings suggest that differences in myelin content may underlie neurodevelopmental differences between infants with DCC and ICC that appear later in childhood. The present study examined neurodevelopmental outcomes in infants at 4 months of age as this stage of infancy marks the onset of the most rapid period of myelin development.[46] We observed no neurodevelopmental differences between the DCC and ICC groups at this early time. VFm differences between children with above-average and below-average cognitive ability do not present until early toddlerhood (1-2 years).[53] Thus, neurodevelopmental gains resulting from DCC may not be observable until later in development. Assessment of the infants enrolled in our current RCT at 12 and 24 months of age will allow us to examine whether these differences manifest over time.

One potential mechanism underlying our findings of early myelination in infants with DCC and ICC may be related to iron. Iron is involved in myelinogenesis and is a necessary component for the maturation and function of the oligodendrocytes.[21] Studies in animals have demonstrated that ID can lead to altered myelin lipid synthesis,[15,54] changes in myelin basic protein transcripts,[55] and fundamental changes to the myelin-producing oligodendrocyte populations.[21] ID can disrupt the trajectory of myelination growth and subsequently result in long-lasting myelin alterations.[13] Our findings associating VFm and blood ferritin levels have not been reported previously. The increased iron stores afforded by increased red cell volume at birth facilitated by DCC appear to lead to increased infant myelination at 4 months of age. Myelin-producing oligodendrocytes, the predominant cell type containing iron, are composed of a mixture of ferritin subunits, which allows these cells to both store and use iron in the biosynthesis of cholesterol and lipids for myelin production.[21] Thus, increased iron endowed through placental transfusion as measured by ferritin may enable oligodendrocytes to more rapidly accumulate iron and initiate and sustain myelination more quickly. However, this theory should be more specifically investigated with additional research in humans and animals. Nonetheless, our findings provide further evidence of an association between iron or ferritin and early brain myelination and may have important implications for clinical practice based on these underlying mechanisms.

This study used a 5-minute delay for DCC. When the study began in 2010, skin-to-skin care was adopted by the hospital as the standard of care for healthy infants born at term. We chose the 5-minute delay based on our pilot study,[56] which showed that RPBV was significantly greater in infants placed skin-to-skin with ICC or a 2-minute delay compared with infants with a 5-minute delay or cord milking (×5). We wanted to obtain the maximum difference in placental transfusion between groups to optimize variances in the MRI results. One concern was that a delay of 5 minutes in this RCT resulted in a RPBV of 20 mL/kg, which was more residual blood than expected. It is also more than we found in our earlier pilot study, which yielded 11 mL/kg for infants born at term after 5 minutes. In addition, Yao reported 13.8 mL/kg of RPBV after a 3-minute delay with infants held below the level of the perineum, suggesting that placing the infant on the maternal abdomen slows the placental transfusion.[2]

Although we demonstrated greater ferritin levels at 4 months with DCC, the levels were lower than those in a study by Andersson et al, who reported a 3-minute delay but did not discuss placement of the infant.[3] In a personal conversation,

the lead author reported that the midwives held the infants below the level of the placenta for about 30 seconds as cord blood gases were obtained. Infants were then placed skin-to-skin. It is possible that the infants obtained more placental transfusion during those first 30 seconds.

Despite the findings of greater ferritin levels in the DCC group at 4 months, we found no differences in the hemoglobin and hematocrit levels. This finding is consistent with other studies in infants born at term,[3,57] suggesting that hemoglobin and hematocrit levels do not adequately represent the infant's body iron stores. Yet, ferritin levels are not assessed routinely at 4 months. Thus, most pediatric providers rely on the hemoglobin and hematocrit to reflect iron status.[58]

Although the current study suggests DCC results in better VFm outcomes in infants at 4 months of age, and mcDESPOT has shown qualitative agreement with myelin histology,[59,60] future studies are needed to quantitatively validate mcDESPOT measures. Nonetheless, the extant literature using mcDESPOT[31-33,37,38] provides confidence that mcDESPOT-derived VFm measurements are sensitive to myelin content.

Placental transfusion via DCC facilitates a transfer of residual iron-rich placental blood and increases iron stores without adverse effects. Our findings show that infants who received a placental transfusion have increased myelin content at 4 months of age compared with infants who received ICC, adding to a growing number of studies that describe the benefits of DCC. Moreover, given that DCC is a feasible, low-tech, no-cost approach, it has the potential to have widespread impact on early life development. Future studies examining the long-term effects of DCC on child development would be important, but the ethical concerns regarding comparisons to ICC are to be considered. ■

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Appendix

Supplementary Materials

Methods: Blood Samples. The complete blood count samples were collected in a 0.5-mL EDTA tube (BD Microtainer, Franklin Lakes, New Jersey) and then analyzed using an automated hematology analyzer (Sysmex XN 3000; Sysmex America Inc, Lincolnshire, Illinois). The iron indices and C-reactive protein were collected in a 0.5-mL serum separator tube (BD Microtainer) and analyzed with a clinical chemistry analyzer (Architect ci4100, Abbott Laboratories, Abbott Park, Illinois). All samples, except ferritin, were processed at Women & Infants Hospital. Ferritin was processed at the Mayo Medical Laboratories (Rochester, New York) using an immunoassay system (Beckman Coulter Unicel DXL 800; Beckman Coulter Inc, Brea, California).

MRI Data Acquisition and Processing. Parents were contacted to schedule the 4-month MRI. Children were brought to the MRI center either at nap or bedtime. Special sleep rooms were provided for parents to get the infant to sleep. When sleeping, the infant was placed securely on an MRI-compatible cart and transported to the MRI scanner. Parents (after appropriate screening) were invited to stay with the infant during the MRI. The MRI scan lasted approximately 30-45 minutes once the infant was asleep. If an infant was unable to fall asleep or to return to sleep after waking, the MRI examination was rescheduled. Within 1 week after a successful MRI scan, children were scheduled for developmental testing.

Measures of brain myelin content were acquired with the mcDESPOT MRI technique. mcDESPOT is a multicomponent relaxometry technique that decomposes the measured MRI signal into contributions from myelin and nonmyelin water-based on the unique relaxation properties of each of these water pools.[1-4] Unlike traditional multicomponent relaxometry techniques,[1,2] mcDESPOT uses rapid and time-efficient gradient echo sequences, acquired over a range of flip angles, to quantify the relaxation characteristics of multicompartment water pools.[5,6] Specifically, the mcDESPOT protocol included 8 T_1-weighted spoiled gradient-recalled echo (SPGR) and 16 T_1/T_2-weighted balanced steady-state free precession (bSSFP) images acquired over multiple flip angles.[5,6] Two inversion-prepared (IR)-SPGR images additionally were acquired for correction of radio-frequency (B_1) inhomogeneities, and bSSFP images were acquired with 2 phase cycling patterns ($\varphi = 180°$ and 0°) for correction of main magnetic field (B0) inhomogeneities.[7] Choice of scan acquisition parameters for the mcDESPOT protocol have been optimized according to the relaxation characteristics at various stages of infancy and early childhood.[8] Specific acquisition parameters of the SPGR, bSSFP, and IR-SPGR scans used in the current study are as follows:

SPGR: repetition time (TR) = 12 milliseconds; echo time (TE) = 5.8 milliseconds; flip angles (α) = [2, 3, 4, 5, 7, 9, 11, 14] degrees; receiver bandwidth = 350 Hz/voxel; and 6/8 partial k-space in the phase and slice-encode directions.

bSSFP: TR = 10 milliseconds; TE = 5 milliseconds; α = [9, 14, 20, 27, 34, 41, 56, 70]; bandwidth = 350 Hz/voxel; 6/8 partial k-space in the phase and slice–encode directions.

IR-SPGR: TR = 12 milliseconds; TE = 5.8 milliseconds; inversion times = [600, 950] milliseconds; $\alpha = 5$ degrees; 6/8 partial k-space in the phase-encode directions. Half the resolution in the slice direction.

All data were acquired from each participating 4-month-old infant on a Siemens Tim Trio 3 Tesla scanner (Siemens) with a 12-channel head radiofrequency array. To help the children sleep during the scan, acoustic noise levels were minimized by reducing imaging gradient slew rates and peak values. Additional passive sound attenuation was achieved with a sound-insulating bore liner (Ultra Barrier HD Composite; American Micro Industries, Chambersburg, Pennsylvania) and MiniMuff ear pads. Electrodynamic and sound-attenuating headphones (MR Confon GmbH, Magdeburg, Germany) also were used and provided constant white noise throughout the duration of the scan.[9]

Following successful acquisition, image data were inspected visually for motion-related image artifacts (eg, edge blurring and ghosting). Each participant's SPGR, bSSFP, and IR-SPGR images were then linearly coregistered to account for subtle head movement[10] and nonbrain (ie, skull) signal was removed.[11] SPGR and IR-SPGR images were used to estimate the flip angle correction map.[12] VFm values were calculated at each image voxel by fitting the SPGR and bSSFP data to a multicomponent relaxometry model of 3 microstructural water compartments: intra/extra-axonal water, myelin-associated water, and nonexchanging free water.[6]

For correlation analysis and group comparisons, individual VFm maps were nonlinearly aligned to a common study template[8] using a fully 3-dimensional image registration approach.[13] Before statistical analyses, aligned VFm data were smoothed with a modest 4-mm full-width-at-half-maximum 3D Gaussian kernel to account for residual registration inaccuracies.[14]

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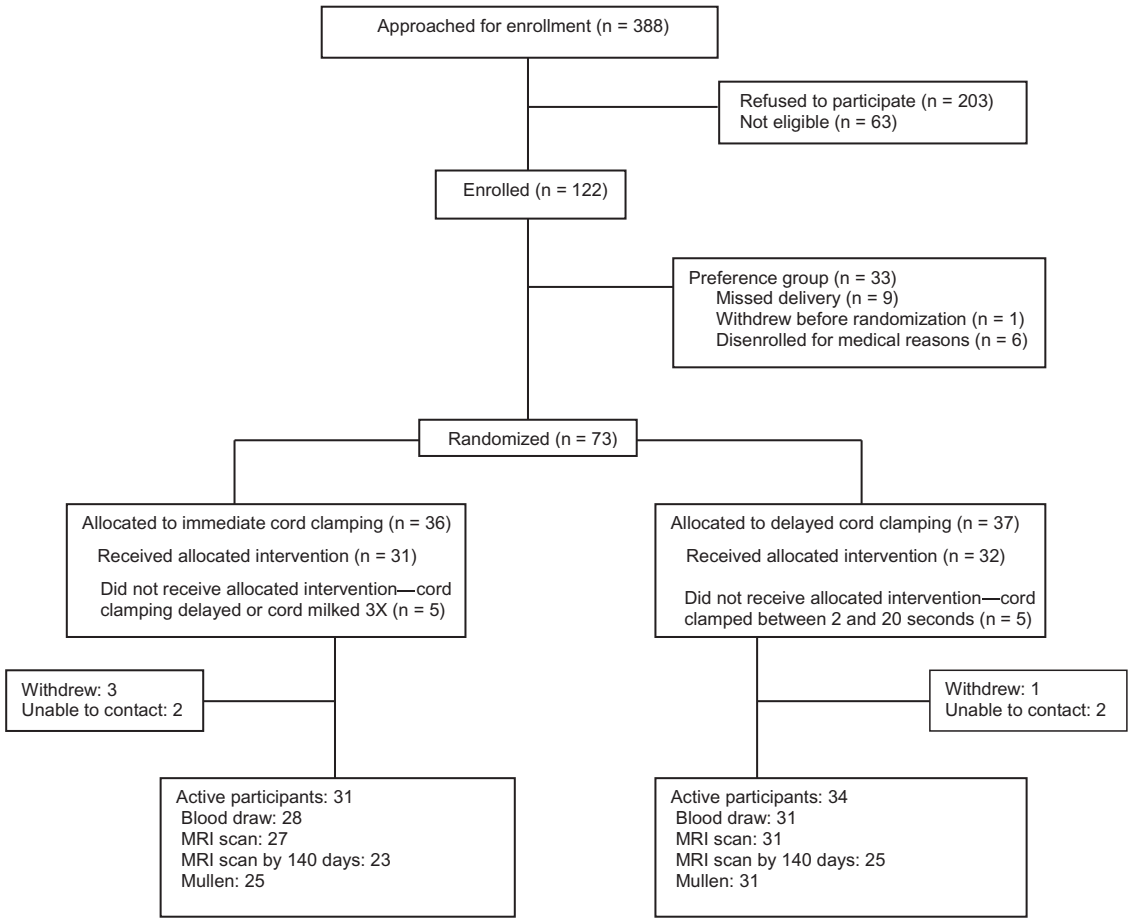

Figure 1. Infant brain study 4-month randomized cohort flowchart.

Preventing Continuous Positive Airway Pressure Failure

Evidence-Based and Physiologically Sound Practices from Delivery Room to the Neonatal Intensive Care Unit

Clyde J. Wright, MD[a,*], Laurie G. Sherlock, MD[a], Rakesh Sahni, MD[b], Richard A. Polin, MD[c]

KEYWORDS

• Continuous positive airway pressure • Bronchopulmonary dysplasia
• Ventilatory-induced lung injury • Sustained lung inflation • INSURE
• Randomized controlled trial • Mechanical ventilation • Infant flow driver

KEY POINTS

- The incidence of bronchopulmonary dysplasia, and the competing outcomes death or bronchopulmonary dysplasia, is decreased with early initiation of nCPAP.
- The best available evidence supports the premise that efforts to minimize CPAP failure start in the delivery room.
- Various modes and interfaces to deliver CPAP exist; although there may be considerable differences in the ability of these various CPAP devices to prevent failure, little data from RCT exist to support this.

Continued

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Continued

- Compared with infant flow driver, bubble CPAP may decrease the risk of postextubation failure in infants less than 30 weeks' gestation who are ventilated ≤14 days.
- Available data demonstrate that the INSURE approach is not superior to use of CPAP without prophylactic surfactant in preventing CPAP failure.
- Sustained lung inflation may increase the rate of CPAP success, but may not decrease the incidence of BPD if positive pressure ventilation is needed.

WHY PREVENT CONTINUOUS POSITIVE AIRWAY PRESSURE FAILURE?

The need to identify safe and effective interventions to prevent bronchopulmonary dysplasia (BPD) has reached a critical point. In the simplest terms, BPD is the most common morbidity affecting a cohort of patients whose survival is increasing at the greatest rate. Data collected by the Neonatal Research Network recently on more than 34,000 infants born at 22 to 28 weeks gestation between 1993 and 2012 demonstrated significant increases in survival among infants born at 23, 24, and 25 weeks' gestational age (GA).[1] Importantly, these tiny babies are at the highest risk of developing BPD, with an incidence of 60% to 80%. In this same cohort of patients, it seems that practice changes over this period did little to improve the incidence of BPD.

An alternative to identifying additional interventions to prevent BPD is improving the interventions clinicians already make to support the highest risk neonates. More than 85% of the 34,000 infants in the Neonatal Research Network cohort were exposed to mechanical ventilation during their neonatal intensive care unit (NICU) stay.[1] Recent clinical data continue to support a direct relationship between exposure to mechanical ventilation and an increased risk of developing BPD.[2–6] As the survival of the tiniest babies increases, it is important to determine if a better modality of invasive mechanical ventilation exists to minimize these exposures and prevent BPD. High-frequency ventilation does not reduce the incidence of BPD in the smallest, high-risk babies.[7] Volume-targeted ventilation still remains promising, but randomized trials remain small and unconvincing.[8] Newer approaches, including neurally adjusted ventilator assist, have not yet been adequately studied.[9] These data may point to the reality that the developing human lung at 22 to 26 weeks' gestation is uniquely susceptible to injury caused by invasive mechanical ventilation. If this is true, reducing the burden of BPD will come only with limiting the exposure to invasive mechanical ventilation.

Data from randomized controlled trials (RCTs) demonstrate that routine use of continuous positive airway pressure (CPAP) significantly reduces the combined outcome of BPD (assessed at 36 weeks' gestation) or death in at-risk preterm infants, with an number needed to treat of 17.7.[10] Two other similar meta-analyses have been performed, each including slightly different combinations of trials whose comparison groups go beyond strictly CPAP versus prophylactic surfactant.[11,12] In all of these meta-analyses, the signal for benefit always points toward CPAP. Unfortunately, the routine use of CPAP does not provide a larger treatment effect; the numbers needed to treat determined across these three analyses were 17.7,[10] 25,[11] and 35.[12] It is reasonable to ask why the treatment effect is not larger, and can more be done to enhance the benefit of CPAP.

If CPAP prevents BPD by limiting the exposure to mechanical ventilation, efforts to prevent CPAP failure would likely lead to increased protective effects. In the preterm infant at highest risk for developing BPD, CPAP failure is common. Data from three large RCTs evaluating routine CPAP versus routine intubation show that 45% to 50% of high-risk babies fail CPAP within the first week of life (**Table 1**). Data from

Table 1
Incidence of CPAP failure in large RCTs evaluating CPAP alone as primary mode of respiratory support

Trial	Year	Subjects Enrolled	GA	ACS, % (Any)	CPAP Failure, % (5–7 d)
COIN[13]	2008	610	25 0/7–28 6/7	94	46
SUPPORT[19]	2010	1316	24 0/7–27 6/7	>95	51.2
CURPAP[20]	2010	208	25 0/7–28 6/7	>95	33
Dunn[18]	2011	648	26 0/7–29 6/7	>98	45.1

Abbreviations: ACS, antenatal corticosteroids; GA, gestational age.

observational studies and RCT demonstrate that rates of CPAP failure are highest for the smallest babies, approaching 60% at 25 to 26 weeks' GA.[13–16] These data inform practice in one of two ways: either efforts to minimize CPAP failure in this group of infants will result in less BPD and improved outcomes; or, despite best efforts, CPAP failure in this group of patients will remain unacceptably high and the ability to detect who will fail must be improved to provided supportive therapy (eg, mechanical ventilation and/or surfactant) as soon as possible.

HOW TO PREVENT CONTINUOUS POSITIVE AIRWAY PRESSURE FAILURE: EVIDENCE-BASED INTERVENTIONS, FROM THE DELIVERY ROOM TO THE NEONATAL INTENSIVE CARE UNIT

Does Receipt of Antenatal Corticosteroids Decrease the Risk of Continuous Positive Airway Pressure Failure?

Antenatal corticosteroids (ACS) are considered "one of the most important antenatal therapies available to improve newborn outcomes," and are now recommended for threatened delivery at 24 0/7 weeks to 33 6/7.[17] It is reasonable to hypothesize that rates of CPAP failure would be higher among neonates that did not receive ACS. Among neonates enrolled in RCTs evaluating CPAP versus routine intubation, receipt of ACS was high (>90%, see **Table 1**).[13,18–20] These data suggest that even with the benefit of ACS, rates of CPAP failure remain high (~60%). So, the question remains: in the unfortunate circumstance that a baby at high risk of developing BPD (23–28 weeks) did not receive the benefit of ACS, should there be a lower threshold to intervene and provide exogenous surfactant?

Randomized studies performed in the 1980s and 1990s demonstrated that in large (>28 weeks' GA) intubated infants with respiratory distress syndrome (RDS), who often had not received ACS, early and even prophylactic surfactant treatment decreased mortality and air leak.[21,22] It is likely that a protective signal exists for earlier treatment of RDS in more immature infants 24 to 28 weeks' GA who did not receive ACS, but an RCT will never likely provide these answers.

*Therefore, we recommend that a trial of CPAP should be attempted for all neonates born at less than 28 weeks' GA, but the threshold for intervention (*ie, *intubation and exogenous surfactant) should be considered early in the course of RDS if ACS were not administered. Quality of evidence: low, based on the lack of data in patient population of interest (24–28 weeks' GA). Strength of recommendation: weak, based on the lack of clear data guiding practice.*

Does Routine Use of Sustained Lung Inflation Prevent Continuous Positive Airway Pressure Failure?

At delivery, term infants provide a sustained pressure (30–35 cm H_2O) over a long inspiratory time (4–5 seconds) to clear lung fluid and establish functional residual

capacity (FRC).[23] Assisting preterm infants in the delivery room by providing positive pressure at 20 to 25 cm H_2O for 5 to 20 seconds via a nasopharyngeal tube or face-mask has been proposed as a method to establish FRC.[23] Smaller RCTs demonstrate that use of sustained lung inflation (SLI) decreases the need for mechanical ventilation at 72 hours, without increasing the risk of air leak.[24–27] A much larger trial powered to determine if use of SLI is safe and decreases the incidence of BPD or death in neonates born at 23 to 26 weeks' GA is ongoing.[28]

Therefore, we recommend SLI should be considered for all neonates born at less than 28 weeks' GA. Quality of evidence: moderate, based on consistent findings across multiple smaller RCTs. Strength of recommendation: strong recommendation, based on potential benefit and lack of data demonstrating harm.

Does the Modality of Assisted Ventilation Used in the Delivery (Resuscitation) Room Affect Continuous Positive Airway Pressure Failure?

Assisted ventilation in the delivery room is provided using one of three devices: (1) self-inflating bag, (2) flow-inflating bag, and (3) T-piece resuscitator. The theoretic advantages of the T-piece resuscitator include delivering a consistent end expiratory pressure while precisely delivering the desired peak inspiratory pressure. Whether use of the T-piece in the resuscitation suite prevents CPAP failure in the babies at highest risk of CPAP failure (<26 weeks' GA) is unknown. However, in babies greater than or equal to 26 weeks' GA, use of a T-piece resulted in less intubation in the delivery room when compared with use of a self-inflating bag. Importantly, use of the T-piece did not increase the need for chest compressions or air leak.[29]

Therefore, we recommend that when available, a T-piece resuscitator should be used to resuscitate neonates born at less than 28 weeks' GA. Quality of evidence: low, based on the lack of data in the population of interest (24–28 weeks' GA). Strength of recommendation: weak, based on the lack of clear data guiding practice balanced by the absence of evidence of harm.

Does Intubation, Surfactant, Extubation Improve Continuous Positive Airway Pressure Success?

Isayama and colleagues[30] recently published a systematic analysis comparing the intubation, surfactant, extubation (INSURE) approach with nasal CPAP. There were no statistically significant differences between the nasal CPAP and INSURE groups. However, the relative risks seemed to favor the INSURE group with a nonsignificant (12%) reduction in chronic lung disease and/or death (moderate-quality evidence), a 14% decrease in chronic lung disease (moderate-quality evidence), and a 50% decrease in air-leak (very-low-quality evidence).

We recommend that nasal CPAP should be offered to all preterm neonates with RDS; however, there is no benefit to routine surfactant administration followed by rapid extubation (INSURE) unless the likelihood of CPAP failure is very high. When the likelihood of CPAP failure is greatly increased, surfactant should be administered followed by rapid extubation. Quality of evidence: moderate. Strength of recommendation for using CPAP without prophylactic surfactant: strong.

Recently, there has been renewed interest in the INSURE approach using surfactant administration through a thin plastic catheter (minimally [or less] invasive surfactant therapy and less invasive surfactant administration [LISA]) (**Table 2**). Isayama and colleagues[31] recently published a meta-analysis comparing seven ventilation strategies (including LISA and INSURE). The primary outcome was death or BPD at 36 weeks' postmenstrual age. Compared with all other ventilatory strategies, LISA had the lowest risk of the primary outcome. However, this outcome was not robust for death when

Table 2
Need for CMV and incidence of BPD in preterm infants with RDS treated with INSURE approach using surfactant administration through a thin plastic catheter versus ETT

Study	N (Gestation, wk)	Need for CMV, % Catheter vs ETT	Incidence of BPD Catheter vs ETT, %	Entry Criteria for Catheter
Gopel et al,[80] 2015	2206 (26–28)	41 vs 62 (P<.001)	12 vs 18 (P = .001)	Cohort study not specified
Kanmaz et al,[81] 2013	200 (<32)	40 vs 49 (P = NS)	10.3 vs 20.2 Moderate-severe (P = .009)	F_{IO_2} >0.4 and CPAP
Gopel et al,[82] 2011	220 (26–28)	33 vs 73 (P<.0001)	8 vs 13 (P = .268)	F_{IO_2} >0.3 and CPAP
Kribs et al,[83] 2015	211 (23–26.8)	74.8 vs 99 (P<.001)	67.3 vs 58.7 Survival without BPD (P = NS)	F_{IO_2} >0.3 and CPAP in first 2 h
Mohammadizadeh et al,[84] 2015	38 (<34)	15.8 vs 10.5 (P = NS)	P = NS	CPAP and need for surfactant
Bao et al,[85] 2015	90 (27–32)	17.0 vs 23.3 (P = NS)	P = NS	F_{IO_2} = 0.30–0.35 and CPAP
Mirnia et al,[86] 2013	136 (27–32)	19 vs 22 (P = NS)	7.5 vs 7.1 (P = NS)	F_{IO_2} >0.3 and CPAP

Abbreviations: CMV, conventional mechanical ventilation; ETT, endotracheal tube; F_{IO_2}, fraction of inspired oxygen; NS, nonsignificant.

limited to higher quality studies. Rigo and colleagues[32] recently published a systematic analysis of four trials comparing surfactant administration through a thin plastic catheter versus INSURE. Compared with INSURE, less invasive surfactant therapy decreased of death/BPD or CPAP failure.

We do not recommend administration of surfactant using a thin plastic catheter (LISA). Quality of evidence for LISA: low, given the small number of patients randomized to this intervention. Strength of recommendation: strong, based on lack of large RCTs comparing LISA with other modes of surfactant administration.

Does Bubble Continuous Positive Airway Pressure Improve Rates of Continuous Positive Airway Pressure Success?

CPAP delivery devices are broadly grouped into continuous-flow and variable-flow systems. With continuous-flow devices this is achieved by using water-seal bubble CPAP (Fisher and Paykel Healthcare, Auckland, New Zealand; Babi-Plus, A Plus Medical, Hollister, CA; home-made) systems or via flow opposition, where the patient's expiratory flow opposes a constant flow from nasal prongs (conventional ventilator provided neonatal CPAP). Variable-flow devices that include the infant flow driver (IFD; infant flow nasal CPAP system, Care Fusion, Yorba Linda, CA), Benveniste gas jet valve CPAP (Dameca, Copenhagen, Denmark), Aladdin, and Arabella systems (Hamilton Medical AG, Reno, NV) use flow opposition with fluidic flow reversal during expiration, where gas is entrained during inspiration to maintain stable pressure and expiratory flow is diverted via a separate fluidic flip-flop.

Randomized Trials Comparing Continuous Positive Airway Pressure Devices

Randomized controlled trials performed at birth

Mazzella and colleagues[33] compared IFD CPAP with bi-nasal prongs and bubble CPAP through a single nasopharyngeal tube in preterm infants with RDS at less

than 12 hours of age. They reported a significant beneficial effect on oxygen requirement and respiratory rate with IFD CPAP, compared with bubble CPAP, and a trend toward a decreased need for mechanical ventilation. Tagare and colleagues[34] compared the efficacy and safety of bubble CPAP with ventilator-derived CPAP in preterm neonates with RDS. A higher percentage of infants was successfully treated with bubble CPAP (83% vs 63%; $P = .03$), suggesting superiority of bubble CPAP. Mazmanyan and colleagues[35] randomized preterm infants to bubble CPAP or IFD CPAP after stabilization at birth in a resource-poor setting. They reported bubble CPAP equivalent to IFD CPAP in the total number of days CPAP was required.

Randomized trials of continuous positive airway pressure after extubation

Stefanescu and colleagues[36] examined extremely low birth weight infants and compared IFD CPAP with ventilator-derived CPAP using INCA prongs and found no difference in the extubation success rate between the two groups. In a subsequent trial, Gupta and colleagues[37] randomized preterm infants 24 to 29 weeks' gestation or 600 to 1500 g at birth to receive bubble CPAP or IFD CPAP following the first attempt at extubation. Infants were stratified according to duration of initial ventilation ($\leq$14 days or >14 days). Although there was no statistically significant difference in the extubation failure rate (16.9% on bubble CPAP, 27.5% on IFD CPAP) for the entire study group, the median duration of CPAP support was 50% shorter in the infants on bubble CPAP, median 2 days (95% confidence interval, 1–3 days) on bubble CPAP versus 4 days (95% confidence interval, 2–6 days) on IFD CPAP ($P = 0$ .03). In infants ventilated for less than or equal to 14 days, the extubation failure rate was significantly lower with bubble CPAP (14.1%; 9 of 64) compared with IFD CPAP (28.6%; 18 of 63) ($P = .046$). This well-designed clinical trial suggests the superiority of postextubation bubble CPAP over IFD CPAP in preterm babies less than 30 weeks, who are initially ventilated for less than 14 days.

Therefore, we recommend the use of bubble CPAP over variable-flow CPAP devices for postextubation respiratory support, especially in infants ventilated for less than or equal to 2 weeks. Quality of evidence: low, for device preference when used to treat RDS after birth; moderate, for use of bubble CPAP following postextubation. Strength of recommendation: weak, based on only a slight difference between continuous- or variable-flow CPAP devices when used after birth but a trend in favor of bubble CPAP for postextubation support, especially in infants ventilated for less than 2 weeks.

Does the Interface Used to Deliver Continuous Positive Airway Pressure Affect Continuous Positive Airway Pressure Failure?

The ideal interface would reliably deliver consistent distending pressure while being comfortable to the infant and easy to use. Several options are available, including short binasal prongs, nasopharyngeal prongs, masks, and the RAM cannula. No adequately powered trial has directly compared all interfaces. Several have examined nasal mask versus nasal prongs to prevent CPAP failure, with one demonstrating less CPAP failure in infants less than 31 weeks with the use of nasal mask.[38] However, another found no difference in CPAP failure between mask and binasal prongs.[39] The variability in these results may be caused by different definitions of CPAP failure and difference in maximum noninvasive support provided (CPAP level, noninvasive positive-pressure ventilation).

RAM cannula has been used to deliver CPAP in neonates.[40] It provides positive distending pressure through longer nasal cannula prongs made from softer material.[41] Unfortunately, there are no clinical studies directly comparing RAM with other nasal interfaces for preventing CPAP failure. However, there are several preclinical studies

using lung model systems that attempt to determine whether RAM cannula can reliably deliver mean airway pressure or peak inspiratory pressures. One demonstrated that when used as recommended with a 60% to 80% nasal occlusion, even with a closed mouth, the RAM cannula delivered on average 60% less mean airway pressure to the lungs than the set pressure.[42] Another showed RAM cannula resulted in significantly higher resistance and dramatically lower peak inspiratory pressures to the lungs than short binasal prongs.[43] The direct clinical relevance of these findings is unknown and deserves further study.

Therefore, we recommend use of either nasal mask or short binasal prongs for early CPAP administration. We recommend against the use of RAM cannula during the critical period determining CPAP success. Quality of evidence: low, based on the small number of patients studied. Strength of recommendation: strong, based on lack of clinical data directly comparing RAM cannula with CPAP.

Does Prone or Lateral Body Positioning Improve Continuous Positive Airway Pressure Success?

Prone positioning improves oxygenation in mechanically ventilated neonates,[44] infants, and children with acute respiratory distress.[45] Results in neonates on CPAP are conflicting, with several demonstrating improvements in oxygenation, respiratory rate, and end-expiratory lung volume with prone and lateral positioning.[46–48] However, another found no difference in vital signs or oxygen saturations regardless of position.[49] None of the studies found evidence of harm or adverse effect associated with prone or lateral positioning.

We recommend the prone and lateral positions for infants with the goal of increasing CPAP success. Quality of evidence: low, based on lack of trials evaluating position to prevent initial CPAP failure. Strength of recommendation: moderate, based on potential benefit and lack of demonstrated harm.

Does Timing of Caffeine Administration Affect Continuous Positive Airway Pressure Failure?

Importantly, the Caffeine for Apnea of Prematurity trial demonstrated that caffeine use was associated with a significant reduction in the duration of mechanical ventilation.[50] An enhanced protective effect on BPD and the duration of mechanical ventilation is observed when caffeine therapy is initiated early (before 2–3 days of life vs later than 2–3 days of life).[51–54] It is possible that these observations may be explained by later initiation of caffeine in infants with greater illness severity.[55] Additional prospective studies are needed to identify ideal timing of caffeine dosing.

Therefore, we recommend that caffeine should be administered to neonates both at and less than 28 weeks' GA, and there may be additional benefit of administering caffeine early in the first 24 to 72 hours of life. Quality of evidence: high, based on data from RCTs and large observational studies. Strength of recommendation: strong, based the consistent finding of benefit and the absence of evidence of harm.

WHEN NO EVIDENCE EXISTS, CAN ONE SUPPORT "BEST PRACTICE"?

Does Aggressive Airway Clearance Prevent Continuous Positive Airway Pressure Failure?

Effective delivery of noninvasive positive distending pressure cannot occur in the presence of obstructed nasal passages or oropharynx. Little evidence guides practice regarding how frequently one should preform nasal and oral suctioning. Although maintaining airway patency is paramount, aggressive suctioning can lead to edema, trauma, and bleeding, thus exacerbating plugging. In addition to the loss of positive

distending pressure during suctioning, other more serious complications can occur including bradycardia, laryngospasm, and arrhythmias. In practice, indications and frequency of suctioning is variable.[56] Instructions on nontraumatic suctioning have been published.[57] Units with long experience in successful application of CPAP in the most premature infants recommend suctioning every 3 to 4 hours.[58]

Therefore, we recommend that nasal and oropharyngeal suctioning should be performed every 3 to 4 hours, and more frequently with signs of obstruction (apnea, desaturation, acute increase in work of breathing). Attention must be paid to avoiding excessive suctioning and causing trauma. Quality of evidence: low. Strength of recommendation: strong, based on physiologic benefit and the low likelihood of harm.

Can Quality Improvement Projects Improve Continuous Positive Airway Pressure Success Rates?

Multiple obstacles stand in the way of implementing early, aggressive, and successful CPAP in high-risk neonates. It takes time to technically train the multidisciplinary team (eg, nursing, respiratory therapist, neonatal nurse practitioner.) in correct CPAP application, administration, and maintenance. It requires education and consensus of the attending physicians, trainees at multiple levels, and nurse practitioners who are making decisions regarding what defines CPAP failure, and when invasive mechanical ventilation should be used. Not surprisingly, time and experience with CPAP has been shown to increase CPAP success and decrease rates of BPD.[59]

Several groups have implemented quality improvement studies demonstrating short-term success increasing CPAP use and decreasing rates of intubation.[60–63] Some,[60,61] but not all,[62,63] have decreased unit BPD rates during the study period. Importantly, sustained practice improvement and decreased rates of BPD have been demonstrated.[64] These findings support that targeted multidisciplinary quality improvement efforts can help improve CPAP success.

We recommend that any institution dedicated to adopting a strategy of early CPAP develop a multidisciplinary team to champion this cause, whether it is through a formal quality improvement project or as an annual unit goal. Quality of evidence: low, based on small number of studies. Strength of recommendation: strong, based on potential benefit.

IF BABIES MUST FAIL, CAN ONE PREDICT WHO WILL FAIL, AND INTERVENE EARLY?

Are There Antenatal Characteristics that Reliably Predict Continuous Positive Airway Pressure Failure?

Studies of antenatal identifiers of CPAP failure report discordant results. Many establish early GA and lower birth weight as predictive as CPAP failure.[16,65,66] Lack of ACS and male sex have correlated with CPAP failure in some studies.[66–68] However, others have shown aspects of medical history, including GA and birth weight, are not predictive of CPAP failure.[15,69]

None of these studies identified factors with adequate sensitivity or positive pressure ventilation in predicting CPAP failure. Thus, we recommend against using antenatal characteristics to exclude infants from a trial of CPAP. Quality of evidence: moderate, based on lack of convincing evidence. Strength of recommendation: strong, based on potential benefit of CPAP success.

Are There any Clinical Variables or Diagnostic Tests that Predict Continuous Positive Airway Pressure Failure?

Multiple studies have attempted to define clinical features of a neonate's initial NICU course that predict CPAP failure. Several groups have shown early higher fraction of

inspired oxygen (F_{IO_2}) correlates with CPAP failure.[15,65,69] However, this relationship is confounded by including F_{IO_2} requirement in the definition of CPAP failure. The same can be said for the relationship between higher levels of CPAP and ultimate CPAP failure.[69] Importantly, one trial identified that infants who succeeded CPAP were started earlier (4.3 minutes vs 29 minutes), emphasizing the importance of early FRC establishment.[61] Multiple studies have performed sophisticated analyses to identify early clinical findings that predict CPAP failure (**Table 3**). Although no clinical variable is foolproof, thematic links begin to emerge. These studies would suggest that CPAP failure is more common in the most premature neonates, those with severe RDS on initial chest radiograph (CXR), and those requiring high levels of supplemental oxygen. Although none of these associations is surprising, these factors must be in the clinician's mind when attempting to determine if a neonate is "failing" CPAP. Other groups have recommended composite scoring and combining variables to help predict CPAP failure, such as birth weight less than 800 g, male sex, and F_{IO_2} greater than 0.25 at 1 or 2 hours,[14] the product of F_{IO_2} and CPAP level being greater than or equal to 1.28,[68] or creating a clinical score with features including GA, lack of antenatal corticosteroids, prolonged premature rupture of membranes, and the product of F_{IO_2} and CPAP level,[68] has also been considered.

Surfactant activity and/or production tests

A screening test able to identify surfactant deficiency would allow clinicians to target surfactant administrations to select patients at high risk of CPAP failure secondary to RDS. Surfactant activity level has been evaluated to predict CPAP failure using the surfactant adsorption test. The surfactant adsorption test is done on amniotic fluid and has demonstrated correlation with lamellar body counts and lung ultrasound scores. In a pilot study, infants failing CPAP have lower surfactant adsorption test levels than those who succeeded.[70]

The rapid bedside stable microbubble test evaluates if surfactant is present in tracheal, gastric, and amniotic fluid samples. This test has been used to stratify infants into high or low risk for CPAP failure.[71–74] Other tests of surfactant production include

Table 3
Clinical predictors of CPAP failure

Study	Infants Studied	Clinical Characteristics as Predictors of CPAP Failure	Odds Ratio (95% CI)
Ammari et al,[16] 2005	261 infants ≤1250 g	Severe RDS on initial CXR	6.42 (2.75–15.0)
		PPV at delivery	2.37 (1.02–5.52)
		A-a DO_2 >180 mm Hg	6.42 (2.75–15.0)
Pillai et al,[68] 2011	62 infants ≤1500 g	Product of CPAP and F_{IO_2} ≥1.28	3.9 (1.0–15.5)
		PPROM	5.3 (1.2–24.5)
		GA <28 wk	6.5 (1.5–28.3)
Dargaville et al,[14] 2013	66 infants 25–28 wk GA	F_{IO_2} by 2 h	1.19 (1.06–1.33)
		Caesarean delivery	14.77 (1.47–148.55)
Tagliaferro et al,[66] 2015	235 infants ≤1000 g	GA ≤26 wk	6.19 (2.79–13.73)
		A-a DO_2 >180 mm Hg	2.18 (1.06–4.47)
		pH ≤7.27	2.69 (1.27–5.69)
		Severe RDS on initial radiograph	10.81 (3.5–33.3)

Abbreviations: A-a DO_2, alveolar-arterial oxygen difference; CI, confidence interval; CXR, chest radiograph; F_{IO_2}, fraction of inspired oxygen; PPROM, prolonged premature rupture of membranes; PPV, positive pressure ventilation.

the click test, the shake test, and lamellar body counts, but have not been evaluating ability to predict CPAP failure.[75–78]

Chest radiographs

Severe RDS on a CXR obtained in the first hours of life has been identified as a predictive variable for CPAP failure in multiple studies.[14,16] A repeat study corroborated this finding in extremely low birth weight infants, finding that early radiologic evidence of severe RDS was a strong predictor of CPAP failure with a positive predictive value of 0.81. However, its utility as a screening tool is somewhat limited because the sensitivity of severe RDS on a CXR to predict CPAP failure was only 32%.[66] Because obtaining CXR is already a common part of clinical practice for these infants, incorporating a thoughtful interpretation of this modality to clinical decision making seems feasible and prudent to use it in decision making.

Lung ultrasound

Furthermore, a lung ultrasound score obtained in the first hours of life evaluating the patterns of aeration in different lung quadrants correlated well with CPAP level and oxygenation indices, such as alveolar-arterial gradient, oxygenation index, and arterial to alveolar ratio in infants 27 to 41 weeks.[79] Whether this information can be used to predict CPAP failure is unknown. Several of these diagnostic tools require further study before recommendation could be made for broad implementation.

We recommend against using a single antenatal risk factor or clinical finding to predict CPAP failure and implement surfactant treatment. At this point and pending further study, predicting CPAP failure depends on an individual's unique clinical characteristics. Quality of evidence: weak, based on lack of large studies and standardized criteria for defining CPAP failure. Strength of recommendation: strong, based on current available information. We also recommend that if an extremely premature neonate (<26 weeks GA) has a CXR with evidence of severe RDS, they be monitored closely and considered for early intubation and surfactant administration. Quality of evidence: moderate, based on support from multiple retrospective trials. Strength of recommendation: strong, based on ease of practice.

SUMMARY

Multiple studies support using CPAP as first-line therapy for many preterm infants requiring respiratory support. However, rates of CPAP failure remain high among neonates at highest risk for developing lung injury. Multiple interventions, from the delivery room to the NICU, stand to minimize the risk of CPAP failure. Future studies will determine whether SLI will decrease CPAP failure, and criteria used to predict CPAP failure require further refinement.

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The effect of caffeine loading on cerebral autoregulation in preterm infants

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Abstract

Aim: To evaluate cerebral autoregulation changes in preterm infants receiving a loading dose of caffeine base.

Methods: In a cohort of 30 preterm infants, we extracted measures of cerebral autoregulation using time and frequency domain techniques to determine the correlation between mean arterial pressure (MAP) and tissue oxygenation index (TOI) signals. These measures included the cerebral oximetry index (COx), cross-correlation and coherence measures, and were extracted prior to caffeine loading and in the 2 hours following administration of 10 mg/kg caffeine base.

Results: We observed acute reductions in time domain correlation measures, including the cerebral oximetry index (linear mixed-model coefficient -0.093, standard error 0.04; p = 0.028) and the detrended cross-correlation coefficient (ρ_5 coefficient -0.13, standard error 0.055; p = 0.025). These reductions suggested an acute improvement in cerebral autoregulation. Features from detrended cross-correlation analysis also showed greater discriminative value than other methods in identifying changes prior to and following caffeine administration.

Conclusion: We observed a reduced correlation between MAP and TOI from near-infrared spectroscopy following caffeine administration. These findings suggest an acute enhanced capacity for cerebral autoregulation following a loading dose of caffeine in preterm infants, contributing to our understanding of the physiological impact of caffeine therapy.

Key notes:

- Following caffeine base administration, preterm infants exhibit falls in tissue oxygenation index (TOI) and cerebral blood flow velocity.
- Preterm infants exhibited reduced correlation between arterial blood pressure and cerebral oxygenation, suggestive of enhanced cerebral autoregulation which may counter the direct effects of vasoconstriction
- Detrended cross-correlation analysis may be used to describe cerebral autoregulation in preterm infants

Introduction

Cerebral autoregulation is a mechanism by which cerebral blood flow is maintained relatively constant over a range of perfusion pressures. Impaired cerebral autoregulation is common in very preterm infants (1) and is considered a risk factor for brain injury including intraventricular haemorrhage (IVH) (2). Early work in this area advanced umbilical artery catheters to collect cerebral blood flow data (3), whereas recent studies have focused on applying analysis techniques to quantify the relationship between arterial blood pressure and the tissue oxygenation index (TOI) signal as an indirect measure of autoregulatory function (1, 4-7). The applied techniques include time domain correlation (1, 4), frequency domain coherence (5) and transfer function analyses (6, 7). Most of these studies have been cross-sectional, with consistent findings of impaired cerebral autoregulation in the more preterm, low birthweight and distressed preterm infant. There has been limited work evaluating the effect of treatments or procedures common to neonatal intensive care on the cerebral autoregulation.

Caffeine therapy is commonly administered to preterm infants, many of which are extremely premature, to reduce apnoea of prematurity and prevent the need for intubation. Caffeine is a non-specific inhibitor of adenosine receptors (8) and among the most frequently-used medication in neonatal intensive care (9). Evaluation of long-term outcomes from the Caffeine for Apnea of Prematurity (CAP) trial has shown improved neurodevelopmental outcomes at 18-21 months corrected age (10), though differences were attenuated and no longer significant at 5 years follow-up (11). At 11 years follow-up however, caffeine therapy was associated with reduced risk of motor impairment (12), though little is known on its underlying mechanisms.

Following a loading dose of caffeine, our group previously showed reduced cerebral perfusion using Doppler blood flow velocity and TOI (13), and increased pulse pressure variability from continuous arterial blood pressure data (14). The potential effect of these acute changes on cerebral autoregulation required further evaluation. A study in adults examining the effects of caffeine in 12 healthy adult subjects found an acute increase in an index of cerebral autoregulation (15). Given its capacity to attenuate adenosine-induced vasodilation (16), we hypothesise that caffeine therapy in preterm infants may have acute effects on cerebral autoregulation. The aim of this study was to evaluate these effects in a published cohort of preterm infants (13), using a range of correlation analyses, including the cerebral oximetry index (COx) proposed by Brady et al. (4), the regression coefficient (reg) and measures of mean coherence at the very low and low frequency ranges (coh_{VLF} and coh_{LF}, respectively). These techniques have previously been evaluated and compared by Eriksen et al. (17) in a cohort of preterm infants. We also sought to extend this evaluation to cross-correlation and detrended cross-correlation analyses, two additional time domain measures that may reflect changes in cerebral autoregulation.

Patients and Methods

Data collection

Physiological data were collected as part of a study approved by the Western Sydney Area Health Service Human Research and Ethics and conducted according to the World Medical Association Declaration of Helsinki. Informed parental consent was obtained in all cases. The examined cohort comprised of infants with gestational age < 34 weeks who required caffeine therapy for any of the following reasons: weaning from mechanical ventilation, reducing risk of extubation failure, and treatment of apnoea of prematurity. Infants with significant congenital anomalies and high-grade peri-intraventricular haemorrhage at time of study were excluded.

Thirty infants had concurrently available MAP and TOI data. Arterial blood pressure data were collected via an umbilical or peripheral arterial catheter via the Phillips CMS modular system (Phillip Healthcare, North Ryde, Australia). Cerebral near-infrared spectroscopy (NIRS) data were collected simultaneously via the NIRO-300 system (Hamamatsu Photonics, Hamamatsu City, Japan), with smoothed mean values acquired at 6 Hz. Both signals were recorded by an analogue data acquisition system (ADInstruments, Sydney, Australia), with 6 Hz sampling for NIRS data and 1 kHz for MAP data.

NIRS offers a measure of cerebral oxygenation by emitting and receiving NIR light at specific wavelengths (775, 825, 850 and 904 nm) to determine a range of variables: oxygenated haemoglobin (HbO_2) and deoxygenated haemoglobin (HHb). TOI is defined as:

$$TOI = \frac{HbO_2}{HbO_2 + HHb}$$

Physiological data acquisition commenced in the 20-30 minutes prior to caffeine administration. MAP and TOI data were extracted from two timepoints relative to intravenous administration of 10 mg/kg of caffeine base: i) prior to start of dose (pre-caffeine) and ii) up to 2 hours following dose completion (post-caffeine).

Signal processing

All signal processing and feature extraction were completed in Python v2.7 (Python Software Foundation, https://www.python.org/). We down-sampled the arterial blood pressure signal to 100 Hz, and completed beat-to-beat extraction of MAP. We then applied a running 10-minute window shifted in increments of 5 minutes, and extracted a range of correlation features to those that satisfied the quality criteria (pulse rate of 40-250 beats per minute). The techniques applied to the aligned time-series of MAP and TOI are described in the following sections.

Coherence analysis

Magnitude-squared coherence (MSC) is defined as:

$$MSC(f) = \frac{|S_{xy}(f)|^2}{[S_{xx}(f)S_{yy}(f)]}$$

where S_{xx} is the autospectrum of changes in mean arterial pressure, S_{yy} is the autospectrum of changes in cerebral oxygenation and S_{xy} the cross-spectrum between the two signals. Magnitude-squared coherence approaching 1 suggests an increasing linear relationship while coherence approaching 0 suggests a loss of this relationship or a potentially non-linear relationship between the given input (MAP) and output (TOI).

MAP and TOI signals were first resampled to 2 Hz in the Fourier domain. Each 10-minute running window was further divided into three 5-minute windows with 50% overlap (5). We applied a Hanning window and mean-centred both signals prior to power spectral density calculations. The coherence was then determined in the very low frequency (coh_{VLF}; <0.003 Hz) and low frequency (coh_{LF}; 0.003 – 0.004 Hz) ranges.

Time domain correlation analysis

The COx index is defined as the moving linear correlation coefficient between cerebral perfusion pressure and cerebral oximeter waveforms. They defined a sliding window of 5 minutes in length and shifted it in increments of 1 minute to obtain 6 correlation coefficient *r* values for a 10-minute epoch, with the mean of these being the calculated COx value for the given epoch (4).

The MAP and TOI signals were resampled to 0.1 Hz in the Fourier domain, and we determined the corresponding COx and corresponding regression coefficient (reg, slope of the fitted line) for each qualifying 10-minute window.

Cross-correlation analysis

Cross-correlation analysis involves incrementally shifting one signal relative to another and determining the linear correlation between them. For a positively correlated signal, the corresponding coefficient is the maximum value that this function takes, and the time delay represents shift (or lag) at which this occurs. Like in linear correlation, potential coefficient values range from -1 to 1, denoting perfectly negative and positive correlation, respectively.

As in the COx evaluation, the MAP and TOI time series were down-sampled to 0.1 Hz in the Fourier domain. We then determined the cross-correlation coefficient *r* and time delay τ within ± 30 seconds, sufficient to account for the reported <10-second time lag associated with normal autoregulation (18).

Detrended cross-correlation analysis

Detrended cross-correlation analysis is a generalisation of the detrended fluctuation analysis method (19, 20) which has been applied widely to physiological data. The corresponding coefficient ρ_{DCCA} has been proposed by Zebende et al. (19) to quantify the degree of cross-correlation between fluctuations in detrended time series at a given time scale. Like the linear correlation coefficient, it is bound by -1 and 1, however, may be better suited data where non-stationarities are present (21).

It is calculated as follows: the two series $y_1(k)$ and $y_2(k)$ with same length *N* are first mean-centred and integrated to obtain $R_1(k)$ and $R_2(k)$, respectively, where *k = 1, …, N*. For a given box size *n*, the time series are divided into *N-n* overlapping boxes and the covariance of the residuals is determined:
$f^2_{DCCA}(n,i) = 1/(n+1)\sum_{k=i}^{i+n}(R_1(k) - \tilde{R}_{1,i}(k))(R_2(k) - \tilde{R}_{2,i}(k))$ where $\tilde{R}_{1,i}(k)$ and $\tilde{R}_{2,i}(k)$ are the local linear trend in each box beginning at *i*. The covariance of residuals across all boxes is averaged to determine $F^2_{DCCA}(n)$. The coefficient ρ_{DCCA} is then expressed as:

$$\rho_{DCCA} = \frac{F^2_{DCCA}(n)}{F_{DFA1}(n)F_{DFA2}(n)}$$

where $F^2_{DCCA}(n)$ is the detrended covariance function, and $F_{DFA1}(n)$ and $F_{DFA2}(n)$ are the detrened variance functions for $y_1(i)$ and $y_2(i)$, respectively. Figure 1 shows two sets of raw MAP and TOI traces corresponding to a low and high absolute value of ρ.

To maintain consistency between the time domain analyses, we down-sampled the MAP and TOI signals to 0.1 Hz in the Fourier domain. We extracted detrended cross-correlation coefficient at the following three time scales: 1 minute (ρ_1), 2 minutes (ρ_2) and 5 minutes (ρ_5).

Statistical analysis

R version 3.4 (R Core Team, 2012) and lme4 (Bates, Maechler & Bolker, 2012) were used for statistical analysis. Statistical significance for all models was defined as $p < 0.05$. To determine the mean weighted feature for a single subject, features were weighted according to the variability (SD) of the MAP time series (5, 17). Using univariate linear regression modelling, we first determined the relationship between weighted features and the corresponding gestational age and birthweight z scores from Fenton growth charts (22). We also determined the Spearman rank correlation between the weighted features of cerebral autoregulation.

All qualifying windows were taken into consideration via linear mixed modelling. We evaluated the effect of caffeine on the extracted features, adjusting for gestational age and birthweight z scores and including a random intercept for each subject. Statistical significance of independent variables was evaluated using likelihood ratio tests of the model with and without the variable in question (23). As part of a sensitivity analysis, we

independently adjusted for IVH and low Apgar score (5-minute Apgar score < 7) in addition to the above covariates.

Results

The cohort characteristics (n = 30) are summarised in Table 1. Infants had a mean (SD) gestational age of 27 (2.3) weeks, with birthweight 1080 (400) grams and postnatal age at evaluation of 2.6 (2.2) days. A median (interquartile range; IQR) of 5 (2.8) and 24 (17.8) 10-minute windows were extracted for each patient at the pre- and post-caffeine timepoints were extracted. This corresponded to a median (IQR) duration of 30 (10) and 125 (31.2) minutes, respectively.

Effect of caffeine therapy

Figure 2 provides examples of the change in weighted mean for a) a coherence feature (coh_{LF}), b) time domain correlation analysis (COx) and c) a detrended cross-correlation feature (ρ_2). From mixed model analysis (Table 2), coherence features did not change significantly between timepoints (coh_{VLF}; p = 0.915 and coh_{LF}; p = 0.479). In contrast, caffeine base administration contributed significantly to the reduction in time domain correlation metrics: COx (p = 0.028), ρ_1 (p = 0.046), ρ_2 (p = 0.006) and ρ_5 (p = 0.025). Following adjustments of IVH and low Apgar score in two separate models, the effect of caffeine and statistical significance remained consistent.

Relationship between extracted features, gestational age and birthweight

Univariate linear regression modelling showed that coh_{LF} was mildly and inversely correlated with gestational age (linear coefficient -0.0073, standard error 00.0033; p = 0.037, supplementary table S1). In this dataset, COx and ρ_1 exhibited a negative linear relationship

with birthweight, independent of sex and gestational age. Examples of these relationships are also presented in supplementary figure S1.

Associations between cerebral autoregulation features

We identified significant associations between the time domain features (Supplementary table S2). Mean coherence at very low frequencies (coh_{VLF}) was mildly correlated with COx and ρ_5, whereas coh_{LF} was not correlated with any of time domain features, nor coh_{VLF}. COx was strongly and linearly correlated with ρ_5. The coefficient from cross-correlation was correlated with both COx and ρ_5, though the time delay was not correlated with any of the other metrics.

Discussion

In this study, we evaluated various time and frequency domain features to describe cerebral autoregulation in preterm infants following a loading dose of caffeine base. To our best knowledge, this is the first paper to examine these changes in preterm infants, and the first to apply detrended cross-correlation analysis to describe cerebral autoregulation. We observed a reduction in time domain correlation as characterised by COx, ρ_1, ρ_2 and ρ_5 in order of increasing sensitivity. Coherence in the low frequency range similarly trended towards a reduction, though was not statistically-significant. This reduced correlation between changes in TOI and those in MAP is congruent with an improved capacity to autoregulate and may offer insight into the CAP trial findings (10, 24). The findings are also in agreement with a recent study in adults (15) examining the effect of 200 mg caffeine which reported reduced cerebral blood flow with concurrent improved cerebral autoregulation, quantified by rate of regulation (25). A possible explanation for these observations may be the caffeine-induced inhibition of the adenosine receptors: adenosine induces dilation of cerebral vessels (26), and may thus play a role in cerebral autoregulation

(15, 27). The resulting cerebral vasoconstriction may then alter the dynamic autoregulation. Further work is required to understand if the observed effects are consistent in other cohorts and persist through maintenance dose administration, especially given the tolerance effect observed in adults (28).

Our original study with the same cohort showed significant reduction in two different parameters of cerebral blood flow: doppler cerebral blood velocity and reduced TOI (13), which had suggested some cause for caution. However, in the context with the potentially improved measures of cerebral autoregulation observed in this analysis, these findings suggest there may be benefits that accrue acutely following loading dose of caffeine in preterm infants at risk of impaired cerebral autoregulation.

We observed significant associations between the time domain features (Supplementary table S2), especially between COx and ρ_5, which may have been due to similar window sizes (5 minutes) over which these correlations were evaluated. The coh_{VLF} feature was associated with COx, reg and ρ_5, though in contrast, coh_{VLF} was not significantly associated with any of the extracted features. This lack of association may reflect differences in sensitivity to phase shifts between the methods. For example, a phase delay between the TOI and MAP signals may alter correlations in the time domain, while mean coherence measures may be less affected. This also suggests that time domain measures may be more sensitive in detecting changes in autoregulation. Eriksen et al. also noted that decreases in cerebral oxygenation as blood pressure increased at low frequency may lead to spuriously high coherence measures (17).

Frequency domain metrics were showed relatively poor discriminative value in this analysis. A contributing factor may have been the quantity of data available, where the infants in our cohort had median collection times of 30 and 125 minutes at pre- and post-caffeine timepoints, respectively. Previous evaluation of coherence measurements by Hahn et al. (5) found a minimum of 1.3-3.7 hours required to discriminate between patients. This approach may be better suited to long term monitoring of cerebral autoregulation, rather than the detection of acute changes as in this study.

Despite earlier speculation that the time delay may hold autoregulatory information (29), this feature was not particularly discriminative, nor related to other measures of autoregulation. The cross-correlation coefficient similarly remained unaltered by caffeine. The sampling frequency (0.1 Hz) may not have been sufficiently high to capture changes in both metrics.

The detrended cross-correlation coefficient was proposed by Zebende et al. (19) as a means of quantifying the level of cross-correlation between two non-stationary time series. In this analysis, this coefficient demonstrated strong discriminative power in identifying changes following caffeine administration, which may have been due in part to the local linear detrending inherent to its application. It is also possible that detrending or pre-processing of the signals to mitigate non-stationarities may improve the discriminative power of other methods such as the COx index, however these methods have been applied as they were originally validated and published, and validation over longer monitoring periods incorporating detrending is required.

Limitations

Data quality and the concurrent availability of MAP and TOI signals limited the available data for analysis; not all subjects had arterial blood pressure lines and of those that did (n = 30), the presence of artefact necessitated the exclusion of certain pre- or post-caffeine timepoints. The total evaluation time at each timepoint may also have been insufficient to discriminate between infants, with Hahn et al. reporting a minimum time of 1.3-3.7 hr required for coherence analysis (5). There may also have been other influencing factors which were not accounted for in statistical analysis: for example, the partial pressure of CO_2 (5) is an important regulator of cerebral blood flow and can thus affect the TOI signal. We also cannot attribute the observed effect to entirely caffeine base administration, given the absence of a control group not receiving caffeine.

Conclusion

We applied a range of time and frequency domain techniques to characterise cerebral autoregulation in preterm infants. We observed a reduction in COx and detrended cross-correlation coefficients over a range of time windows (ρ_1, ρ_2 and ρ_5), suggestive of an improved capacity of cerebral autoregulation following a loading dose of caffeine therapy. These observations help to clarify the underlying mechanisms and serve as a first step towards understanding the findings of the Caffeine for Apnoea of prematurity trial. These further observations of the caffeine cohort reported in this journal (13) help to clarify the underlying cerebrovascular physiological changes and potential mechanisms of harm and benefit. The discriminative value of the detrended cross-correlation coefficient also support its potential for cerebral autoregulation monitoring in preterm infants, an important step in understanding commonly-used treatments and risk stratification.

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Conflict of interests

The authors declare no conflict of interest.

Abbreviations

BW - birthweight

CAP - Caffeine for Apnea of Prematurity

CC - cross-correlation

coh_{LF} - low frequency coherence

coh_{VLF} - very low frequency coherence

COx - cerebral oximetry index

HBO_2 - oxygenated haemoglobin

HHB - deoxygenated haemoglobin

IQR - interquartile range

IVH - intraventricular haemorrhage

MAP - mean arterial pressure

NEC - necrotizing enterocolitis

NIRS - near-infrared spectroscopy

reg - linear regression coefficient

SD - standard deviation

TOI - tissue oxygenation index

Table 1 Summary of cohort characteristics. Continuous variables are summarised as mean (SD) and binary variables are expressed as number (percentage, %) of the specified category. IVH = intraventricular haemorrhage, NEC = necrotizing enterocolitis.

Variable	Summary (n = 30)
Gestational age (weeks)	27 (2.3)
Birthweight (grams)	1080 (400)
Male sex	16 (53.3 %)
Postnatal age caffeine loading (days)	2.6 (2.2)
Continuous Positive Airway Pressure	1 (3.3 %)
Ventilated (%)	29 (96.7 %)
Respiratory distress syndrome (%)	27 (90 %)
IVH (%)	7 (23%)
Grade I IVH	2 (6.6%)
Grade II IVH	4 (13.3%)
Grade III IVH	1 (3.3%)
Low 5 min Apgar Score (<7)	6 (20%)
Surfactant administered (%)	27 (90 %)
Died (%) NEC at 4wks	1 (3.3 %)

Table 2 Linear mixed model coefficients (standard error) and statistical significance for characterising the impact of caffeine on multivariable features, adjusted for gestational age and birthweight z scores from Fenton charts. BW = birthweight, CC = cross-correlation.

	Caffeine	p	Gestational age	p	BW z scores	P
Coh_{VLF}	-0.0035 (0.033)	0.915	-0.0016 (0.0047)	0.734	-0.023 (0.011)	0.033
Coh_{LF}	-0.0057 (0.0081)	0.479	-0.0029 (0.0021)	0.186	-0.0083 (0.0046)	0.083
COx	-0.093 (0.04)	0.028	0.0029 (0.0089)	0.746	-0.056 (0.019)	0.007
reg	-0.05 (0.047)	0.287	-0.0089 (0.01)	0.398	-0.054 (0.022)	0.039
CC r	0.017 (0.021)	0.414	-0.0044 (0.0056)	0.434	0.019 (0.012)	0.122
CC τ	0.024 (0.22)	0.913	0.035 (0.039)	0.377	0.012 (0.087)	0.889
ρ_1	-0.061 (0.029)	0.046	0.0013 (0.0066)	0.84	-0.05 (0.014)	0.002
ρ_2	-0.12 (0.04)	0.006	-0.0015 (0.01)	0.885	-0.048 (0.021)	0.034
ρ_5	-0.13 (0.055)	0.025	0.003 (0.015)	0.845	-0.054 (0.032)	0.107

Figure legends

Figure 1 Examples of mean arterial pressure (MAP) and tissue oxygenation (TOI) traces corresponding to a lesser ρ (panels a and c) and greater ρ (panels b and d). Closed and open circles denote MAP and TOI time series, respectively.

Figure 2 Changes in cerebral autoregulation prior to (pre) and in the 2 hours following (post) caffeine administration, measured by a) coh_{LF}, b) COx and c) ρ_2. Each point represents the MAP variability (SD) weighted features for each patient at each of the pre- and post-caffeine timepoints.

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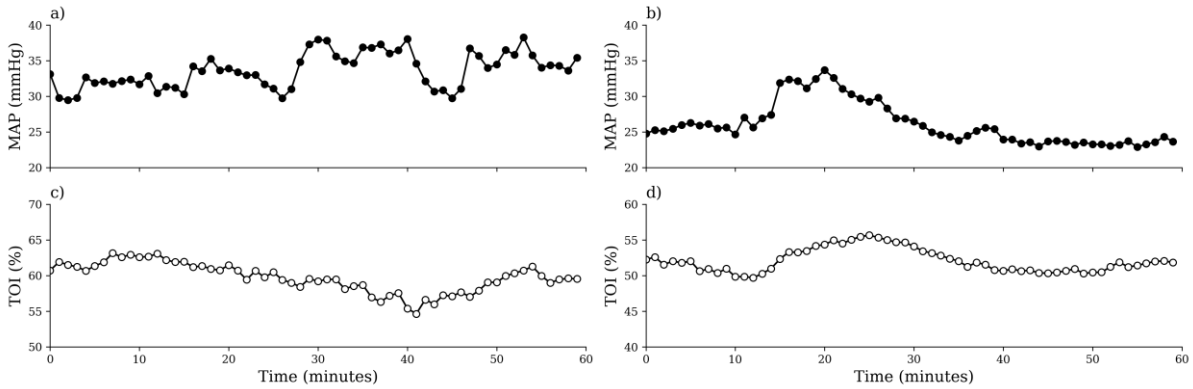

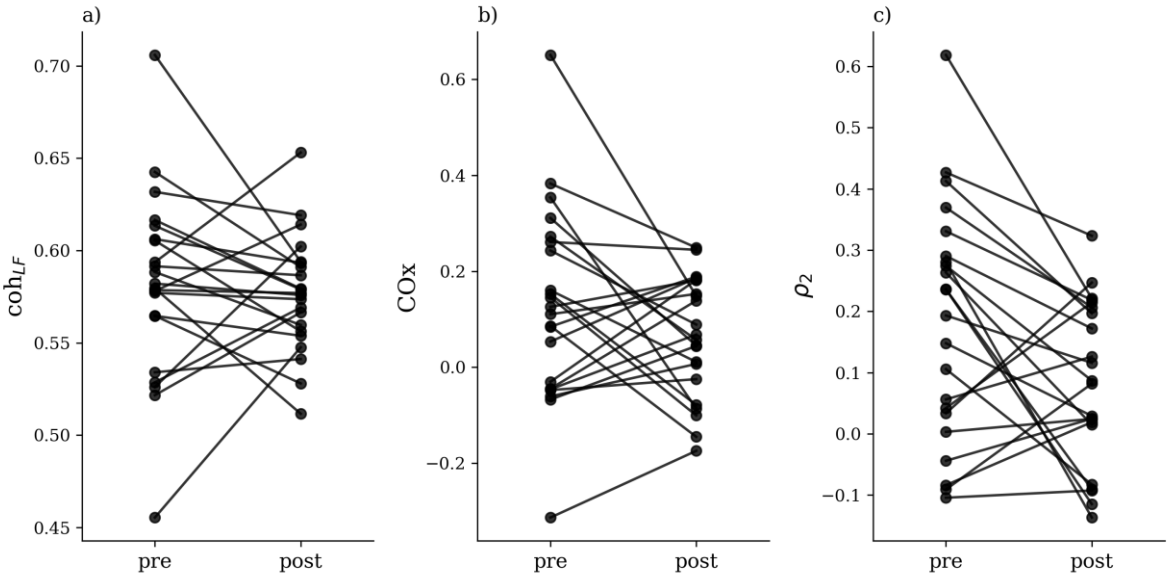

Effect of Prophylaxis for Early Adrenal Insufficiency Using Low-Dose Hydrocortisone in Very Preterm Infants: An Individual Patient Data Meta-Analysis

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Objective To assess the effect of prophylaxis for early adrenal insufficiency using low-dose hydrocortisone on survival without bronchopulmonary dysplasia (BPD) in very preterm infants using an individual patient data meta-analysis.

Study design All existing randomized controlled trials testing the efficacy of the prophylaxis of early adrenal insufficiency using low-dose hydrocortisone on survival without BPD were considered for inclusion when data were available. The primary outcome was the binary variable survival without BPD at 36 weeks of postmenstrual age.

Results Among 5 eligible studies, 4 randomized controlled trials had individual patient data available (96% of participants identified; n = 982). Early low-dose hydrocortisone treatment for 10-15 days was associated with a significant increase in survival without BPD (OR, 1.45; 95% CI, 1.11-1.90; $P = .007$; $I^2 = 0\%$), as well as with decreases in medical treatment for patent ductus arteriosus (OR, 0.72; 95% CI, 0.56-0.93; $P = .01$; $I^2 = 0\%$) and death before discharge (OR, 0.70; 95% CI, 0.51-0.97; $P = .03$; $I^2 = 0\%$). The therapy was associated with an increased risk of spontaneous gastrointestinal perforation (OR, 2.50; 95% CI, 1.33-4.69; $P = .004$; $I^2 = 31.9\%$) when hydrocortisone was given in association with indomethacin exposure. The incidence of late-onset sepsis was increased in infants exposed to hydrocortisone (OR, 1.34; 95% CI, 1.02-1.75; $P = .04$; $I^2 = 0\%$), but no adverse effects were reported for either death or 2-year neurodevelopmental outcomes as assessed in an aggregate meta-analysis.

Conclusions This individual patient data meta-analysis showed that early low-dose hydrocortisone therapy is beneficial for survival without BPD in very preterm infants. *(J Pediatr 2018;■■:■■-■■).*

See related article, p •••

Bronchopulmonary dysplasia (BPD) is a major morbidity of very preterm birth, associated with increased risk for broad array of adverse outcomes, including respiratory complications, growth failure, neurodevelopmental impairment (NDI), and death.[1] In contrast to many other morbidities of preterm infants, its incidence has not decreased over time and actually may be increasing.[2] Evidence of early lung inflammation in infants developing BPD[2-5] had led to early treatment with high doses of anti-inflammatory glucocorticoids such as dexamethasone, resulting in short-term improvement but unacceptable short-term and long-term adverse effects.[6] The use of lower doses and alternative formulations may improve the risk:benefit.[7] Jobe recently suggested that clinicians reconsider postnatal corticosteroid treatments together with continued efforts to minimize oxygen and ventilation injury in very preterm infants to decrease the incidence and severity of BPD.[8]

Data reported since 1995 have supported the hypothesis that very preterm infants who develop BPD often have relative adrenal insufficiency during the first postnatal week, suggesting that early hydrocortisone replacement could be beneficial.[4,9,10] Among 11 randomized controlled trials (RCTs) that included hydrocortisone treatment initiated before 7 postnatal days in very preterm infants,[7] 5 were designed specifically to test the efficacy of early prophylaxis of early adrenal insufficiency

BPD	Bronchopulmonary dysplasia
NDI	Neurodevelopmental impairment
PDA	Patent ductus arteriosus
PMA	Postmenstrual age
RCT	Randomized controlled trial

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to improve survival without BPD.[11-15] These trials extended hydrocortisone therapy beyond the first postnatal week and used a dose of 1-2 mg/kg/day, which has been shown to moderately but significantly increase serum cortisol concentrations in extremely preterm neonates compared with placebo.[12]

Although 2-year follow-up data have been consistently reassuring,[7,16-19] the effect of early hydrocortisone treatment on survival without BPD and potential side effects remain unclear. Therefore, we undertook an individual patient data meta-analysis of clinical trials to examine the effect of prophylaxis of early adrenal insufficiency on these outcomes.

Methods

The PRISMA-IPD checklist of items requested to report a meta-analysis of individual patient data is available at www.jpeds.com (**Supplement**). In addition, some data items are available in the statistical analysis plan (**Appendix**; available at www.jpeds.com). Two meta-analyses identified published RCTs of early hydrocortisone therapy conducted before 2017.[7,20] We also searched MEDLINE for the terms "hydrocortisone," "cortisone," "preterm infant," "randomized," and "human." The last search was done in July 2018. We did not identify any RCTs of early low-dose hydrocortisone therapy to prevent BPD other than those included in these 2 reports.

Individual Patient Data Acquisition, Data Processing, and Quality Assessment

The principal investigators of the 5 eligible trials agreed to share deidentified data to perform an individual patient data meta-analysis. Individual patient data from 1 pilot trial (n = 40) were no longer available[11]; this individual patient data meta-analysis includes all data from the remaining 4 studies (n = 982). Because an individual patient data meta-analysis can improve the ability to address confounders or covariates of interest, we were able to account for individual patient-level factors that affected outcomes, which would not have been possible with an aggregate meta-analysis based on published data without the risk of drawing potentially incorrect conclusions owing to ecological fallacy with the application of meta-regression. In addition, meta-regression often has low power to detect relationships.[21-23] Individual patient data also allowed for inclusion of data not previously reported and standardization of outcomes and exposures across studies. In addition, the cooperation of all authors of the original publications allowed for detailed data checking.

We created a common data dictionary and asked corresponding authors to identify which data elements were available, or to suggest alternative measures if data were not available. After receiving all authors' available data, we created a final data capture template to request the individual patient datasets from all authors to reduce the amount of postprocessing needed to harmonize the datasets. Any questions regarding the individual patient datasets were discussed with the authors and corrected.

The statistician created any necessary derived variables and checked the summary statistics against available published data. All data summaries by study and treatment group were shared with the corresponding authors to check for discrepancies, and any identified errors were corrected.

Outcomes and Subgroups of Interest

The primary outcome of interest was the binary variable survival without BPD at 36 weeks postmenstrual age (PMA), and the primary predictor was receipt of early low-dose hydrocortisone treatment. Adjustment variables to be included in all models were birth weight, sex, gestational age, and antenatal steroid use. Predefined subgroups of interest included sex, histologic chorioamnionitis, gestational age strata (<26 or ≥26 weeks), and indomethacin treatment.

Secondary outcomes included days of ventilation, continuous positive airway pressure, and oxygen; supplemental oxygen at discharge; and medical or surgical treatment for patent ductus arteriosus (PDA). Prespecified potential adverse outcomes included pneumothorax, spontaneous gastrointestinal perforation, necrotizing enterocolitis, severe intraventricular hemorrhage, cystic periventricular leukomalacia, severe retinopathy of prematurity, late onset sepsis (bacterial or fungal), and the effects of hydrocortisone on weight or head circumference at 36 weeks PMA and on the 2-year neurodevelopmental outcomes.

Statistical Analyses

An a priori statistical analysis plan (**Appendix**) was created to describe and prioritize the outcomes and analyses of interest, including subgroup and sensitivity analyses, before the analysis was begun. No multiple comparisons adjustments were used for subgroup analyses. We used a 1-step approach to individual patient data meta-analysis using generalizations of logistic regression models for binary outcomes and linear regression models for quantitative outcomes based on generalized linear mixed models with Kenward-Roger approximation of degrees of freedom.[24,25] Logistic regression models were summarized using ORs and associated 95% CIs. Linear regression models were summarized using mean differences and associated CIs. We attempted to account for clustering of patients within different studies by specifying a random intercept term, assuming that the baseline is drawn at random from a normal distribution. We first considered treatment a random effect, but then simplified the models to fixed treatment effects, which yielded similar findings in terms of magnitude, direction, and significance. Statistical heterogeneity was summarized as I^2 value and associated P value. I^2 values were computed using the meta package in R (R Foundation for Statistical Computing, Vienna, Austria). We also conducted a traditional aggregate random-effects meta-analysis based on available published data for comparison of long-term developmental outcomes.[16-18]

Statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, North Carolina) for the individual patient data analysis and using Stata 12.0 (StataCorp, College Station, Texas) for the aggregate meta-analysis. Findings were considered significant at $P < .05$.

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Results

Among 11 RCTs testing hydrocortisone early after birth in neonates (**Table I**; available at www.jpeds.com), 5 were specifically designed to test the efficacy of prophylaxis of early adrenal insufficiency to improve survival without BPD.[11-15] The other 6 trials were excluded because of significant differences in study design, such as larger study group and use of hydrocortisone at higher doses[26] or for a different purpose, including refractory hemodynamic failure,[27-30] or in combination with another treatment.[26,31] The PRISMA-IPD flow diagram is depicted in the **Figure** (available at www.jpeds.com).

Although this individual patient data meta-analysis was not prospectively planned, the studies were quite similar in hypothesis, design, and primary outcome. As shown in **Table II**, patient eligibility varied slightly across the studies, as did the dose and duration of hydrocortisone therapy; however, these differences were minor and the populations were generally comparable. **Table III** presents summary statistics by study and treatment group for all patient characteristics and primary and secondary outcomes of interest.

Primary Outcome

Table IV presents the results of the individual patient data meta-analysis for the primary outcome and its components. **Table V** (available at www.jpeds.com) provides heterogeneity estimates of individual patient data meta-analysis of all outcomes unadjusted. Heterogeneity was low in most of the outcomes, with the exception of a few respiratory support items for which not all trials had data available.

Treatment with early low-dose hydrocortisone was associated with greater odds of survival without BPD at 36 weeks PMA (unadjusted OR, 1.37; 95% CI, 1.07-1.76). Findings were similar after adjustment for sex, gestational age, and antenatal steroid use (aOR, 1.45; 95% CI, 1.11-1.90; $I^2 = 0\%$). For the components of the primary outcome, receipt of hydrocortisone was associated with significantly lower odds of BPD (aOR, 0.73; 95% CI, 0.54-0.98; $I^2 = 0\%$), but not with a significant decrease in death before 36 weeks PMA (aOR, 0.76; 95% CI, 0.54-1.07; $I^2 = 0\%$). However, hydrocortisone treatment was associated with a significant decrease in death before discharge (aOR, 0.70; 95% CI, 0.51-0.97; $I^2 = 0\%$).

Secondary Outcomes

Table IV also presents the results of the individual patient data meta-analysis for all secondary outcomes. Days of ventilation, continuous positive airway pressure, and oxygen were not significantly different between the hydrocortisone and placebo groups, and BPD severity was similar in the 2 groups. There was no significant difference in exposure to oxygen at discharge. There were significantly lower odds of any medical treatment for PDA (aOR, 0.72; 95% CI, 0.56-0.93; $I^2 = 0\%$), including both indomethacin and ibuprofen; however, there was no difference in the odds of ligation.

Exposure to hydrocortisone was associated with a significant increase in spontaneous gastrointestinal perforation (aOR, 2.50; 95% CI, 1.33-4.69; $I^2 = 31.9\%$). However, in the absence of indomethacin cotreatment, hydrocortisone was not associated with a significant increase in gastrointestinal perforation (**Table VI**). Exposure to hydrocortisone also was associated with significantly increased odds of late sepsis, both bacterial and fungal (aOR, 1.34; 95% CI, 1.02-1.75; $I^2 = 0\%$). This observed difference was not associated with increased mortality or other in-hospital adverse outcomes, or with any detectable adverse effect on 2-year neurodevelopmental outcomes in the hydrocortisone-treated group. There were no significant differences between the hydrocortisone and placebo groups for any of the remaining adverse outcomes (**Table IV**) of

Table II. Characteristics of 4 included studies providing individual patient data

Characteristics	Sources			
	Watterberg et al, 2004[12]	Peltoniemi et al, 2005[13]	Bonsante et al, 2007[14]	Baud et al, 2016[15]
Country	US	Finland	Italy	France
Funding source	National Institute of Child Health and Human Development	Foundation for Pediatric Research	University of Bari	Public Hospitals of Paris
Ethics Committee review	Yes	Yes	Yes	Yes
Parental informed consent	Yes	Yes	Yes	Yes
Loss to follow-up for primary outcome, n/N (%)	3/360 (<1)	None	None	2/523 (<1)
Design	Double-blind RCT	Double-blind RCT	Double-blind RCT	Double-blind RCT
Inclusion criteria				
Gestational age, wk		$23^{0/7}$-$29^{6/7}$	$24^{0/7}$-$29^{6/7}$	$24^{0/7}$-$27^{6/7}$
Birth weight, g	500-999 g	501-1250	500-1249	
Respiratory status	Need for mechanical ventilation at study entry	Need for mechanical ventilation before 24 h of life*	Need for mechanical ventilation after rescue surfactant	
Enrolled	Between 12 and 48 h postnatal age	Before 36 h	Before 48 h	Before 24 h
Duration of exposure	1 mg/kg/d for 12 d, then 0.5 mg/kg/d for 3 d	10 d tapered from 2.0 to 0.75 mg/kg/d	1 mg/kg/d divided into 2 doses/d for 9 d, then 0.5 mg/kg/d for 3 d	1 mg/kg/d divided into 2 doses/d for 7 d, then 0.5 mg/kg/d for 3 d

If an empty cell appears under inclusion criteria, the study did not have this criterion specified.
*A subgroup of infants with birth weight of 1000-1250 g had the additional requirement of supplemental oxygen and mechanical ventilation beyond 24 h despite surfactant therapy.

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Table III. Patient characteristics and outcomes of 4 included studies providing individual patient data

Source	Watterberg et al, 2004[12]		Peltoniemi et al, 2005[13]		Bonsante et al, 2007[14]		Baud et al, 2016[15]	
Characteristic	Hydrocortisone (n = 180)	Placebo (n = 180)	Hydrocortisone (n = 25)	Placebo (n = 26)	Hydrcortisone (n = 25)	Placebo (n = 25)	Hydrocortisone (n = 255)	Placebo (n = 266)
Birth weight, g, mean (SD)	730 (126)	734 (126)	888 (204)	903 (220)	840 (200)	869 (189)	867 (151)	862 (160)
Gestational age, wk, mean (SD)	25.2 (1.5)	25.3 (1.7)	26.7 (1.6)	26.9 (1.5)	26.2 (1.5)	26.3 (1.9)	26.4 (0.9)	26.4 (0.9)
Female sex, n (%)	84 (46.7)	90 (50.0)	9 (36.0)	12 (46.2)	12 (48.0)	9 (36.0)	124 (48.6)	117 (44.0)
Race, n (%)								
White	108 (60.0)	93 (51.7)	25 (100)	26 (100)	25 (100)	25 (100)	105/247 (42.5)	112/259 (43.2)
Black	65 (36.1)	70 (38.9)	0	0	0	0	101/247 (40.9)	96/259 (37.1)
Asian	3 (1.7)	12 (6.7)	0	0	0	0	8/247 (3.2)	12/259 (4.6)
Other	3 (1.7)	4 (2.2)	0	0	0	0	31/247 (12.6)	36/259 (13.9)
Unknown	1 (0.6)	1 (0.6)	0	0	0	0	2/247 (0.8)	3/259 (1.2)
Antenatal steroid use, n (%)	138 (76.7)	146 (81.1)	23 (92.0)	25 (96.2)	17 (68.0)	20 (80.0)	238 (93.3)	246 (92.8)
Rupture of membranes >24 h, n (%)	42/168 (25.0)	47/172 (27.3)	5 (20.0)	5 (19.2)			76 (29.8)	83 (31.2)
Vaginal delivery, n (%)	77 (42.8)	63 (35.0)	14 (56.0)	13 (50.0)	4 (16.0)	4 (16.0)	132/254 (52.0)	143/264 (54.2)
Histologic chorioamnionitis, n (%)	73/140 (52.1)	78/146 (53.4)	7/15 (46.7)	7/14 (50.0)	9 (36.0)	13 (52.0)	62/218 (28.4)	72/240 (30.0)
Preeclampsia, n (%)	24 (13.3)	30 (16.7)	4 (16.0)	6 (23.1)	8 (32.0)	4 (16.0)	34 (13.3)	23 (8.7)
Multiple birth, n (%)	42 (23.3)	38 (21.1)	5 (20.0)	7 (26.9)	4 (16.0)	5 (20.0)	82 (32.2)	90 (33.8)
Inborn, n (%)	152 (84.4)	165 (91.7)	25 (100)	26 (100)	25 (100)	25 (100)	255 (100)	266 (100)
Intubated at entry, n (%)	180 (100)	180 (100)	25 (100)	26 (100)	25 (100)	25 (100)	204 (80.0)	218 (82.0)
Age at entry, h, mean (SD)	31.4 (11.2)	33.1 (12.1); n = 178	27.2 (13.5); n = 24	21.5 (9.6)	13.5 (8.9)	13.3 (12.1)	15.2 (11.6); n = 253	14.4 (11.8); n = 265
Inotropic therapy at entry, n (%)	72 (40.0)	62 (34.4)	17 (68.0)	16 (61.5)	16 (84.0)	21 (84.0)	75 (29.4)	95 (35.7)
Outcomes at 36 wk PMA, n (%)								
Survival without BPD	73/179 (40.8)	67/178 (37.6)	16 (64.0)	14 (53.9)	16 (64.0)	8 (32.0)	153 (60.0)	136 (51.1)
Death	27/179 (15.1)	28/178 (15.7)	2 (8.0)	1 (3.9)	3 (12.0)	9 (36.0)	47 (18.4)	60 (22.6)
BPD	79/152 (52.0)	83/150 (55.3)	7/23 (30.4)	11/25 (44.0)	6/22 (27.3)	8/16 (50.0)	55/208 (26.4)	70/206 (34.0)
Weight, mean (SD)	2.01 (0.32); n = 150	2.03 (0.35); n = 147	2.00 (0.30); n = 22	1.95 (0.30); n = 24	1.74 (0.28); n = 21	1.81 (0.38); n = 14	2.09 (0.33); n = 197	2.11 (0.32); n = 194
Head circumference, cm, mean (SD)	31.2 (1.5); n = 147	30.9 (1.6); n = 145	31.8 (1.3); n = 22	31.2 (1.5); n = 23	30.7 (2.1); n = 17	30.7 (2.0); n = 14	30.8 (1.6); n = 160	30.8 (1.5); n = 155
Respiratory support								
Days of ventilation, median (IQR)	26 (9-50); n = 178	30 (13-46); n = 176	4 (2-17)	13 (3-40)	4 (2-21); n = 23	15 (2-27); n = 19		
Days of CPAP, median (IQR)			16 (2-28); n = 22	25 (17-32); n = 24	15 (5-27)	9 (0-20)		
Days of oxygen, median (IQR)	73 (40-102); n = 178	71 (32-95); n = 176	55 (35-91)	93 (41-162)	58 (26-72); n = 23	50 (28-76); n = 19		
Oxygen at discharge, n/N (%)	56/150 (37.3)	58/146 (39.7)	0/23	1/23 (4.4)	0/21	0/15	17/207 (8.2)	16/202 (7.9)
Open-label steroid use, n (%)	72 (40.0)	76 (42.2)	11 (44.0)	15 (57.7)	7 (28.0)	12 (48.0)	105 (41.2)	108 (40.6)
Pneumothorax, n (%)	23 (12.8)	18 (10.0)	1 (4.0)	3 (11.5)	2 (8.0)	4 (16.0)	5 (2.0)	7 (2.6)
Insulin treatment, n (%)	74 (41.1)	62 (34.4)	9 (36.0)	7 (26.9)	9 (36.0)	10 (40.0)	112 (43.9)	115 (43.2)
Treatment for PDA, n (%)								
Medical treatment (indomethacin or ibuprofen)	69 (38.3)	73 (40.6)	9 (36.0)	17 (65.4)	5 (20.0)	9 (36.0)	119 (46.7)	147 (55.3)
Any prophylactic indomethacin	127 (70.6)	123 (68.3)	4 (16.0)	8 (30.8)	0	0	0	0
Surgical ligation	26 (14.4)	21 (11.7)	5 (20.0)	7 (26.9)	0	0	37 (14.5)	55 (20.7)
Necrotizing enterocolitis, n (%)	7 (3.9)	14 (7.8)	2 (8.0)	1 (3.9)	1 (4.0)	2 (8.0)	17 (6.7)	12 (4.5)
Spontaneous gastrointestinal perforation, n/N (%)	17/178 (9.6)	4/180 (2.2)	4 (16.0)	0	1 (4.0)	0	13 (5.1)	11/(4.1)
Late-onset sepsis (bacterial/fungal), n (%)	80 (44.4)	73 (40.6)	8 (32.0)	4 (15.4)	8 (32.0)	5 (20.0)	80 (31.4)	66 (24.8)
Severe IVH (grade 3-4), n/N (%)	33/172 (19.2)	29/176 (16.5)	4 (16.0)	3 (11.5)	1 (4.0)	2 (8.0)	38 (14.9)	37 (13.9)
Cystic PVL, n/N (%)	12/142 (8.5)	10/142 (7.0)	5 (20.0)	3 (11.5)	1 (4.0)	2 (8.0)	4 (1.6)	10 (3.8)
Severe ROP, n/N (%)	41/153 (26.8)	47/150 (31.3)	1 (4.0)	1 (3.9)	4 (16.0)	4 (16.0)	4 (1.6)	2 (0.8)
Death before discharge, n (%)	31 (17.2)	32 (17.8)	2 (8.0)	3 (11.5)	4 (16.0)	10 (40.0)	48 (18.8)	67 (25.2)

CPAP, continuous positive airway pressure; *IVH*, intraventricular hemorrhage; *PVL*, periventricular leukomalacia; *ROP*, retinopathy of prematurity.
For any cell with missing data, the denominator is provided within the cell. An empty cell indicates that not of the data were not available.

Table IV. Results of individual patient data meta-analysis of all outcomes adjusted for sex, gestational age, and any antenatal steroids

Outcomes	Hydrocortisone	Placebo	OR or Mean Difference	95% CI of OR or Mean Difference	*P* Value
Survival without BPD at 36 wk PMA, n/N (%)	258/484 (53.3)	225/495 (45.5)	1.45	1.11-1.90	.007
Death before 36 wk PMA, n/N (%)	79/484 (16.3)	98/495 (19.8)	0.76	0.54-1.07	.12
BPD at 36 wk PMA, n/N (%)	147/405 (36.3)	172/397 (43.3)	0.73	0.54-0.98	.038
Death before discharge, n/N (%)	85/485 (17.5)	112/497 (22.5)	0.70	0.51-0.97	.0327
Weight at 36 wk PMA, g, mean	2036 (n = 390)	2061 (n = 379)	−24.11	−71.36 to 23.14	.32
Head circumference at 36 wk, cm, mean	31.0 (n = 346)	30.9 (n = 337)	0.19	−0.05 to 0.42	.12
Respiratory support					
Days of ventilation, mean	32.3 (n = 226)	31.7 (n = 221)	−0.63	−7.28 to 6.01	.85
Days of CPAP, mean	17.2 (n = 47)	17.7 (n = 49)	−0.12	−5.78 to 5.55	.97
Days of oxygen, mean	74.1 (n = 226)	75.2 (n = 221)	−2.17	−12.07 to 7.73	.67
Oxygen at discharge, n/N (%)	73/401 (18.2)	75/386 (19.4)	0.92	0.64-1.33	.65
Open-label steroid use, n/N (%)	195/485 (40.2)	211/497 (42.5)	0.90	0.70-1.17	.44
Pneumothorax, n/N (%)	31/485 (6.39)	32/497 (6.44)	0.98	0.58-1.64	.93
Insulin treatment, n/N (%)	204/485 (42.1)	194/497 (39.0)	1.12	0.86-1.45	.42
Medical treatment for PDA (indomethacin or ibuprofen), n/N (%)	202/485 (41.7)	246/497 (49.5)	0.72	0.56-0.93	.012
Any prophylactic indomethacin, n/N (%)	61/485 (12.6)	63/497 (12.7)	0.96	0.65-1.41	.83
Surgical ligation, n/N (%)	68/485 (14.0)	83/497 (16.7)	0.80	0.56-1.14	.21
Necrotizing enterocolitis, n/N (%)	27/485 (5.57)	29/497 (5.84)	0.95	0.55-1.63	.85
Spontaneous gastrointestinal perforation	35/483 (7.25)	15/497 (3.02)	2.50	1.33-4.69	.004
Late-onset sepsis (bacterial/fungal), n/N (%)	176/485 (36.3)	148/497 (29.8)	1.34	1.02-1.75	.0357
Severe IVH (grade 3-4), n/N (%)	76/477 (15.9)	71/493 (14.4)	1.10	0.76-1.59	.60
Cystic PVL, n/N (%)	22/447 (4.92)	25/459 (5.45)	0.89	0.49-1.60	.69
Severe ROP, n/N (%)	50/458 (10.9)	54/467 (11.6)	0.92	0.59-1.45	.72

pneumothorax, necrotizing enterocolitis, severe intraventricular hemorrhage, cystic periventricular leukomalacia, and severe retinopathy of prematurity. There also were no significant differences in weight or head circumference at 36 weeks PMA between the 2 groups.

Table VI. Subgroup analyses of primary outcome and other selected outcomes adjusted for sex, gestational age, and any antenatal steroids unless the adjustment factor is used to define the subgroup

Outcomes	OR	95% CI	*P* value
Survival to 36 wk without BPD			
Male	1.40	0.97-2.02	.074
Female	1.52	1.02-2.26	.038
Gestational age <26 wk	1.38	0.91-2.09	.13
Gestational age ≥26 wk	1.52	1.07-2.17	.020
No chorioamnionitis	1.40	0.97-2.02	.074
Chorioamnionitis	2.01	1.19-3.39	.009
Death before discharge			
Male	0.73	0.47-1.14	.17
Female	0.66	0.41-1.07	.094
Gestational age <26 wk	0.87	0.58-1.32	.53
Gestational age ≥26 wk	0.46	0.26-0.82	.008
No chorioamnionitis	0.71	0.44-1.15	.16
Chorioamnionitis	0.43	0.23-0.82	.010
Late-onset sepsis			
Male	1.41	0.96-2.05	.076
Female	1.23	0.83-1.83	.29
Gestational age <26 wk	1.60	1.08-2.37	.019
Gestational age ≥26 wk	1.14	0.78-1.65	.50
No chorioamnionitis	1.06	0.72-1.55	.77
Chorioamnionitis	1.91	1.18-3.08	.009
Spontaneous gastrointestinal perforation			
No indomethacin	1.52	0.73-3.15	.26
Indomethacin	9.37	2.02-43.49	.004

Planned Subgroup Analyses

Table VI summarizes the effect of treatment group on the primary study outcome as well as on late-onset sepsis and mortality before discharge, by subgroup of interest (sex, gestational age, histologic chorioamnionitis, and indomethacin exposure) adjusted for sex, gestational age, and any antenatal steroids unless the adjustment factor is used to define the subgroup of interest. Although individual odds ratios vary somewhat among subgroups, the effect is generally consistent for improvement in survival without BPD at 36 weeks PMA. Of particular interest is that the effect was similar for boys and girls. The outcomes for the subgroup chorioamnionitis showed that the incidence of late-onset sepsis was significantly increased (OR, 1.91; 95% CI, 1.18-3.08), but at the same time the incidence of survival without BPD was increased (OR, 2.01; 95% CI, 1.19-3.39) and mortality before discharge was decreased (OR, 0.43; 95% CI, 0.23-0.82).

The results of the individual patient data meta-analysis were compared with aggregate meta-analysis based on the published data of the four studies included. For the aggregate meta-analysis of the four studies, there was no significant difference in the odds of survival without BPD at 36 weeks PMA (OR, 1.40; 95% CI, 0.98-2.00).

Long-Term Outcomes

Because of differences in assessment tools used (the Griffiths Developmental Scale, Bayley Scale of Infant Development, and revised Brunet-Lezine Scale), only cerebral palsy (CP) and NDI were compared in 709 of 785 (90%) and 706 of 785 (90%) children at age 2 years, respectively, using aggregate meta-analysis. These analyses were performed based on the available data collected from the 4 RCTs included in the individual patient data

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meta-analysis (**Table VII**; available at www.jpeds.com).[16-18] Hydrocortisone therapy did not show a significant benefit; however, the direction of effect consistently favored the hydrocortisone-treated group for NDI (OR, 0.76; 95% CI, 0.52-1.12). For CP, individual study results were mixed in direction, but overall there was no significant relationship between hydrocortisone exposure and CP (OR, 0.95; 95% CI, 0.56-1.60).

Discussion

In this study, an individual patient data meta-analysis of 4 published RCTs showed that early low-dose hydrocortisone treatment in very preterm infants was associated with significantly increased survival without BPD, as well as a decreased need for PDA treatment and reduced mortality before discharge. The fifth published study of this therapy, a 40-patient pilot RCT for which data were no longer available, also showed a benefit; therefore, its omission does not affect the conclusions of our analysis.[11]

Other findings of note include a significant decrease in the incidence of treatment for PDA in infants treated with hydrocortisone. We have previously reported significantly lower cortisol concentrations in infants diagnosed with PDA, as well as in infants who subsequently develop BPD,[4,9,32] suggesting that adrenal insufficiency may be a contributing factor to the well-known association of PDA with BPD.[33] In addition, in the absence of indomethacin exposure, hydrocortisone therapy did not have an effect on the incidence of spontaneous gastrointestinal perforation. Studies in which ibuprofen was used as treatment for PDA also reported no effect of hydrocortisone therapy on perforation.[14,15,17]

Our analysis confirms an association between early low-dose hydrocortisone exposure and late-onset sepsis; nonetheless, treatment was associated with a significantly improved survival without BPD at 36 weeks PMA and survival to discharge, with no adverse effects on neurodevelopmental outcomes at 2 years.[16-19] Follow-up of a small number of children (n = 27) at age 5-7 years suggested a correlation between early hydrocortisone treatment and later neurocognitive impairment[34]; however, the 2-year outcomes of 694 children enrolled in all these studies showed no adverse neurodevelopmental effects and identified possible benefits. Longer-term follow-up of previous cohort studies also have been reassuring.[35] Children in the PREMILOC study will be assessed at age 5-7 years.[18]

Planned subgroup analyses showed that hydrocortisone appears to be similarly efficacious for both boys and girls. The direction of effect was beneficial in both gestational age strata; however, effects were more pronounced in the infants born at ≥26 weeks of gestation, consistent with the increased fragility and resistance to therapies of the most immature infants.[2] In the presence of chorioamnionitis, the incidence of late-onset sepsis was increased with hydrocortisone therapy, but a benefit was still seen in the primary outcome and in survival to discharge. Chorioamnionitis is a risk factor for late-onset sepsis[36]; treatment with hydrocortisone may affect the immune response, yet reduce inflammatory injury and thereby improve outcomes in exposed infants, because systemic inflammation has been shown to precede clinical symptoms of the early phase of BPD.[5] As always, subgroup analyses, even when preplanned, should be interpreted with caution.

Only 5 trials, including the 4 included in this analysis and that reported by Watterberg et al in 1999,[11] were specifically designed to assess the effect of early low-dose hydrocortisone as prophylaxis of early adrenal insufficiency in very preterm infants. Four other RCTs tested the effect of early hydrocortisone in hypotensive preterm infants,[27-30] including 1 trial testing hydrocortisone in association with dopamine[30] and 1 trial investigating the effect of early triiodothyronine therapy on mortality and respiratory morbidity that included low-dose hydrocortisone as an adjunct therapy.[31] Those studies found no significant benefit in survival without BPD at 36 weeks; however, the shorter treatment periods in those studies might have affected their results. We have reported lower cortisol concentrations and a decreased response to ACTH stimulation continuing beyond the first postnatal week in infants who subsequently developed BPD.[9,32,37]

Strengths of this study include access to individual patient data for 982 patients, harmonization of data and outcome definitions across studies, and very close comparability of the study populations and the therapeutic intervention. Our results differ from those of an aggregate meta-analysis of the 4 studies showing no difference in the odds of survival without BPD at 36 weeks PMA, demonstrating that an individual patient data meta-analysis can improve the ability to address important confounders at the individual patient level.

Limitations of the study include the loss of 40 patients in the original pilot study[11] and loss of accuracy regarding the time of first dose. In addition, exposure to indomethacin as a confounding variable was not balanced across all studies.

In conclusion, this individual patient data meta-analysis shows that early, low-dose hydrocortisone therapy provides significant benefits in survival without BPD, PDA closure, and survival to discharge in very preterm infants. Increases in intestinal perforation and late-onset sepsis, 2 reported adverse effects of this hydrocortisone treatment, did not appear to negate the overall benefits of hydrocortisone in this population. ■

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Appendix

Brief Statistical Analysis Plan for Hydrocortisone Meta-Analysis

Overview. Five RCTs that tested low-dose hydrocortisone during the first postnatal days with the primary outcome of improving survival without BPD have been completed and published. Individual patient data are no longer available for the first trial of 40 patients. We will conduct an individual patient data meta-analysis of the remaining 4 trials. Although this individual patient data meta-analysis was not prospectively planned, the studies are quite similar in hypothesis, design, and primary outcome. Patient eligibility varies slightly across the studies, as do the dose and duration of hydrocortisone therapy; however, these differences are minor, and the populations generally overlap.

Data Analysis. Descriptive data will be presented for each study when available, and overall, including the variables shown in **Appendix Table I**. We will take a 1-step approach to individual patient data meta-analysis using generalizations of logistic regression models for binary outcomes and linear regression models for quantitative outcomes based on generalized linear mixed models with Kenward-Rogers approximation of degrees of freedom. We will account for clustering of patients within different studies by specifying a random intercept term, assuming that the baseline is drawn at random from a normal distribution. We will consider treatment a random effect and adjustment factors random effects. We will assume different residual variances for each study because patient eligibility varies slightly from study to study, as well as dose and duration of hydrocortisone therapy. Simplifications of modeling assumptions, such as fixed effects in place of random effects and a common residual variance, will be considered if models fail to converge.

The primary outcome of interest is the binary variable survival without BPD at 36 weeks, and the primary predictor is receipt of hydrocortisone treatment. Primary and secondary outcomes of interest are summarized in **Appendix Table II**. Adjustment variables included in all models are birth weight, sex, gestational age, antenatal steroids, and age at first dose.

Similar subgroup analyses will be conducted for the following groups: boys/girls, histologic chorioamnionitis, gestational age strata, and receipt of indomethacin.

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Appendix Table I. Descriptive variables to be summarized overall and by study

Variable	Availability				
	Bonsante et al, 2007[1]	Peltoneimi et al, 2005[2]	Watterberg et al, 2004[3]	Baud et al, 2016[4]	Scale
Birth weight	Y	Y	Y	Y	Quantitative (g)
Gestational age	Y	Y	Y	Y	Quantitative (wk)
Sex	Y	Y	Y	Y	Binary
Apgar 1-min score	Y	Y	Y	N	Quantitative
Apgar 5-min score	Y	Y	Y	Y	Quantitative
Race/ethnicity	Y	All white	Y	Y	Categorical: 1, white; 2, black; 3, Asian; 4, other; 9, unknown
Antenatal steroids	Y (any/full)	Y (any/full/partial)	Y (detailed)	Y	Binary (any vs none)
Rupture of membranes	N	>24 h Y/N	Y (h)	Y (>24 h)	Binary (>24 h Y/N)
Vaginal/Cesarean delivery	Y	Y	Y	Y	Binary
Chorioamnionitis	Y (histologic)	Y (histologic)/Y (clinical)	Y (histologic detailed, clinical)	Y (histologic/ clinical)	Binary (histologic Y/N); binary (clinical Y/N)
Preeclampsia	Y	Y	Y	Y	Binary
Multiple birth	Y (individual random)	Y (individual random)	Y (twin, random together)	Y (how random?)	Binary (Y/N)
Inborn/outborn	Y (all inborn)	Y (all inborn)	Y	Y (inborn)	Binary
Intubated at entry	Y (all)	Y (all)	Y (all)	Y (both)	Binary
Age at entry	Y (at first dose)	Y (at first dose)	Y (at first dose)	Y (at first dose)	Quantitative, h
CRIB score	Y	N	Y	N	Quantitative
Blood pressure					
Daily	N	Y	Y	Y	Daily systolic
Inotropic therapy at study entry	Y	Y	Y	Y	Binary (any Y/N)

CRIB, Clinical Risk Index for Babies.

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Appendix Table II. Primary and secondary outcomes

Outcomes	Availability				Scale
	Bonsante et al, 2007[1]	Peltoneimi et al, 2005[2]	Watterberg et al, 2004[3]	Baud et al, 2016[4]	
Survival without BPD	Y (clinical)	Y (clinical)	Y (clinical, physiological)	Y (physiological)	Binary (Y/N clinical and Y/N physiological)
Severity at 36 wk	FiO_2 >30%/vent; Home on O_2	FiO_2/CPAP/vent	FiO_2/MAP/vent/CPAP	FiO_2/MAP/vent/CPAP	Categorical (moderate, O_2 <30% at 36 wk; severe, >30% or any positive pressure)
Days of ventilation/CPAP/oxygen	Y/Y/Y	Y/Y/Y	Y/N/Y	N/N/N	Quantitative
Oxygen at discharge	Y	Y	Y	N	Binary
Pneumothorax/pulmonary interstitial emphysema	Y/N	Y/N	Y/Y	Y/N	Binary/binary
PDA treatment	Y	Y (indomethacin/ibuprofen/ligation/other)	Y (indomethacin/ligation/other)	Y (ilbuprofen/ligation)	Binary (any treatment Y/N)
Insulin treatment	Y	Y	Y	Y	Binary
Necrotizing enterocolitis	Y	Y	Y (stage)	Y	Binary
Gastrointestinal perforation/indomethacin	Y/Y	Y/Y	Y/Y	Y (ibuprofen)	Binary/binary
Late-onset sepsis (bacterial or fungal)	Y	Y	Y	Y	Binary/binary
IVH grade 3-4/PVL	Y/Y	Y/Y	Y/Y	Y severe/Y	Binary (severe Y/N)/binary
ROP grade	Y	Y	Y	Y (severe)	Binary (severe Y/N)
Death before discharge	Y	Y	Y	Y	Binary
36 wk weight and head circumference	Y *z*-scores	Y actual values	Y actual values; length not available	Y actual values	*z*-scores
Open-label steroid use/type of steroid use	Y (dex BPD hydrocortisone-BP)	Y (+ inhaled)	Y (dex all)	Y (Y, inhaled)	Binary (use Y/N); binary (inhaled Y/N); binary (systemic Y/N)
Any indomethacin exposure	Inbuprofen prophylaxis for PDA	Indomethacin Rx	Prenatal or subsequent indomethacin Rx	Ibuprofen	Any exposure (Y/N)

CPAP, continuous positive airway pressure; *IVH*, intraventricular hemorrhage; *MAP*, mean airway pressure; *PVL*, periventricular leukomalacia; *ROP*, retinopathy of prematurity.

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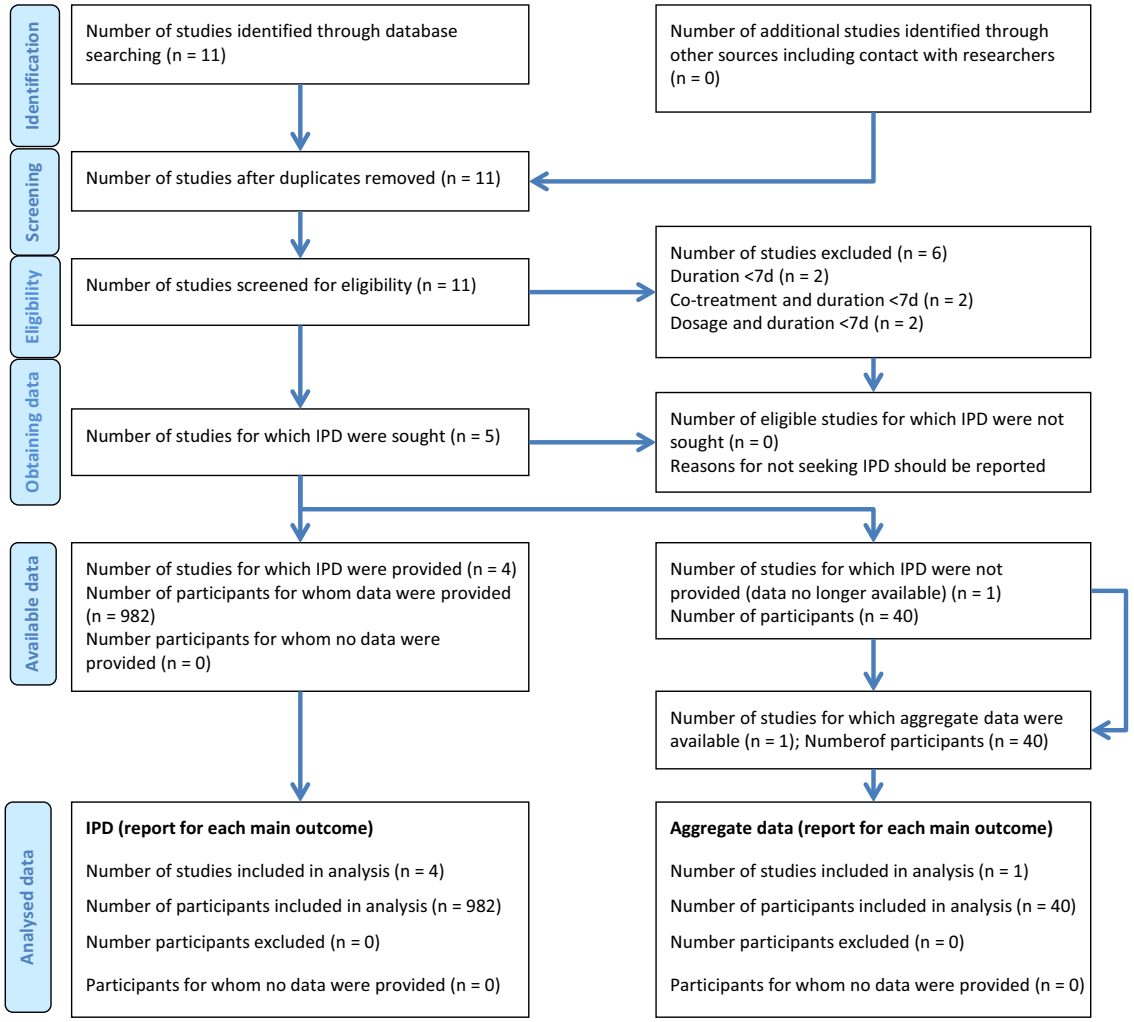

Figure. PRISMA-IPD flow diagram.

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Table I. RCTs using early hydrocortisone in preterm neonates and selection of studies in individual patient sata meta-analysis

Study									
Authors	Year	Dosage	Cotreatment	Exposure	Population	Number of Patients	Included in Individual Patient Data	Excluded in Individual Patient Data	Reason for Exclusion
Baden et al[26]	1972	15 mg/kg	No	12 h	26-36 wk with respiratory distress syndrome	44		X	Dosage; duration <7 d
Watterberg et al[11]	1999	0.5-1 mg/kg/d	No	12 d	500-999 g, ventilated	40		X	Data not available
Watterberg et al[12]	2004	0.5-1 mg/kg/d	No	12 d	500-999 g, ventilated	360	X		Data not available
Biswas et al[31]	2003	0.5-1 mg/kg/d	Yes (triiodothyronine)	5 d	<30 wk, ventilated	253		X	Cotreatment, duration <7 d
Efird et al[27]	2005	0.3-1 mg/kg/d	No	5 d	24-28 wk and <1000 g, with hypotension	34		X	Duration <7 d
Peltoniemi et al[13]	2005	0.75-2 mg/kg/d	No	10 d	<31 wk or <1251 g, ventilated	51	X		
Ng et al[28]	2006	1 mg/kg/8 h	No	5 d	<1500 g, refractory hypotension	48		X	Dosage; duration <7 d
Bonsante et al[14]	2007	0.5-1 mg/kg/d	No	12 d	24-30 wk or <1250 g, ventilated	50	X		
Batton et al[29]	2012	0.5-1 mg/kg/12 h	Yes (dopamine)	3.5 d	23-26 wk with hypotension	10		X	Cotreatment; duration <7 d
Hochwald et al[30]	2014	0.5-2 mg/kg/6 h	No	48 h	<31 wk or <1251 g, hypotension	22		X	Duration <7 d
Baud et al[15]	2016	0.5-1 mg/kg/d	No	10 d	24-28 wk, all but severe intrauterine growth retardation	523	X		

Table V. Heterogeneity estimates of individual patient data meta-analysis of all outcomes unadjusted

Outcomes	Heterogeneity	
	I^2, %	*P* Value
Survival without BPD at 36 wk PMA	0	.298
Death before 36 wk PMA	0	.310
BPD at 36 wk PMA	0	.621
Death before discharge	0	.397
Weight at 36 wk PMA, g	0	.853
Head circumference at 36 wk, cm	0	.463
Respiratory support		
Days of ventilation	0	.464
Days of CPAP	67.9	.078
Days of oxygen	54.0	.114
Oxygen at discharge	0	.949
Open-label steroid use	0	.433
Pneumothorax	0	.459
Insulin treatment	0	.722
Medical treatment for PDA (either indomethacin or ibuprofen)	0	.261
Any prophylactic indomethacin	0	.191
Surgical ligation	13.7	.218
Necrotizing enterocolitis	19.6	.238
Spontaneous gastrointestinal perforation	31.9	.322
Late sepsis (bacterial/fungal)	0	.662
Severe IVH (grade 3-4)	0	.887
Cystic PVL	0	.338
Severe ROP	0	.759

Aggregate meta-analysis: CP; $I^2 = 0\%$, $P = .726$ NDI: $I^2 = 0\%$, $P = .897$; BPD: $I^2 = 30.9\%$, $P = .227$.

Table VII. Characteristics of the studies in the long-term outcomes meta-analysis

Characteristics	Watterberg et al, 2007[16]		Peltoniemi et al, 2009[17]		Bonsante et al, 2007 follow-up study as reported in Peltoniemi et al, 2009[17]		Baud et al, 2017[18]	
Treatment group	Hydrocortisone	Placebo	Hydrocortisone	Placebo	Hydrocortisone	Placebo	Hydrocortisone	Placebo
Survivors at follow-up, n	146	145	23	23	20	14	207	199
Lost to follow-up, n (%)	20 (13.7)	19 (13.1)	0	1 (4.35)	0	0	13 (6.28)	14 (7.04)
Age at follow-up, yr	2		2		2		2	
Type of assessment used	BSID-II		BSID-II and Griffiths Developmental Scale		BSID-II		Revised Brunet- Lezine Scale and standardized neurologic exam	
Cutoff score defining severe NDI	DQ <70		MDI or DQ <70		DQ <70		DQ <70	
CP,* n/N (%)	16/126 (12.7)	18/126 (14.3)	2/23 (8.70)	0/22 (0)	2/19 (10.5)	2/14 (14.3)	12/194 (6.19)	10/185 (5.41)
NDI, n/N (%)	48/123 (39.0)	55/125 (44.0)	5/23 (21.7)	5/22 (22.7)	4/20 (20.0)	3/14 (21.4)	14/194 (7.22)	21/185 (11.4)

BSID, Bayley Scale of Infant Development; *DQ*, developmental quotient; *MDI*, mental developmental index.
*All levels of CP.

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Perinatal Brain Injury

Mechanisms, Prevention, and Outcomes

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KEYWORDS

• Perinatal brain injury • Encephalopathy • Intraventricular hemorrhage
• Periventricular leukomalacia • Perinatal arterial ischemic stroke • Cerebral palsy
• Hypothermia • Prevention

KEY POINTS

- Highlight the mechanism contributing to the development of common etiologies of perinatal brain injury in preterm and term neonates.
- Review the most up-to-date research and recommendations regarding preventive strategies aimed at improving outcomes for those neonates with or at risk for common etiologies of perinatal brain injury.
- Highlight the outcomes of neonates diagnosed with common etiologies of perinatal brain injury and the impact of preventive strategies currently used to improve outcomes.

INTRODUCTION

Perinatal brain injury may lead to significant long-term neurodevelopmental impairment, including cognitive, neurologic, motor, and sensory disability. Perinatal brain injury affects infants born at all gestational ages, but its incidence and morbidity increases with decreasing gestational age.[1]

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Improved perinatal care of the very preterm and low birth weight infant, and neuroprotective preventive strategies aimed at reducing the risk and severity of perinatal brain injury, have resulted in a greater number of affected infants surviving later in life with less severe neurodevelopmental disability.[2,3] Increased administration of antenatal corticosteroids is a possible explanation for the observed increases in survival, and decrease in cerebral palsy (CP) and neurodevelopmental impairment in extremely low birth weight infants from 1982 to 2002.[2] A single-center study of 536 very preterm infants born before 33 weeks of gestation with a 2-year follow-up, revealed a significant improvement in motor outcomes and decreased rate of CP from 12% in 2000 to 1% in 2010 that was, in part, attributed to the increased administration of magnesium sulfate to women at risk of preterm birth over the study periods.[3] More recently, improved outcomes are now being recognized for those neonates born at cusp of viability. Data from 4274 infants born between 22 and 24 weeks spanning 3 epochs (2000–2003, 2004–2007, and 2008–2011) at National Institute of Child Health and Human Development (NICHD) Neonatal Research Network centers showed an increase in overall survival from 30% to 36%, and survival without neurodevelopmental impairment from 16% to 20%, between epoch 1 and epoch 3, although the incidence of moderate to severe CP did not decrease significantly across epochs (15% in epoch 1 and 11% in epochs 2 and 3).[4]

In these sections, common etiologies of perinatal brain injury will be reviewed, including hypoxic–ischemic encephalopathy (HIE), intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), perinatal stroke, and CP (**Table 1**). Although these causes of perinatal brain injury are separate clinical entities, they remain interrelated by their risk factors and pathogenesis. The underlying mechanism of injury involves an initial insult to the vulnerable, developing fetal brain that is usually either of hypoxic–ischemic, hemorrhagic, or infectious in nature, and sets off a cascade of events leading to further brain injury.[18]

COMMON MECHANISM OF INJURY

Perinatal brain injury can affect infants born at any gestational age; however, very preterm fetuses (born <32 weeks of gestation) are less equipped to adapt to perinatal insults as term infants, making them more prone to brain injury.[1] In most cases, a common pathway of injury is elicited by an initial hypoxic–ischemic or inflammatory insult that incites a cascade of events that potentiates perinatal brain injury.[18]

An excellent review by Giussani[19] highlights the adaptive physiologic mechanisms that are present in the term fetus that enables it to respond to a period of impaired oxygenation or systemic hypotension. When oxygenated blood supply is limited, the fetus meets its metabolic needs by binding a greater concentration of oxygen to hemoglobin, preferentially shunting oxygenated blood to tissues at greatest risk of hypoxic injury, and limiting oxygen consumption. In response to hypoxia, the fetal heart rate slows, permitting increased cardiac myocardial oxygen extraction, and increasing end-diastolic filling time and ventricular end-diastolic volume. This increases stroke volume, arterial blood pressure, and circulatory redistribution of blood flow secondary to peripheral vasoconstriction with vasodilation of the blood vessels that perfuse the brain, heart, and adrenal glands.

In contrast with the adaptive mechanisms of the term fetus, the preterm fetus has an immature cerebrovascular autoregulation system and exhibits a pressure-passive circulation. When faced with a period of hypoxia or systemic hypotension, preterm fetuses are unable to sustain increased cerebral perfusion, which makes them more prone to hypoxia–ischemia and neurologic injury. The initial hypoxic–ischemic insult is the primary

Table 1
Aspects of common etiologies of perinatal brain injury

Perinatal Brain Injury Type	Gestational Age	Mechanism of Injury	Neuropathologic Findings	Preventive Measures	References
Hypoxic–ischemic encephalopathy	Late preterm, term (>35 wk)	Hypoxia–ischemia leading to common pathway of injury	Diffuse gray and white matter injury affecting most vulnerable regions of brain	Therapeutic hypothermia Postnatal erythropoietin	5–8
Intraventricular hemorrhage	Preterm (primarily <32 wk)	Injury to fragile premature vessels of germinal matrix	Germinal matrix bleeding with extension into ventricular system	Antenatal corticosteroids Delayed umbilical cord clamping	9–11
Periventricular leukomalacia	Preterm (primarily <32 wk)	Hypoperfusion to border zone regions of brain	Periventricular focal necrosis, cystic formation, or diffuse white matter injury	None	18
Perinatal stroke	Preterm, term	Regional ischemia owing to arterial or sinovenous occlusion or hemorrhagic infarction	Regional infarction owing to vascular occlusion or hemorrhage	None	12–14
Cerebral palsy	Preterm, term	Multifactorial, only 10%–20% of cases owing to an intrapartum hypoxic–ischemic event	Clinical syndrome with variable findings depending on underlying etiology	Magnesium sulfate	6,15–17

mechanism of neuronal injury in which cells are unable to meet their metabolic demands.[18] Those regions of the brain with the greatest metabolic demands—the sensorimotor cortex, thalamus, cerebellum, and brain stem—are most vulnerable to injury.[5] After the initial insult and upon reperfusion of cerebral tissues, there is a transient restoration of cellular metabolic function. This period is followed by a secondary decrease in glucose metabolism and deficiency in high-energy phosphates that results in a secondary injury from excitatory amino acids, apoptosis, reactive oxygen species, and inflammation that causes most of the cerebral injury over time.[20–24]

In response to cellular injury, the excitatory amino acids glutamate and aspartate are released in the brain and exert an excitotoxic effect on the susceptible developing brain.[21] Activation of the *N*-methyl-D-aspartate and α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptors found on neurons and oligodendroglial precursors results in the accumulation of toxic intracellular calcium, impaired cellular recovery, cellular death, and microglial activation with the release of toxic factors detrimental to the health of neighboring neural cells.[22] Mitochondrial impairment ensues with the release of proapoptotic proteins resulting in cellular apoptosis.[23] The generation of reactive oxygen species further disrupts cellular structure and function, contributing to neuronal damage.[24] Last, inflammation induced by the activation of microglia and macrophages with the production and release of proinflammatory cytokines, chemokines, proteases, complement factors, excitotoxic amino acids, reactive oxygen species, and nitric oxide further exacerbates secondary brain injury[25] (**Fig. 1**).

In addition to the inciting hypoxic–ischemic event, intrauterine infection or inflammation has been shown to potentiate perinatal brain injury by altering the cerebral response to hypoxia.[25] In humans, chorioamnionitis is a known risk factor for the development of several types of perinatal brain injury. In these cases, the activation of microglia and macrophages secondary to infection leads to an inflammatory milieu in the fetal brain, resulting in brain injury.[18]

HYPOXIC–ISCHEMIC ENCEPHALOPATHY

Definition

HIE, a subtype of neonatal encephalopathy, is a clinical syndrome of central nervous system dysfunction resulting from impaired cerebral blood flow secondary to persistent, interrupted blood flow to the fetus. The impaired placental gas exchange leads to fetal acidemia and neurologic morbidity that is manifested as depressed consciousness, abnormal muscle tone and reflexes, seizures, and respiratory difficulties.[6] The diagnosis of moderate to severe HIE is linked to the later development of CP, which often is attributed to an acute intrapartum event. The majority of CP cases occur before the onset of labor, but approximately 10% to 20% are from acute intrapartum hypoxia–ischemia.[6,26]

Unlike perinatal brain injury in very preterm infants, neonatal encephalopathy and HIE have typically been defined in infants born at or beyond 35 weeks of gestation. The criteria for definite and probable preterm HIE that includes infants born at 33 weeks and younger have been proposed,[27] based on the recognition that biochemical screening and encephalopathy scoring criteria currently in use for infants born at 35 weeks of gestation or greater are also applicable to preterm infants born between 33 and 35 weeks of gestation.[28]

Incidence

Neonatal encephalopathy from all causes affects approximately 3 in 1000 live births, whereas the incidence of HIE ranges from 1 to 2 per 1000 term births.[29] The incidence

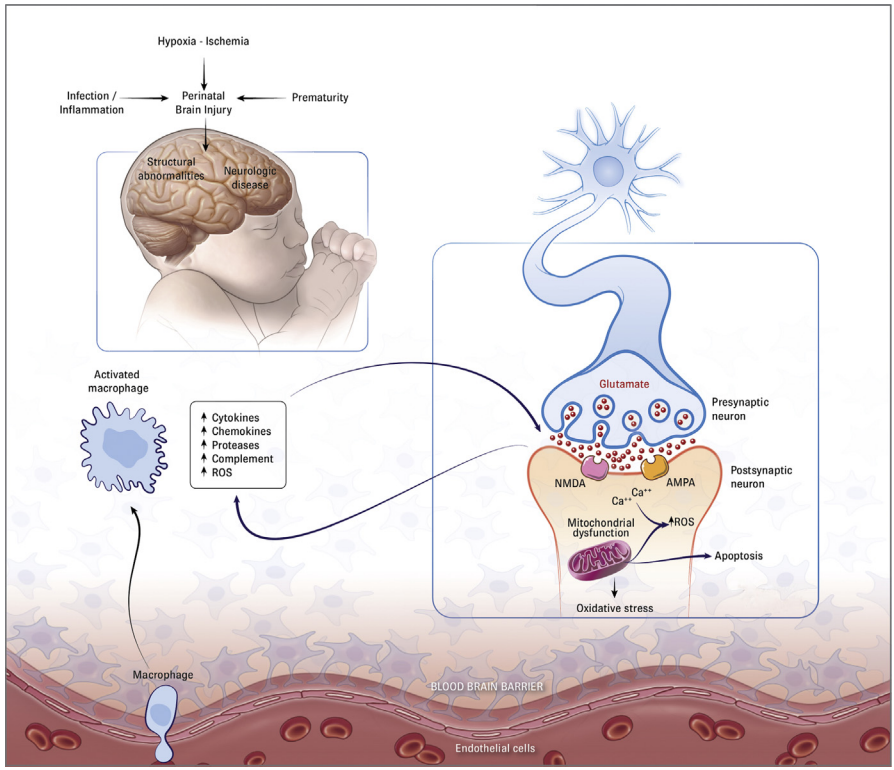

Fig. 1. The effects of hypoxia–ischemia, inflammation, and prematurity on the fetal brain may lead to a common pathway of perinatal brain injury marked by neuronal excitotoxicity, mitochondrial impairment with cellular apoptosis and generation of reactive oxygen species (ROS), and inflammation induced by microglial activation. AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid; NMDA, *N*-methyl-D-aspartate.

of preterm HIE varies from 1.3 in 1000 to 5 to 9 in 1000 live births.[27] In a retrospective study of 586 infants from 2000 to 2005, HIE developed in 10% of infants exposed to an intrapartum sentinel event and 2.5% of infants with isolated nonreassuring fetal heart monitoring during labor.[30] The presence of an isolated intrapartum maternal fever or chorioamnionitis increased the risk of neonatal encephalopathy 3-fold and 5-fold,[31] respectively, likely from potentiation of inflammation induced by a hypoxic–ischemic event.

Mechanism

The underlying cause of HIE is the interruption of fetal cerebral blood flow that can be of a maternal, placental, or fetal etiology.[6,30] Maternal conditions resulting in inadequate placental perfusion can be either acute or chronic, and include cardiopulmonary arrest, acute hypotension, pulmonary embolism, or vascular disease. Placental factors that result in HIE are usually acute disturbances in placental perfusion and include abruptio placentae, uterine rupture, umbilical cord prolapse, or shoulder dystocia. Fetal factors include fetal thrombosis, embolism, or fetomaternal hemorrhage. Regardless of the etiology, hypoxia–ischemia in the term neonate results in acute neuronal injury in the deep gray matter, as described.

Prevention

The prevention of long-term sequelae from HIE is focused primarily on neonatal care because preventive obstetric interventions have largely proven to be unsuccessful. Additionally, most HIE is not from an acute peripartum event, but likely developed at some time before the onset of labor. In the 10% to 20% of cases caused by an acute peripartum event,[6,26] avoidance of the etiologic disturbance of placental perfusion is not always possible, because many cases result from an acute disruption in placental perfusion.[6,30] Continuous fetal heart monitoring, although common in the United States, is not associated with a decrease in the perinatal death rate (relative risk [RR]; 0.86; 95% confidence interval [CI], 0.59–1.23) or CP rate (RR, 1.75; 95% CI, 0.84–3.63) and is associated with an increased cesarean section rate (RR, 1.63; 95% CI, 1.29–2.07) and an increased operative vaginal delivery rate (RR, 1.15; 95% CI, 1.01–1.33); the only benefit reported is a reduction in neonatal seizures (RR, 0.50; 95% CI, 0.31–0.80).[32] Neonatal interventions that may improve outcomes in infants diagnosed with or at risk for HIE include therapeutic hypothermia and erythropoietin (Epo) administration.

Therapeutic hypothermia

Therapeutic hypothermia for infants with moderate to severe HIE is currently the standard of care and increases long-term survival without disability. Options include either whole body hypothermia[33] or selective head cooling.[34] Currently, therapeutic hypothermia is limited to infants with moderate or severe encephalopathy and initiated within 6 hours for a treatment duration of 72 hours at a goal temperature of 33.5°C.[7] The original NICHD trial of whole body hypothermia showed a decrease in death or moderate or severe disability at 24 months of age, from 62% to 44% (RR, 0.72; 95% CI, 0.54–0.95) for therapeutic hypothermia compared with controls.[33] A metaanalysis of 1214 neonates showed that therapeutic hypothermia, either from whole body or head cooling, decreased death or major neurodevelopmental disability (RR, 0.76; 95% CI, 0.69–0.84) and increased survival with normal neurologic function (RR, 1.63; 95% CI, 1.36–1.95) at 18 months of life.[35]

Erythropoietin

Epo has emerged as a possible neuroprotective agent for neonates with HIE. Animal models of hypoxic–ischemic injury have shown that Epo attenuates cytokine-mediated inflammation by reducing reactive astrocytosis and microglia activation, and supports the recovery of neuronal cells and limits the extent of injury.[36] A recent phase II trial to assess if multiple doses of Epo administered with therapeutic hypothermia to newborns with HIE improved neuroradiographic and short-term outcomes showed less moderate/severe and subcortical brain injury on MRI and some improved motor function at 1 year of age.[8] Currently, there is phase III, multicenter, randomized, double-blind, placebo-controlled trial enrolling infants born at 36 weeks of gestation or greater with HIE who are receiving standard therapy with therapeutic hypothermia to assess if the addition of high-dose Epo reduces the rate of death, motor, or cognitive deficits at 2 years of age.[37]

Outcomes

Long-term outcomes of HIE cases secondary to an acute intrapartum event are variable. A recent, 2017 secondary analysis of the original NICHD whole body hypothermia study[33] showed that of the 208 infants in the original study, 84 had an acute perinatal sentinel event, and 55% of those infants had an abnormal brain MRI that most often exhibited thalamic and basal ganglia lesions. At 18 to 22 months of follow-up and at 6 to 7 years of follow-up, there was no difference in the

neurodevelopmental outcomes between neonates who did and did not experience a perinatal sentinel event.[38] In a 2008 retrospective review of 500 term infants diagnosed with encephalopathy, 41 cases identified were owing to an acute intrapartum event with at least 12 months of follow-up, and death, CP, developmental delay, and normal development were noted in 20%, 41%, 15%, and 24% of cases, respectively.[39] The occurrence of normal development in nearly one-quarter of cases highlights the possibility that neonatal brain plasticity and repair in response to an acute event likely plays a significant role in long-term neurodevelopmental outcomes.

INTRAVENTRICULAR HEMORRHAGE

Definition

IVH describes bleeding that originates in the subependymal germinal matrix and ruptures through the ependymal into the lateral ventricle. IVH is graded as 4 categories, can be unilateral or bilateral, and can be symmetric or asymmetric[40]:

- Grade I: Germinal matrix hemorrhage;
- Grade II: IVH without ventricular dilation;
- Grade III: IVH with acute ventricular dilation (clot fills >50% of the ventricle); and
- Intraparenchymal lesion (previously grade IV): Intraparenchymal hemorrhage.

Incidence

IVH incidence is indirectly proportional to gestational age.[41] The overall incidence of IVH from a NICHD study was 32% for infants born between 22 and 28 weeks of gestation with a birth weight between 401 and 1500 g.[42] Severe IVH (grade III and IV) occurred in 38%, 26%, and 7% of infants surviving more than 12 hours born at 22, 24, and 28 weeks of gestation, respectively. Similar to HIE, the presence of chorioamnionitis is another risk factor for IVH, and is associated with up to a 1.6-fold increased risk of severe IVH in preterm infants born before 33 weeks of gestation.[43]

Mechanism

The lack of supportive tissue surrounding thin-walled capillaries in the germinal matrix of the premature infant's brain increases the risk of IVH.[10] The structural integrity of these vessels is related to the presence of glial fibers emanating from astrocyte endfeet that is deficient along with pericytes, tight junctions, and the presence of an immature basal ganglia in preterm infants. The fragility of these vessels makes them more prone to rupture spontaneously or in response to stress, such as hypoxia–ischemia. In addition, the immature cerebrovascular autoregulation system of preterm infants increases the risk of cerebral ischemia in response to systemic hypotension, leading to a greater risk of injury to the fragile vessels of the germinal matrix.[18]

Prevention

Because IVH mostly affects preterm infants, primary prevention should be directed at the prevention of preterm birth. The incidence of IVH has been shown to decrease by 3.5% with each additional week of gestation achieved through 32 weeks.[41] If preterm birth cannot be prevented, the focus should be on optimizing peripartum care to reduce the risk, severity, and potential sequelae of IVH.

Antenatal corticosteroids

Antenatal corticosteroids are a key therapy to decrease the risk of IVH.[44] In a 2016 cross-sectional review of nearly 26,000 very low birth weight infants born 32 weeks or fewer of gestation, antenatal corticosteroid administration was associated with a

decreased incidence of any grade IVH (odds ratio [OR], 0.68; 95% CI, 0.62–0.75) and severe IVH (OR, 0.51; 95% CI, 0.45–0.58). Additionally, these benefits were seen with administration as early as 22 weeks of gestation.[9] In a 2017 metaanalysis of randomized controlled trials that included 6093 infants, antenatal corticosteroids was associated with a decreased incidence of IVH (OR, 0.55; 95% CI, 0.40–0.76).[45] Although the optimal timing of antenatal corticosteroids administration to maximize neonatal benefit, and reduce the risk of severe neonatal brain injury, is 1 to 7 days before delivery,[46,47] administration within 24 hours of delivery, and potentially as early as 3 hours before delivery may reduce infant in-hospital mortality rates by at least 26%.[47]

Maternal transport

For mothers expected to deliver preterm, antepartum transportation to a facility equipped to handle preterm and very low birth weight infants may reduce the incidence of IVH (13.2% vs 27.4%) and severe IVH (32.9% vs 44.1%) compared with infants transferred after birth.[48]

Delayed cord clamping

Several studies have shown a reduction in IVH from delayed umbilical cord clamping in preterm infants delivered at up to 35 weeks of gestation.[49,50] A 2012 systematic review of 10 trials containing 539 infants that defined delayed umbilical cord clamping as a delay of more than 30 seconds and up to 180 seconds found a lower incidence of IVH in the delayed umbilical cord clamping group compared with the immediate clamping group (RR, 0.59; 95% CI, 0.41–0.85).[11] In January 2017, the American College of Obstetricians and Gynecologists defined delayed umbilical cord clamping as a delay of at least 30 to 60 seconds and reaffirmed their position to delay umbilical cord clamping in preterm infants, citing the benefit of decreasing IVH.[51]

Outcomes

Identification of IVH and its complications is achieved by cranial ultrasound screening, with up to 50% of all cases being otherwise asymptomatic.[52] Nearly all cases of IVH in preterm infants occur within the first 5 days of postnatal life,[52] with approximately one-half of cases in very low birth weight infants occurring within 6 hours of postnatal life.[53] For these reasons, guidelines set forth by the American Academy of Neurology and the Pediatric Committee of the Child Neurology Society recommends that routine cranial ultrasound screening be performed on all infants born at less 30 weeks of gestation, or greater than 30 weeks of gestation with any clinical suspicion of IVH, be performed between 7 and 14 days of age, and repeated at 36 to 40 weeks postmenstrual age.[54]

IVH is a significant cause of morbidity and long-term neurodevelopmental impairment. There is no current therapy to limit the extent of injury once it has developed, and treatment is largely supportive, with the goals of preserving cerebral perfusion, minimizing further injury, and detecting complications. Posthemorrhagic hydrocephalus results from the obstruction of cerebrospinal fluid flow and inhibition of cerebrospinal fluid resorption secondary to intraventricular blood clots, and complicates 1%, 4%, 25%, and 28% of cases of grades I through IV IVH, respectively.[55] Obstruction ultimately can lead to scar formation, further ventricular dilatation with increased intracranial pressure and edema, and further periventricular white matter damage.[56] A large, cohort study of extremely low birth weight infants showed that those with severe IVH requiring shunt placement were at greatest risk for adverse neurodevelopmental and growth outcomes at 18 to 22 months compared with those with and without severe IVH and with no shunt.[57] In periviable infants born between 22 and 24 weeks of

gestation, a statistically significant decreased incidence of posthemorrhagic hydrocephalus requiring shunt placement ($P<.001$) has been observed in infants born between 2004 to 2007 and 2008 to 2011, compared with those born between 2000 and 2003, despite the fact that the rates of severe IVH did not change during these times periods.[4]

Morbidity and mortality related to IVH is proportional to its severity. Some data suggest that grade I or II IVH may have a greater degree of neurologic handicap compared with infants without abnormalities on cranial ultrasound examination,[58] although this finding is not universally supported.[59] A single-center retrospective cohort study showed that extremely low birth weight infants with grades I and II IVH had higher rates of Mental Developmental Index scores of less than 70, major neurologic abnormality, and neurodevelopmental impairment at 20 months corrected age compared with infants with normal cranial ultrasound examinations.[60] In contrast, in a longitudinal multicenter NICHD study involving 1472 infants born at less than 27 weeks cranial ultrasound, grades I and II IVH were not associated with an increased risk of neurodevelopmental impairment at 2 years of age.[59] The prevalence of CP increases with IVH severity and is seen in 8%, 11%, 19%, and 50% for grades I through IV IVH, respectively.[61] Mortality rates are 4%, 10%, 18%, and 40% for IVH grades I through IV, respectively.[55]

PERIVENTRICULAR LEUKOMALACIA

Definition

PVL is defined as injury to the deep cerebral white matter that can be seen in 2 characteristic patterns: focal periventricular necrosis and diffuse cerebral white matter injury.[18] Focal periventricular necrosis is seen most commonly in the cerebral white matter at the level of the trigone of the lateral ventricles and near the foramen of Monro. These sites are located at the border zones of the immature penetrating cerebral vasculature, making them more susceptible to impaired perfusion at times of systemic hypotension. Diffuse cerebral white matter injury can be seen in conjunction with focal periventricular necrosis, and also occurs as a result of perturbations in cerebral blood flow secondary to vascular immaturity. The result is a loss of premyelinating oligodendrocytes and an increase in hypertrophic astrocytes leading to white matter volume loss and ventriculomegaly.

Incidence

Similar to IVH, PVL most often affects preterm infants born at less than 32 weeks of gestation, with an incidence that increases with decreasing gestational age.[62] White matter changes may not be appreciated on the initial ultrasound and may not be detected until the follow-up ultrasound examination or MRI is performed. PVL is detected by cranial ultrasound at 6 weeks of life in approximately 10% of very low birth weight infants.[62] In infants born at less than 28 weeks of gestation and surviving to near-term postmenstrual age, early cranial ultrasound examination obtained between 4 and 14 days of life has been shown to detect either grade III or IV IVH or cystic PVL in 9.7% of cases. A follow-up brain MRI obtained at 35 to 42 weeks postmenstrual age has been shown to detect moderate to severe white matter abnormalities in 19.3% of cases.[63] The incidence of PVL in periviable infants born between 22 and 24 weeks of gestation has remained stable at 6% to 7% from 2000 to 2011.[4]

Mechanism

The underlying cause of PVL, like IVH, is related to the immature cerebral vasculature and cerebrovascular autoregulation system.[18] In response to systemic hypotension,

preterm infants cannot increase cerebral perfusion to border zone regions of the brain supplied by the immature penetrating cerebral vasculature. This condition sets off the cascade of events caused by hypoxia–ischemia resulting in brain injury that again is potentiated by chorioamnionitis and increases in the setting of positive neonatal cerebrospinal fluid cultures.[62]

Prevention

There are no current strategies that specifically target the prevention of PVL, and the current management of at-risk infants is aimed at maintenance of cerebral perfusion after delivery, although optimal blood pressure targets are unknown. Similar to IVH, the primary preventive strategy is prevention of preterm birth, transfer to an appropriate medical facility for those cases in which preterm delivery is likely,[48] and maternal administration of corticosteroids,[45] which have been shown to decrease the risk of grades III or IV IVH and PVL from 27.6% to 19.2% (adjusted, OR 0.67; 95% CI, 0.57–0.79) in periviable gestations from 22 to 25 weeks.[64]

Outcomes

Long-term neurodevelopmental outcomes correlate with the extent of white matter injury. Moderate to severe cerebral white matter abnormalities detected by MRI studies performed on very preterm infants born before 30 weeks of gestation were predictive of several adverse neurodevelopmental outcomes at 2 years of age, including cognitive delay (OR, 3.6; 95% CI, 1.5–8.7), motor delay (OR, 10.3; 95% CI, 3.5–30.8), neurosensory impairment (OR, 4.2; 95% CI, 1.6–11.3), and CP (OR, 9.6; 95% CI, 3.2–28.3).[65] In a separate study of 186 very preterm infants born at less than 30 weeks of gestation or weighing less than 1250 g who had a brain MRI at term equivalent age and again at the 7-year follow-up, cerebral white matter abnormality scores were normal, mildly abnormal, and moderately or severely abnormal in 45%, 36%, and 19% of cases, respectively. The increased severity of cerebral white matter abnormality scores strongly correlated with lower intelligence quotient scores and worse motor outcomes at 7 years of age.[66] Infants diagnosed with PVL are at risk for the development of spastic quadriplegia or diplegia, a form of CP that affects the lower extremities to a greater extent than the upper extremities, owing to the fact that the descending fibers of the motor cortex responsible for the function of the lower extremities transverse the periventricular area and are most likely to be injured. In a 2013 review of 25 children diagnosed by MRI with PVL, 24 of which were the product of a preterm delivery, 9 (36%) had spastic diplegia and 12 (48%) had spastic quadriplegia.[67]

PERINATAL STROKE

Definition

A perinatal stroke is a cerebrovascular event occurring between 20 weeks of fetal life and 28 postnatal days that is confirmed by neuropathologic studies or neuroimaging findings consistent with a focal cerebral infarction.[12] Perinatal ischemic stroke can be divided into perinatal arterial ischemic stroke (PAIS) and cerebral sinovenous thrombosis, which account for 70% and 10% of cases, respectively. The remaining 20% of perinatal strokes are from intracerebral hemorrhage.[13]

Incidence

The precise incidence of perinatal stroke is difficult to ascertain owing to variations in the definition, diagnosis, and case identification. The reported incidence of PAIS is 1 per 2800 to 5000 live births, whereas perinatal hemorrhagic stroke complicates 1 per

16,000 live births.[12,68,69] Most cases of PAIS occur in term infants,[70] and are identified by neuroimaging evaluation obtained for evaluation of a neurologic abnormality. Seizures are the presenting symptoms of a PAIS in up to 95% of cases,[70] with a delayed onset of seizure of more than 12 hours after birth or the presence of a focal motor seizure being predictors of stroke.[71] Other than seizures, nearly two-thirds of patients also present with diffuse neurologic signs, including abnormal tone or level of consciousness. Focal neurologic signs occur in 30% of patients, the majority of which are lateralizing hemiparesis.[70] Preterm infants with PAIS may present with more subtle signs, including respiratory distress or apnea and poor feeding.[72]

Mechanisms

There are several potential etiologies of a PAIS, all of which result in regional ischemia and hypoxia. In a single-center cohort study, embolism was the underlying cause in one-third of identified cases.[73] Potential sources of emboli in the neonatal circulation include right-to-left shunts in cases of congenital heart disease or the presence of a patent foramen ovale that can permit venous emboli to enter the arterial circulation. Other etiologies of PAIS account for 4% to 6% of cases each and include infection resulting in endothelial injury and meningitis (6%), trauma (5%), blood loss (4.5%), and asphyxia (4%).[73] Placental pathology has also been implicated as a potential cause with the possible release of emboli originating from thrombosed placental vessels into the fetal circulation as placental separation occurs at birth, or by the induction of a thromboinflammatory process in the fetus or neonate.[74]

Prevention

There are currently no strategies that decrease the risk of perinatal stroke. In a study of Epo therapy in neonates with PAIS, 21 neonates with MRI-confirmed PAIS received Epo at the time of diagnosis, and 24 and 48 hours after the first dose. There were no adverse effects on vital signs, or hematologic or coagulation parameters. In a subgroup analysis of 10 treated neonates, there were no differences in residual infarct volumes or neurodevelopmental outcomes compared with historical controls.[14] Once diagnosed, management is supportive and treatment is directed at the underlying condition and prevention of further injury. The American Heart Association[75] and CHEST[76] guidelines recommend anticoagulation for PAIS only in cases with a documented cardiac embolic source or prothrombotic state.

Outcomes

Neurodevelopmental outcomes are variable in survivors of perinatal arterial stroke and depend on the extent and distribution of injury. In 1 study of term infants with an average follow-up of 42 months, 33% had normal neurodevelopment.[77] CP and cognitive impairment were seen in 47% and 41% of children, respectively. In a second cohort of 36 infants diagnosed with perinatal stroke followed for at least 12 months after birth, 81% of children had abnormal outcomes, with CP, epilepsy, language delay, and behavioral abnormalities affecting 58%, 39%, 25%, and 22% of patients, respectively.[78] In a recent study, presumed PAIS, greater infarct volume, and the presence of comorbid epilepsy, but not infarct location or laterality, showed a strong negative correlation with attention and cognitive performance at school age.[79] In neonates with a PAIS, approximately 3% are at risk of having a recurrent symptomatic thromboembolic event that is associated with the presence of a prothrombotic state, cardiac malformation, or other underlying disease.[80]

CEREBRAL PALSY

Definition

CP is a clinical syndrome characterized by the presence of nonprogressive motor disturbances affecting muscle tone, posture, and movement that results from a cerebral abnormality of the developing brain and evolves within the first years of life.[15]

Incidence

Infants born at any gestational age can be affected with CP, but CP increases with decreasing gestational age. Although 58% of CP cases occur in infants born at or beyond 37 weeks of gestation, CP affects only 0.1% of this gestational age cohort. In comparison, very preterm births account for 25% of all CP cases, but 8.7% of those born at less than 32 weeks of gestation will develop CP. Infants born between 32 and 37 weeks of gestation account for 17% of all CP cases, and 3% of those born within this gestational age range will develop CP.[81] Efforts to decrease preterm births have reduced the rate of CP related to very preterm birth, but this measure has had little effect on the prevalence of CP because very preterm births account for only 2% of all births. As a result, the incidence of CP has remained unchanged at 1.5 to 2.5 cases per 1000 live births, despite improvements in perinatal care.[82]

Mechanisms

CP results from injury to the developing brain that can occur during the antepartum, intrapartum, or postnatal periods. An intrapartum hypoxic–ischemic insult is often associated with the development of CP, but only accounts for 10% to 20% of all cases.[6,26] The etiology of CP is multifactorial, and can result from any of the perinatal brain injuries previously discussed. In a cohort review of 235 children diagnosed with CP from 1986 to 2003, the most common clinical factors or pathologies associated with CP were prematurity (78%), intrauterine growth restriction (34%), intrauterine infection (28%), antepartum hemorrhage (27%), and multiple gestation (20%).[16]

Prevention

The prevention of preterm birth, antenatal administration of corticosteroids,[45] and delayed umbilical cord clamping[51] have variably been shown reduce the risk of prematurity, IVH, and PVL, which are all associated with an increased risk for the later development of CP. However, because only a small percentage of CP cases are seen in infants born at less than 32 weeks of gestation, these interventions have not decreased the overall incidence of CP.[15,82] Furthermore, interventions aimed at decreasing HIE and resulting CP, such as the use of continuous fetal heart rate monitoring, have not been shown to be beneficial.[32]

Magnesium sulfate

Magnesium sulfate can stabilize vascular tone, reduce reperfusion injury, reduce cytokine-mediated injury, and ameliorate neuronal injury in animal models.[83–85] Several randomized trials have shown that the administration of magnesium sulfate to mothers at risk of preterm delivery within 24 hours decreases gross motor dysfunction or CP among infants born prematurely.[74,86–88] The largest study by Rouse and colleagues[88] and the NICHD Maternal-Fetal Medicine Network showed a significant decrease in the rate of moderate or severe CP with the antenatal administration of magnesium sulfate to mothers at risk of preterm delivery before 32 weeks of gestation (RR, 0.55; 95% CI, 0.32–0.95). A 2009 metaanalysis of 5 randomized controlled trials found a statistically significant decrease in CP (RR, 0.70; 95% CI, 0.55–0.89) and

moderate to severe CP (RR, 0.60; 95% CI, 0.43–0.84).[17] These findings are further supported by a 2016 metaanalysis of 6 randomized, controlled trials and 5 cohort studies that included 18,655 preterm infants and showed a statistically significant decrease in moderate to severe CP (OR, 0.61; 95% CI, 0.42–0.89).[89] In January 2016, the American College of Obstetricians and Gynecologists, supported by the Society for Maternal-Fetal Medicine, reaffirmed their recommendation on the use of magnesium sulfate as a fetal neuroprotective agent in cases of anticipated preterm birth before 32 weeks of gestation.[90]

Caffeine

The Caffeine for Apnea of Prematurity trial[91] established the efficacy and safety of caffeine for apnea of prematurity in neonates born weighing 500 to 1250 g. Follow-up at 18 to 21 months in this cohort showed that caffeine improved the rate of survival without neurodevelopmental disability (OR, 0.77; 95% CI, 0.64–0.93), and decreased the incidence of CP (OR, 0.58; 95% CI, 0.39–0.87) and cognitive delay (OR, 0.81; 95% CI, 0.66–0.99).[92] At the 11-year follow-up, caffeine reduced the risk of motor impairment (OR, 0.66; 95% CI, 0.48–0.9), although there was no significant decrease in the rate or severity of CP.[93]

Outcomes

In most children, depending on the type and severity of CP, the diagnosis of CP is made within the first 2 years of life.[94] Associated neurodevelopmental or sensory impairments such as pain, intellectual disability, epilepsy, behavioral disorders, bowel and bladder control problems, speech-language disorders, and hearing impairment affect approximately 75%, 49%, 35%, 26%, 24%, 23%, and 4% of patients, respectively, and are more likely to observed in patients with more severe motor disabilities.[95] The management of CP involves a multidisciplinary approach that is largely supportive and aimed at improving the quality of life of those affected by the condition. Although nearly 90% of patients will survive to adulthood,[96] those with severe handicaps may die in early childhood, most often from aspiration pneumonia and respiratory disease.[97]

SUMMARY

Over the last 2 decades, advances and changes in obstetric and pediatric care have resulted in improved survival and neurodevelopmental outcomes of very preterm infants.[2,3] More widespread use of antenatal corticosteroids, delayed cord clamping, and maternal magnesium sulfate administration have reduced the risk of IVH, PVL, and CP.[17,45,51] In term infants, postnatal interventions such as therapeutic hypothermia, changes in mechanical ventilation strategies, and Epo administration have further improved outcomes.[9,33,34]

Despite these improvements, perinatal brain injury continues to be a significant cause of long-term neurodevelopmental disability.[96] Research into novel therapeutic strategies targeting various aspects of the diverse mechanisms of perinatal brain injury is needed to continue improving long-term outcomes. Maternal administration of mesenchymal stem cells,[98] cytokine inhibitor therapy,[99] and maternal progesterone therapy[100] have all shown promise in animal models. The 2016 OPPTIMUM study (Vaginal Progesterone Prophylaxis for Preterm Birth),[101] a double-blind, randomized, placebo-controlled trial of vaginal progesterone for preterm birth prevention found a lower risk of brain injury on ultrasound examination in the progesterone group compared with placebo (OR, 0.50; 95% CI, 0.31–0.84). The understanding that perinatal brain injury is not only secondary to prematurity or

hypoxia–ischemia, but involves a complex cascade of underlying cellular and immunologic factors often triggered by both antenatal and postnatal inflammation in response to these events, is paramount to advancing research for the discovery of novel therapeutic strategies.[102]

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Enteral Feeding of the Preterm Infant

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Education Gaps

1. Clinicians should be able to initiate and advance enteral feedings for the preterm infant safely and effectively.
2. Clinicians should recognize the importance of appropriate enteral feeding and early nutrition for the long-term growth and neurodevelopment of preterm infants.

Abstract

Premature infants commonly suffer from extrauterine growth restriction from inadequate nutrition and the loss of the last months of gestation, a critical period for brain and body growth. Providing optimized nutrition for the premature infant is a crucial task of the neonatologist and has a significant impact on the future growth and neurodevelopment of these infants. Enteral feeding is nuanced in the preterm population and requires specific knowledge of the nutritional requirements of the preterm infant and the various substrates and methods available to achieve proper nutrition.

Objectives After completing this article, readers should be able to:

1. List the macronutrient requirements of the preterm infant.
2. Describe the nutritional composition of human milk, donor breast milk, and preterm infant formula.
3. Recognize the benefits of human milk for the preterm infant and that preterm and term human milk have different compositions.
4. Recognize that human milk needs to be fortified to meet the nutritional needs of preterm infants and describe how standard infant formulas are altered to meet the needs of preterm infants.
5. Explain advantages and disadvantages of the use of donor human milk.

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ABBREVIATIONS

BUN	blood urea nitrogen
CA	corrected age
EUGR	extrauterine growth restriction
GA	gestational age
HM	human milk
HMF	human milk fortifier
NEC	necrotizing enterocolitis
PMA	postmenstrual age
VLBW	very low birthweight

INTRODUCTION

The last months of gestation are characterized by rapid growth and brain development. Infants born prematurely are deprived of this experience. It is not

surprising that most preterm infants experience extrauterine growth restriction (EUGR) and are at risk for developmental delays. Appropriately feeding the preterm infant is one of the most crucial tasks of the neonatologist.

Most infants born at 24 to 29 weeks' gestation experience EUGR and their weights are at less than the 10th percentile at discharge or 36 weeks' postmenstrual age (PMA). There are many reasons for this inadequate growth. The nutritional needs of the preterm infant are not fully understood, so it is difficult to know what to provide and how to do so. Even when good nutrition is prescribed, the infant may not actually receive the full benefit because feedings may be suspended or other complications may ensue. Preterm infants have increased metabolic demands from illness severity and respiratory distress, which affect their ability to absorb and use nutrients. They often have decreased gut motility and poor tolerance of enteral feeding from medication exposure and underdeveloped gut mucosa. An association between severity of illness, poor linear growth, and decreased fat-free mass has been documented. Poor early growth is associated with decreased neurodevelopmental and growth outcomes at 18 to 24 months' corrected age (CA), with early nutrition having an impact of 6 to 15 IQ points in various studies. Children are less likely to have growth parameters lower than the 10th percentile at 18 months' CA if higher in-hospital growth rates are achieved, as well as lower incidences of cerebral palsy, neurodevelopmental impairment (including blindness and deafness), Bayley and Psychomotor Development Index scores less than 70, and rehospitalizations. Faster weight gain has been reported in infants who receive fewer days of parenteral nutrition, initiate enteral feedings sooner, and attain full enteral feedings earlier. Increased severity of illness, particularly the need for mechanical ventilation during the first week of life, greatly influences decisions about early feeding. Less critically ill infants are given significantly more enteral and parenteral nutrition during the first 3 weeks after birth. There is no evidence to support limiting any form of nutrition in infants receiving mechanical ventilation.

Poor nutrition may reduce immune competence and decrease energy stores, rendering preterm infants more susceptible to infection and less able to recover from acute and chronic disease. Lack of enteral nutrition causes gastrointestinal mucosal atrophy and leads to decreases in protective mucus, decreased enzyme activity, and increased gut permeability. These findings may cause dysfunction and feeding intolerance, and are associated with a greater risk for necrotizing enterocolitis (NEC). Enteral nutrition is paramount for gastrointestinal growth and development. Early enteral feeding decreases the time to reach full feeding volume, as well as length of stay without increasing NEC or serious infections. Enteral feeding should not be initiated in infants who are hemodynamically unstable or have severe left-to-right ductal shunting, abnormal gastrointestinal examination, bilious gastric fluid, severe metabolic acidosis, sepsis, or hypoxemia.

GOALS OF ENTERAL NUTRITION

Extreme prematurity is a nutritional emergency. Fetal body composition and size at various stages of gestation are used as a reference standard for extrauterine growth and accretion rates of protein, fat, and minerals for preterm infants. Optimal nutrition should maintain lean body mass and bone density, maximize neurodevelopment, minimize complications (NEC, chronic lung disease, and infection), reduce postnatal weight loss with earlier return to birthweight, and improve catch-up growth. The targeted weight gain is 18 g/kg per day, head circumference growth of more than 0.9 cm/week, and length gain of 1 cm/week. The smallest and least mature infants need the most protein, but energy needs escalate with increasing body weight. Early protein intake is a major contributor to improved weight gain velocity and a decreased risk of neurocognitive impairment. For appropriate growth, a caloric goal of 120 kcal/kg per day and protein goal of 3.8 g/kg per day are recommended in very low birthweight (VLBW) infants within the first 7 days after birth (Table 1). This amount of protein can only be provided through enteral fluid of more than 150 mL/kg per day of fortified human milk or "high protein" preterm formula. Infants born at less than 31 weeks' gestational age (GA) typically have an 18 g/kg protein deficit and 600 kcal/kg deficit by 14 days of age. Proportional growth, rather than absolute weight gain, should be monitored to evaluate growth. Many studies suggest that reduction in practice variation improves patient outcomes. The establishment of feeding guidelines reduces EUGR and achieves full feedings sooner. Consulting a neonatal specialist (registered dietitian or nutritionist) to make recommendations and monitor guideline compliance may facilitate nutritional success.

SUBSTRATES FOR ENTERAL FEEDING

Human Milk

The American Academy of Pediatrics recommends that preterm infants should exclusively receive human milk (HM), preferably from their own mothers if available, or if not available, pasteurized donor HM. Breastfeeding

TABLE 1. **Nutritional Needs of the Preterm Infant**

NUTRIENT	RECOMMENDATION (PER KG/DAY)
Energy	110–130 kcal
Protein	3.5–4.5 g
Fat	4.8–6.6 g
Carbohydrate	11.6–13.2 g
Calcium	120–200 mg
Phosphorus	60–140 mg

Adapted from Koletzko B, Poindexter B, Uauy R. Nutritional Care of Preterm Infants: Scientific Basis and Practical Guidelines. *Basel, Switzerland: Karger; 2014.*

provides developmental benefits that extend into adolescence. The use of exclusive HM when paired with standardized feeding guidelines can improve tolerance of feedings and decrease the incidence of NEC. Decreased rates of NEC have been seen with an exclusive HM-based diet compared with an HM-based diet supplemented with bovine milk–based products. The number needed to treat with exclusively fed HM is 10 to prevent 1 case of NEC, and 8 to prevent 1 case of "surgical NEC" or death. HM-fed infants have decreased rates of late-onset sepsis, urinary tract infection, diarrhea, and upper respiratory infection. The protection against NEC and sepsis appears to be dose-dependent. HM is also associated with decreases in the incidence and severity of retinopathy of prematurity, improved neurodevelopmental and visual outcomes, and improved feeding tolerance compared with formula. Improved tolerance allows infants to receive fewer days of parenteral nutrition, significantly decreases morbidity, and decreases length of stay.

HM contains bioactive factors that benefit growth and development. This includes improved immunity with antibacterial, antiviral, and anti-inflammatory effects. A healthy microbiome is promoted by the high oligosaccharide content of HM. The oligosaccharides have a prebiotic and antiadhesive effect. This blunts the intestinal inflammatory response to pathogenic bacteria. The gut of the HM-fed infant is colonized mostly by *Bifidobacteria* and *Lactobacilli* as opposed to the coliforms, enterococci, and *Bacteroides* species that colonize formula-fed infants. Abnormal colonization is also promoted by delayed enteral feeding, the use of broad-spectrum antibiotics, and exposure to the pervasive organisms in the NICU milieu. Maturation of the gastrointestinal tract is supported by components in HM resulting in improved motility, smaller gastric residuals, and decreased intestinal permeability. Preterm infants have decreased ability to absorb fats. Enzymes in HM allow for improved fat absorption and intestinal lipolysis.

Milk from mothers of preterm infants initially has higher protein and mineral content than term HM. Unfortunately, HM is slightly low in chloride and is deficient in protein, calcium, and phosphorus to meet the needs of the preterm infant. The content of preterm HM varies widely in protein and fat content depending on time of day, the individual mother, stage of lactation, time within a single expression of HM, method of collection, storage, and mode of enteral feeding. By 42 days of lactation, preterm milk protein content stabilizes at approximately 0.8 to 1 g/dL, which is similar to term milk.

Maternal HM

Pumping should be started as soon as possible after delivery. Initiation of lactation can be difficult so the advantages of breastfeeding should be emphasized, along with continued encouragement. Most hospitals in developed countries have lactation consultants to facilitate this. Skin-to-skin contact can increase the success of lactation. Breastfeeding mothers report feeling empowered, self-confident, and more bonded to their infants. Frequent milk expression throughout the day should be implemented; more than 100 minutes of expression per day is optimal. Electric breast pumps are more efficient than hand expression and should be made available to mothers. Mothers must be advised of the importance of colostrum.

Donor HM

For VLBW infants, if maternal HM is not available, pasteurized donor HM is preferred over formula. Many feeding guidelines recommend donor HM through 33 weeks' PMA to reduce the rate of NEC, which normally declines after 32 weeks. Pasteurization removes potentially harmful bacteria, but unfortunately also removes lipases, lymphocytes, and other beneficial components of HM. Analysis of pooled donor HM reveals a consistent content of approximately 0.9 g/dL protein and 4 g/dL fat, with an energy content of 48.3 kcal/100 mL.

Preterm infants fed donor HM demonstrate slower growth rates and biochemical abnormalities that suggest insufficient protein and mineral intake. Decreased weight gain is observed when infants receive larger amounts of milk and more nutritional supplements. Despite these shortcomings, donor HM is a valuable resource. Seventy-two percent of mothers of preterm infants are unable to provide all the milk needed for an exclusive HM diet. Donor

HM costs $27 to $590 per NICU infant during hospitalization (based on an average price of $4/oz).

Premature Formula

Formula specifically designed for preterm infants is appropriate to use if maternal or donor HM is not available. The specific formulations are based on fetal accretion rates and studies of metabolism and gastrointestinal tract development. Premature formula provides greater amounts of protein, calcium, zinc, iron, phosphorus, and copper than term formula without exceeding the overall energy intake goal (Table 2). Despite sodium content being higher than HM or standard infant formula, some infants may still require supplementation. Premature formula is composed mainly of whey, rather than casein, reducing the frequency of metabolic acidosis. Compared with standard formula, the protein content is 50% greater and provides 3 to 4 g/kg per day. This improves weight gain and protein accretion. Vitamin concentration is also higher. Fat content is provided by nearly equal quantities of long-chain and medium-chain triglycerides. Preterm infants have a relative lactase deficiency, and premature formula has a lower lactose concentration. Standard premature formula has low iron concentration (3 mg/L), but higher iron versions are available that provide 15 mg/L, which is optimal for a discharge formula. Use of premature formula results in higher verbal IQ scores (even into adolescence) than when term formula is used for preterm infants.

Infants with a birthweight of less than or equal to 1,800 g and GA of less than or equal to 34 weeks at birth with no available HM or needing HM supplementation should be provided 24 kcal/oz premature infant formula. This formulation is iso-osmolar. Infants who are volume restricted or have inadequate growth may benefit from hypercaloric formula. Ready-to-feed 30-calorie preterm formula is available. It reduces mixing errors and eliminates powdered formula use in this immunocompromised population. It provides the same amount of protein as standard preterm formula but in less volume and has more calories from fat and less calories from carbohydrates. The osmolality of 30 kcal/oz ready-to-feed formula is 325 mOsm/kg of H_2O.

FORTIFICATION

Human Milk Fortifiers

HM does not provide adequate nutrients for optimal growth. Fortification is needed, especially to meet protein needs. Fortification provides additional protein, calcium, phosphorus, vitamin D, and sodium. Human milk fortifiers (HMFs) vary in micronutrients because the requirements of premature infants for most micronutrients are only approximated. Multicomponent HMFs improve postnatal weight gain, linear growth, and brain growth.

Because of the variable composition of HM, appropriate fortification, especially of protein, is challenging and often inadequate, resulting in EUGR. Fat content can also be decreased by the collection, storage, and administration of HM, resulting in lower energy content. HM analyzers can help optimize fortification. Only 76% of the total nitrogen in HM is true protein, so most analyzers overestimate protein content by about 24%. If a milk analyzer is not available, fortification can be adjusted based on blood urea nitrogen (BUN) concentration (goal: 3.2–5 mmol/L) as a surrogate for adequate protein supply. While custom fortification may provide more appropriate amounts of nutrition to an individual infant, generalized fortification strategies are simpler and less prone to error. HMFs provide additional protein from either cow milk fractions or donor HM. Fortification increases the osmolality by 35 to 95 mOsm/kg H_2O, which can be further increased if the fortified milk is left standing.

Fortifiers are available as powders or liquids in premeasured quantities, which are added to specific volumes of HM. No significant long-term adverse effects due to HMFs have been reported. The higher osmolality resulting from the addition of HMF has not been associated with NEC or intestinal injury. Introduction of fortification can slow

TABLE 2. **Nutrition Provided by Unfortified Substrates**

Per 100 mL	kCal	PROTEIN (g)	FAT (g)	CHO (g)	Ca (mg)	P (mg)
Preterm human milk	67	1.4	3.8	6.5	24.4	12.5
Donor milk	65–67	0.9–1.2	3.2–3.6	7.2–7.8	24.4	12.5
Preterm formulas (24 kcal/oz)	80	2.4	4–4.3	8.1–8.7	130–143	66–79

CA=calcium; CHO=carbohydrate; P=phosphorus. From Adamkin DH. Nutritional Strategies for the Very Low Birthweight Infant. *New York, NY: Cambridge University Press; 2009.*

gastric emptying and cause increased residuals. The antibacterial activity of HM can be diminished by added iron in fortifiers.

Fortification to prevent poor growth and osteopenia should be started in infants of less than 32 weeks' GA or less than 1,500 g birthweight. Appropriate fortification must be initiated no later than when HM enteral feedings reach 100 mL/kg per day but may be started as early as 50 mL/kg per day. Fortification of even the first feed has been well-tolerated. When using donor HMF, fortification can be started at low volumes, such as at 40 mL/kg per day. Some NICU feeding guidelines initiate fortification at half strength and advance to full strength; however, it is more commonly started at full strength.

HM can be mixed with 24 kcal/oz preterm formula to make 22 kcal/oz formula with enhanced nutrients. Portions of a 30 kcal/oz ready-to-feed liquid premature formula can be added to HM to make 24 or 25 kcal/oz feeds with the added benefit of avoiding nonsterile powders. As this practice dilutes the HM, the benefits of HM theoretically may decrease (Table 3).

Powder Fortification

Historically, there has been a fear of "high" protein content in premature formulas. These concerns arose after a study in the 1970s demonstrated that high quantities of poor-quality protein (6–7.2 g/kg per day) increased the risk of neurodevelopmental impairment. Powder fortifiers were developed during this era and provide 1 to 1.1 g/dL of protein, levels that do not meet the protein needs of preterm infants. The Academy of Nutrition and Dietetics and the Centers for Disease Control and Prevention do *not* recommend the use of powdered formula fortification in the NICU because of the potential for infectious complications.

Liquid Fortifiers

Bovine milk–based fortifiers add 1 to 1.8 g/dL of protein. HM-based liquid fortifier adds 0.6 g/dL of protein when mixed at 80 kcal/dL. However, the amount of protein added increases as the ratio of fortifier to milk increases and can be as high as 1.6 g/dL when it is mixed 1:1 with HM, resulting in a 100-kcal/dL formula. The dilution of HM increases as fortification increases. Commercially available HM donor milk has +4, +6, +8, and +10 formulations to provide 24 to 30 kcal/oz of protein. Liquid fortification results in better weight, head circumference, and linear growth without differences in tolerance or days to achieve full feedings. Liquid fortification is associated with increased prealbumin, albumin, and BUN but does not appear to increase the incidence of NEC or sepsis.

HOW TO GIVE ENTERAL FEEDINGS

Initiating and Advancing Feedings

There is no consensus on the best approach to provide enteral feedings to a preterm infant. However, there are basic principles. Minimal enteral nutrition/trophic feedings/gut priming are small feedings of less than or equal to 24 mL/kg per day and are thought to promote gastrointestinal maturation, reduce mucosal atrophy, and protect against NEC. Trophic feedings should be started as soon as possible. They are usually given for 1 to 3 days or more, depending on clinical status. Typically, only small amounts of colostrum are available for several days after birth. In such cases, clinicians should consider supplementing with donor breast milk or preterm formula. Ideally, enteral feedings should be started within 48 hours of birth, with delays up to 72 hours because of parental request to await the mother's own milk production. Delays in initiation of enteral feedings may occur because of clinical reasons,

TABLE 3. **Nutrition Provided with Different Commercial Human Milk Fortification Strategies**

Per 100 mL	kCal	PROTEIN (g)	FAT (g)	CHO (g)	Ca (mg)	P (mg)
PTHM + SSC30 (4:3 ratio, 24 kcal/oz)	80	1.7	4	5.6	72	40
PTHM + SHMF (1 pkt/25 mL, 24 kcal/oz)	80	1.9	3.3	6.7	112	63
PTHM + EHMF (1 pkt/25 mL, 24 kcal/oz)	80	1.8	3.8	5.6	77	42
PTHM + SSC30 (1:1 ratio, 24 kcal/oz)	83	1.9	4.2	6.2	84	47
Prolacta +4 (25 kcal/oz)	100	2.3	4.9	7.3	128	70

CA=calcium; CHO=carbohydrate; EHMF=Enfamil® Human Milk Fortifier; P=phosphorus; PTHM=preterm human milk; SHMF=Similac® Human Milk Fortifier; SSC30=Similac® Special Care®.
Adapted from Adamkin DH. 2009. Nutritional Strategies for the Very Low Birthweight Infant. *New York, NY: Cambridge University Press.*

such as treatment with vasopressor agents in a severely ill premature infant.

Advancement of feedings by increments of 20 to 30 mL/kg per day is reasonable for 1,000 to 1,499-g birthweight infants. However, for those weighing less than 1,000 g, lower volume advancement is generally used. Nevertheless, slower rates of advancement (<24 mL/kg per day) have not been shown to reduce the risk of NEC in VLBW infants. Faster advancement (up to 35 mL/kg per day) shortens the time to achieve full feedings and regain birthweight without increasing NEC. Feedings should be advanced with goals of achieving an enteral volume intake of 150 to 160 mL/kg per day, as well as 110 to 130 kcal/kg per day energy and 3.5 to 4.5 g/kg per day protein.

Bolus versus Continuous Feedings

Studies have failed to demonstrate differences between bolus and continuous feedings for VLBW infants. Systematic reviews comparing these methods have shown no differences in time to achieve full oral feedings, length of stay, NEC incidence, or postnatal growth rate. However, in infants weighing less than 1,250 g, continuous feedings may improve weight gain and lead to earlier discharge. Traditionally, gavage tube feedings were given as intermittent boluses using gravity for 10 to 30 minutes every 2 to 3 hours. Studies suggest that feedings every 2 hours improve feeding tolerance and reduce the time to achieve full volume. For some infants, especially those with feeding intolerance, slow bolus feedings for 30 to 120 minutes may be better. Continuous infusions can lead to fat loss, with up to 30% of the energy lost in the tubing. However, for VLBW infants, continuous feedings have been used to decrease energy expenditure, improve gastrointestinal maturation, reduce reflux, and improve feeding tolerance.

Route of Feeding

Prolonged gavage tube feeding is often necessary for preterm infants secondary to neurologic immaturity. Systematic reviews have not found benefits of nasal versus oral gavage tube placement. Transpyloric feeding should generally be avoided when possible, because it has been associated with increased mortality and gastrointestinal disturbances. This may be due to bypassing gastric acids (which destroy bacteria). Non-nutritive sucking starting around 32 weeks' PMA can facilitate the transition from tube feedings to nipple feedings. Once breastfeeding begins, higher caloric supplementation may be needed to provide adequate energy and protein.

Assessing Intolerance

Gastric residuals do not have predictive value for feeding tolerance. They occur frequently in the neonatal period from gestationally appropriate physiologic slow gastric motility and are virtually always benign and not indicative of NEC. Abdominal examination (assessing for distention), pattern and consistency of stools, and other clinical findings are much more informative than residuals. Volumes less than 4 mL/kg or less than 50% of a feeding given 3 hours earlier are not indications to withhold or reduce enteral feeding unless other significant clinical signs are present. Occult blood in the stool, increased abdominal girth, high urine specific gravity, and delayed passage of meconium or stool are all typically minimal obstacles in initiating and advancing feedings. If enteral feedings are held to evaluate for NEC or another disease, they should be restarted as soon as the clinical status of the infant allows, even if it is only within a few hours.

CONCLUSION

Premature infants commonly suffer from EUGR from inadequate nutrition and loss of the last months of gestation, a critical period for brain and body growth. Providing optimized nutrition for the premature infant is a crucial task of the neonatologist and has a significant impact on the future growth and neurodevelopment of these infants. Enteral feeding is nuanced in the preterm population and requires specific knowledge of the nutritional requirements of the preterm infant and the various substrates and methods available to achieve proper nutrition.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the differences in the nutritional composition of human milk and infant formula.
- Recognize the effects of different methods of processing of human milk, such as freezing, pasteurization, sterilization, and microwaving.
- Know that human milk needs to be fortified in order to meet the nutritional needs of preterm infants.

Suggested Reading

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1. Early enteral nutrition is important for gastrointestinal growth and development and has been shown to improve weight gain in preterm infants. Which of the following statements regarding early enteral nutrition is FALSE?
    A. The lack of enteral nutrition causes mucosal atrophy.
    B. Early enteral nutrition decreases the time to reach full feeding volumes.
    C. Early enteral nutrition decreases length of stay.
    D. Early enteral nutrition is associated with a greater risk of necrotizing enterocolitis.
    E. The lack of enteral nutrition leads to increased gut permeability.
2. The goals of enteral nutrition are to maintain lean body mass and bone density, maximize neurodevelopment, minimize complications, and optimize weight gain. Which of the following recommended targets for appropriate growth is correct?
    A. A weight gain of 18 g/kg per day.
    B. A head circumference growth of 0.5 cm/week.
    C. A length gain of 0.75 cm/week.
    D. A caloric goal of 90 kcal/kg per day.
    E. A protein goal of 3 g/kg per day.
3. Pasteurized donor human milk is recommended over formula for very low birthweight infants. Which of the following statements regarding pasteurized donor human milk is correct?
    A. Approximately 50% of mothers of preterm infants are unable to provide all the milk needed for an exclusive human milk diet.
    B. The pasteurization process removes lymphocytes but preserves lipase levels in donor human milk.
    C. The protein content of pooled donor human milk is typically similar to that of term milk.
    D. Infants fed donor human milk demonstrate similar growth rates as preterm infants fed their own mothers' milk.
    E. The use of pasteurized donor human milk is recommended through 35 weeks' postmenstrual age to decrease the risk of necrotizing enterocolitis.
4. Human milk contains many bioactive factors shown to be beneficial for growth and development. However, human milk is low in protein, calcium, and phosphorus; therefore, fortification is required to meet the nutritional needs of the preterm infant. Which of the following statements regarding human milk fortifier (HMF) is correct?
    A. The use of HMF increases the osmolality by 150 mOsm/kg H_2O.
    B. The introduction of HMF leads to faster gastric emptying.
    C. Fortification should be held until feeds have advanced to 120 mL/kg per day and are well tolerated.
    D. The antibacterial activity of human milk is not affected by the addition of HMF.
    E. Bovine milk–based fortifier adds 1 to 1.8 g/dL protein.

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5. Enteral nutrition is very important to optimize outcomes in preterm infants. Although there is no consensus on the best approach to feed a preterm infant, which of the following basic principles regarding enteral nutrition in the preterm infant is correct?
    A. The terms *minimal enteral nutrition*, *trophic feedings*, and *gut priming* describe small feedings of no more than 10 mL/kg per day.
    B. Daily enteral feeding advancement of 20 to 30 mL/kg per day is reasonable in preterm infants with birthweights more than 1,000 g.
    C. Rates of advancement of less than 24 mL/kg per day have been shown to decrease the risk of necrotizing enterocolitis.
    D. Trophic feeds for a minimum of 5 days are recommended to promote gastrointestinal maturation, reduce mucosal atrophy, and protect against necrotizing enterocolitis.
    E. Enteral feedings should be advanced to a maximum enteral volume intake of 130 to 140 mL/kg per day.

Enteral Feeding of the Preterm Infant

Kate D. Brune and Steven M. Donn

NeoReviews 2018;19;e645
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Enteral Feeding of the Preterm Infant

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The Rapidity of Advancement of Feedings in Premature Infants: Evidence Basis and Current Recommendations

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Education Gaps

1. Extreme prematurity is a state of nutritional emergency that requires careful attention to avoid catabolism.
2. A number of feeding strategies are commonly used in practice that are not based on evidence.

Abstract

It is every neonatologist's aspiration to achieve "optimal postnatal growth" in preterm infants, because nutrition and growth of this population affect long-term neurodevelopmental outcomes. However, despite having this common goal, there are huge variations in the enteral feeding practices of preterm infants across the globe. One such practice is the rate of advancement of enteral feedings; there is no consensus about the optimal approach, even among international nutritional experts. In this review, we aim to provide readers with the rationale for different practices in feeding advancement and summarize the current literature.

Objectives After completing this article, readers should be able to:

1. Recognize the importance of nutritional management of preterm infants and variations in clinical practice.
2. Explain the rationale of varying opinions about the rate of feeding advancement in preterm infants.
3. Describe the current literature about feeding advancement in preterm infants.

AUTHOR DISCLOSURE Drs Garg and Sinha have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

ADEPT	Abnormal Doppler Enteral Prescription Trial
CI	confidence interval
IQR	interquartile range
NEC	necrotizing enterocolitis
RCT	randomized controlled trial
RR	relative risk
SIFT	Speed of Increasing Milk Feeds

INTRODUCTION

Preterm birth, in addition to the problems associated with respiratory, cardiovascular, and immune functions, is also a state of nutritional emergency. As the survival rates of extremely preterm infants have improved over the last few decades, the focus has gradually shifted toward not only keeping these infants alive but also providing the optimum nutrition to improve long-term neurodevelopmental outcomes. (1) It is important that evidence-based nutritional practices are adopted in the general management of preterm infants to provide adequate nutrition and reduce nutritional deficits, facilitate brain growth, and minimize neurodevelopmental morbidities. (2)

Necrotizing enterocolitis (NEC) is a common disorder in the preterm neonatal population that is associated with increased mortality and major long-term morbidity. A number of observational studies indicate that the incidence of NEC may be lower in neonatal units where standardized feeding regimens are practiced. (3) The main aim of most feeding strategies is to safely reach full enteral feedings, avoid significant weight loss, maintain adequate growth, and decrease the incidence of NEC. However, even if a neonatal unit adopts a feeding strategy, there are still substantial variations in the routine day-to-day practical aspects of feeding preterm infants as individual clinicians may have differing preferences. (4)(5) One of the most widely accepted and well-studied practices is the use of mother's own breast milk during initial enteral feeding of preterm infants to minimize the risk of NEC. (6)(7) In contrast, clinicians still have not reached a consensus on other preterm feeding practices such as:

- Time to initiate enteral feeding in the extremely preterm infant.
- Initiation of trophic feedings versus complete fasting for the first few days after birth.
- Rate of advancement (increase of enteral volume).
- Timing for introduction of breast milk fortifiers.
- Use of hydrolyzed protein versus standard preterm formula.
- Role of assessing gastric residuals (quantifying and qualifying).
- Use of probiotics.

ENTERAL FEEDING AND RISK OF NEC

The incidence of NEC in preterm infants has been steady over the last few decades, ranging from 3% to 10% with a mortality rate as high as 30%. (8) The pathophysiology is likely multifactorial and outlined in Fig 1. (8) As mentioned earlier, using mother's own milk remains a significant factor in reducing the incidence of NEC; it is also true that NEC is very rare in infants who have never been fed. (9) Most of the feeding interventions that neonatologists adopt aim to encourage rapid achievement of full enteral feedings to improve postnatal growth but this approach may potentially increase the risk for NEC. It is important for the reader to understand that NEC cannot be prevented by a single strategy intervention. However, the provision of a full package of standardized feeding regimens and practices may decrease the frequency of the disorder. One particular strategy may not be practical or feasible in an individual unit depending on the other influencing or confounding factors. In this review, we mainly focus on the consensus and evidence available for the rapidity of advancement of enteral feeding volume in preterm infants.

CURRENT FOCUS ON ENTERAL FEEDING OF PRETERM INFANTS

Over the past several decades, neonatal clinicians have focused their attention on the day-to-day nutritional care of premature infants. Neonatal dietitians or nutritionists are becoming an integral part of the neonatal team. Pharmacists also work in close collaboration with these clinicians to provide the various regimens of parenteral nutrition that ensure an optimal balance of various macro- and micronutrients. This is particularly crucial in the first several days to weeks after birth while enteral feedings are being advanced and when the maintenance of protein, energy, and lipids may potentially translate into better brain growth and accelerated white matter maturation. (10) Various feeding guidelines written by neonatologists aim to achieve full enteral feeding within the first 1 to 2 weeks after birth. This is an attempt by clinicians to rely more on physiologic enteral feeding and less on parenteral nutrition. Promotion of early enteral nutrition could mean fewer days for invasive lines to be in place and reduce the risk of catheter-related sepsis and other complications. In our neonatal unit, we conducted a retrospective observational study to compare short-term nutritional outcomes in infants born at less than 32 weeks' gestational age during 2 periods (1991 and 2009). (11) The clinicians were much more liberal (aggressive) in providing enteral nutrition to the preterm infants in the 2009 cohort, starting feedings earlier by a mean of 5 days (P=.0001). During the later period, birthweight was achieved earlier by a mean of 4 days (P=.005) and the infants were fully orally fed (breast or bottle) earlier by a mean of 9 days (P=.0001). A similar mindset of providing full enteral feedings sooner rather than later has led to a number of trials over the last few years comparing various rates of feeding advancement to assess safety.

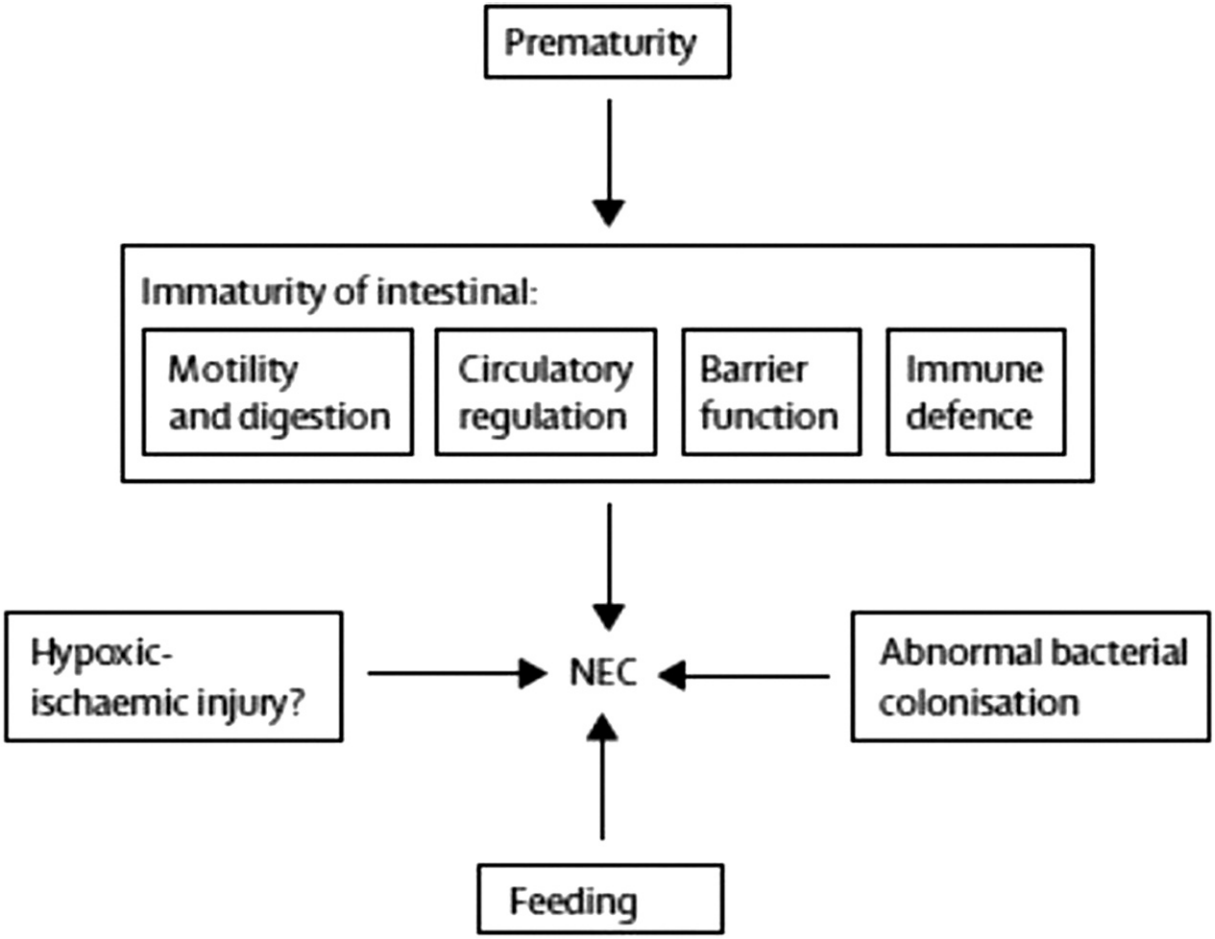

Figure 1. Pathophysiology and interaction of factors responsible for necrotizing enterocolitis. (Reproduced with permission from *Lancet*. 2006;368:1271-1283.)

INITIATION OF ENTERAL FEEDINGS IN PRETERM INFANTS

Most clinicians are in agreement that if the mother's own milk is available, there is no benefit in delaying enteral feedings in hemodynamically stable preterm infants. Initially, preterm infants may only receive a small amount of expressed/pumped colostrum that is placed directly into the child's mouth. As milk production increases, regular interval feedings of a standard minimal volume are given either continuously or as bolus nasogastric feedings, depending on the preferences of individual clinicians or as per local guidelines. This practice is described as *trophic feeding* and the typical volume of milk ranges from 10 to 24 mL/kg per day. Trophic feedings are continued for a variable number of days, as tolerance is established. Once clinicians believe a certain minimal volume is being tolerated, typically after 1 to 3 days, they undertake advancement in volume.

ADVANCEMENT OF ENTERAL FEEDING

The rate of increase of feeding volume in premature infants is variable, as there is no current consensus among physicians. The slowest rate of volume advancement for one neonatal unit may be considered to be the fastest rate for others and vice versa. The decision to start advancing feeding is based on clinical evaluation of tolerance of feedings, which is assessed regularly by checking presence/absence of vomiting and abdominal distention. The routine measurement and evaluation of gastric residuals are of unclear clinical significance. (12)(13) There is no definite evidence to suggest that routine evaluation of gastric residuals in the preterm population provides a good monitoring tool for assessment or prediction of NEC. Although bloody gastric residuals need to be considered seriously, routine low-volume gastric residuals in an otherwise well infant should not affect the advancement of enteral feedings. Several trials have been conducted to study the intestinal motility effects of various medications (eg, erythromycin,

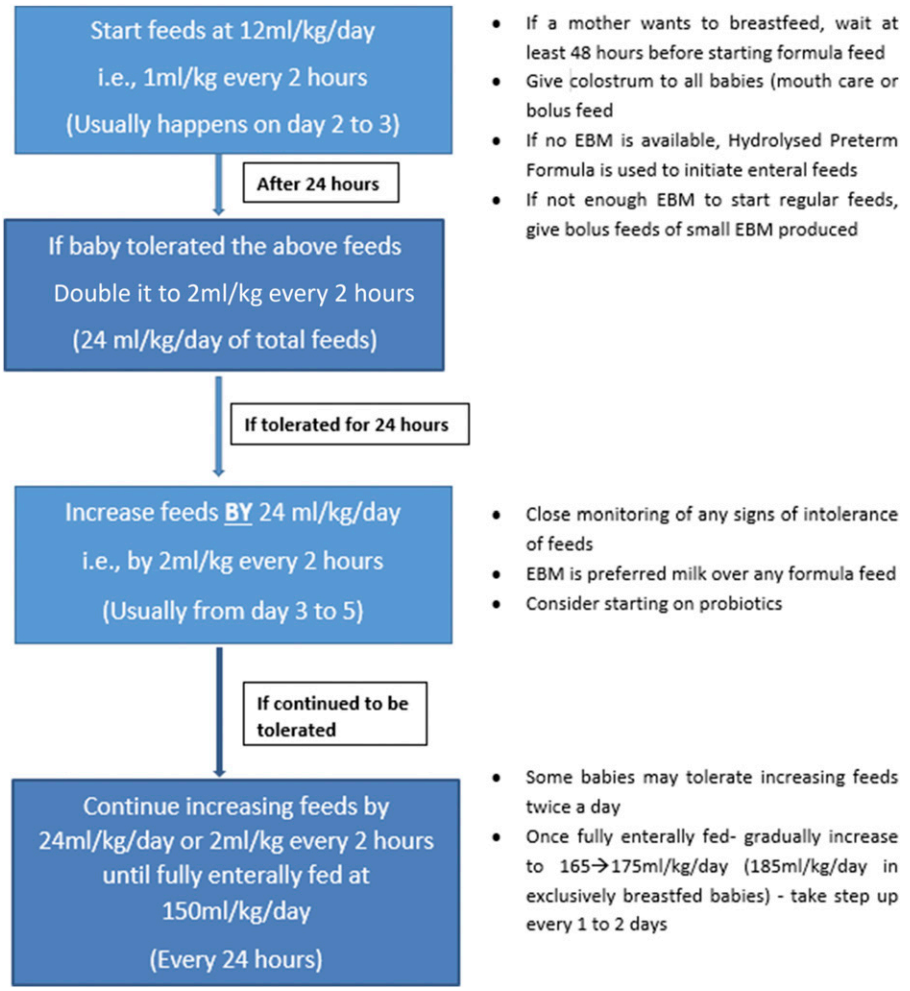

Figure 2A. An example of feeding guidelines for infants of less than 32 weeks' gestation and/or less than 1.5 kg birthweight. This reflects current practice in the authors' unit based on multiple factors and has not been previously published or compared with other feeding guidelines in a randomized controlled trial. EBM=expressed breast milk.

lactulose) in achieving full enteral volume. (14)(15) However, use of such medications is not widely accepted. The assessment of tolerance to feedings has subjective variations depending on several factors, including gestational age of the infant, postnatal age, associated clinical and hemodynamic parameters, sepsis-related concerns, the experience of the bedside nurses and physicians, and occasionally, parental anxiety. In addition to the differences in the daily volume or rate of advancement of feedings, variations in advancement may be seen (either once daily or more frequently). There are also differences in whether continuous or bolus feeding is administered, even within the same unit. Of note, no differences have been found between these methods of administration (bolus vs continuous) in the time to achieve full enteral volume, risk of NEC, rapidity of weight gain, or duration of hospitalization. (16)

Many neonatal units around the world have developed their own guidelines for the advancement of enteral nutrition in preterm infants. Some practices are evidence-based, having considered the most current literature, whereas others are "historical" in nature, using the same feeding guidelines that have been in place for years, reflecting a degree of comfort with a particular practice. As mentioned previously, whatever feeding regimen is used, there is evidence that having a standardized practice does have an impact in decreasing NEC frequency. Different concepts of what is considered to be feeding intolerance play an important role in advancing enteral volumes. (17) A particular feeding protocol in one unit may not be suitable or practical in another unit. Fig 2A provides an example of a feeding guideline for premature and low birthweight infants. This regimen is currently in use in our own unit and should only be considered an example of a feeding practice. Clinicians should make their own pragmatic decisions about developing feeding guidelines based on the available evidence, unit preferences, and consensus of the

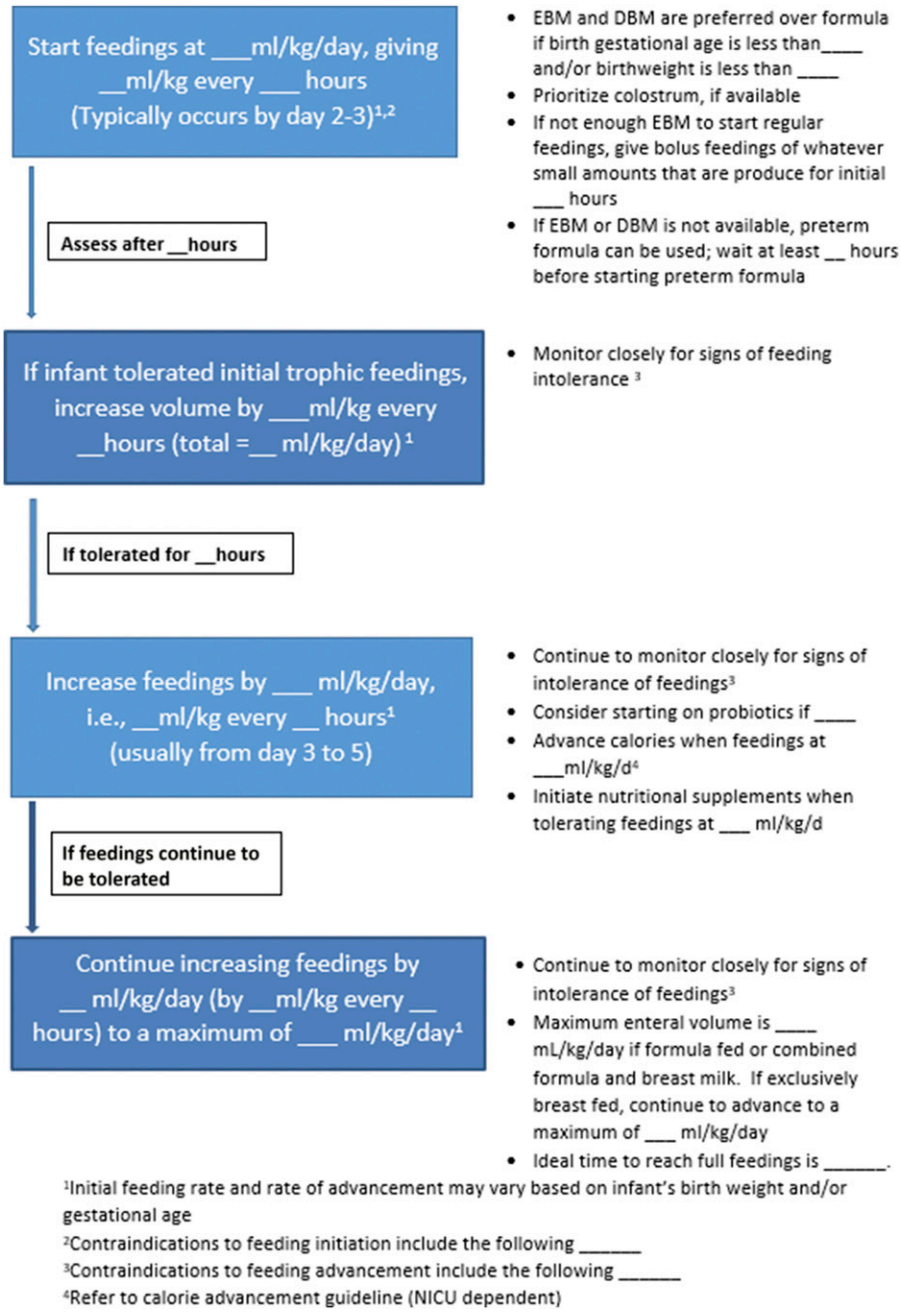

Figure 2B. A template that neonatal providers can use to develop feeding advancement guidelines in their own units. DBM=donor breast milk; EBM=expressed breast milk.

practitioners regarding multiple factors, such as the use of donor breast milk, maximum enteral feeding volume, timing of adding breast milk fortifiers, and using probiotics, as well as the practice of continuous versus bolus feeding. In Fig 2B we provide a template for readers to consider using when creating feeding guidelines for their own units based on the aforementioned factors.

A single feeding regimen may not be appropriate for the wide range of preterm gestations, for example, 23 to 26 weeks' gestation versus 27 to 31 weeks' gestation. Infants of lower gestation may have considerably different problems and medical needs as compared to more mature preterm infants because of different physiologic and maturational intestinal functions. Hence, our approaches and aspirations to achieve full enteral feedings in these infants need to be realistic. This is also true for infants who may be unwell (eg, hemodynamically unstable) and are in need of significant (or disproportionate) cardiorespiratory support. This was

demonstrated in the subgroup analysis of a randomized controlled trial (RCT) conducted in the United Kingdom, which compared early feeding after birth (2 days) with delayed feeding (6 days) in growth-restricted preterm infants with abnormal antenatal Doppler findings (the Abnormal Doppler Enteral Prescription Trial [ADEPT]). (18) The mean gestational age was 31 weeks. The authors found that the early introduction of enteral feedings in growth-restricted preterm infants resulted in earlier achievement of full enteral feeding and did not appear to increase the risk of NEC. The subgroup analysis of this trial showed that full feedings were achieved later in infants of less than 29 weeks' gestation (median age 28 days; interquartile range [IQR] 22-40) compared with 19 days (IQR 17-23) in infants of greater than or equal to 29 weeks' gestation (hazard ratio 0.35; 95% confidence interval [CI] 0.3-0.5). The incidence of all stages of NEC was also higher in this group: 39% (32/83) in infants of less than 29 weeks' gestation compared with 10% (32/312) in those of greater than or equal to 29 weeks' gestation (relative risk [RR] 3.7; 95% CI 2.4-5.7). Hence, the authors concluded that a slower advancement of feedings may be required for this population of infants. (19)

CLINICAL TRIALS COMPARING FEEDING RATES

Over the last 15 years, numerous trials have tried to address the question of optimal rate of feeding advancement in preterm infants. Most of these were RCTs and of good methodological design. During our review of the literature, it was clear to us that the dilemma of slower versus faster rates of feeding volume advancement has long existed. Moreover, the definitions and goals for providing enteral feeding, as well as the rates of advancement, have been changing over the years. One of the earliest comparisons of feeding rates was from the 1970s; the feeding advancement rate that was considered fast at that time is in fact considered a slow rate in recent trials. (20) Almost all recent trials define a slow advancement as a rate of 15 to 20 mL/kg per day and a fast rate as 30 to 40 mL/kg per day. Thus, even with progress in our knowledge of preterm nutrition, some of the long-held beliefs concerning feeding rates and their relationship to NEC may not be evidence-based. Moreover, neonatologists who currently practice may be more at ease with increasing enteral feedings at more liberal rates.

A number of units have enteral volume advancement rates more or less in the middle of slow and faster feeding regimens. We and others may change our practices in the future depending on evidence from well-conducted RCTs. One of the criteria for advancing is the tolerance to the previous volume(s). We acknowledge that the assessment of feeding tolerance can be quite variable and subjective depending on the threshold of individual clinicians. With the exception of the recently conducted Speed of Increasing Milk Feeds (SIFT) trial, virtually all other RCTs assessing rapidity of advancement of enteral volumes have included very small sample sizes. (21)(22) Outcome variables have generally included the number of days to the achievement of full enteral feedings, the number of days to regain birthweight, and the incidence of NEC. There have been some differences in the RCTs based on the type of feedings (expressed breast milk, formula feedings, or a combination). These may have resulted in some of the differences in the results. All published RCTs have been included in a recent systematic review. (21)

RATE OF FEEDING ADVANCEMENT AND SHORT-TERM NUTRITIONAL OUTCOMES

As discussed elsewhere in this article, the reservation about faster rates of feeding advancement is mainly because of the belief that this approach increased the risk of NEC. The evidence supporting this belief is not of high quality (mainly based on observational studies). In fact, a number of published RCTs have concluded the contrary as addressed in the Cochrane review. (21) The population included infants of less than 32 weeks' gestation or birthweight less than 1,500 g. The included trials compared outcomes of infants who were advanced slower (15-20 mL/kg per day) versus those advanced faster (35-40 mL/kg per day). No significant difference was found in the risk of NEC (RR 1.07; 95% CI 0.83-1.39) or in all-cause mortality (RR 1.15; 95% CI 0.93-1.42). In the subgroup analysis, the results were similar in extremely preterm (<28 weeks' gestation) and extremely low birthweight (<1,000 g) neonates. The total number of infants included in the systematic review was 3,753. The RCT contributing the greatest number of infants was the SIFT trial (almost 2,800 infants). The findings from the SIFT trial have not yet been formally published, but investigation data have been presented at various international meetings, (22) as well as in the aforementioned Cochrane review. Jon Dorling, the principal investigator of the SIFT trial has summarized the main outcomes as follows: "At hospital discharge, SIFT did not demonstrate any harms from faster feed increments (30 mL/kg per day vs 18 mL/kg per day), and benefits were seen in terms of reaching full feeds quicker and being given less parenteral nutrition. Indeed, there was more NEC and late-onset sepsis in the slower feed increment group although this did not reach statistical significance. Outcomes at 2 years of age (corrected for prematurity) will be available later this year" (J. Dorling,

MBChB, DCH, MD, personal communication, 2018). Details of this study are forthcoming.

CONCLUSION

The weeks after the delivery of an extremely preterm or low birthweight infant are a period of relative nutritional deprivation. Clinicians caring for such infants need to adopt strategies that provide adequate nutrition to this vulnerable population. Optimal strategies should not put infants at increased risk for feeding-related complications. Feeding regimens that are created for this population should be mindful of providing adequate proteins and calories, with the goals of 1) achieving full enteral feeding volume as soon as possible, 2) achieving optimal growth, and 3) perhaps, improving neurodevelopmental outcomes, without increasing the risk for NEC. Admittedly, feeding practices vary widely around the world and not all have a strong evidence base to support them. The debate about slower versus faster advancement of feeding volumes in preterm infants has been subjected to a number of RCTs over the past 2 decades. The results have been reassuring regarding faster rates of advancement without increasing the risk of NEC. With the advancement of our knowledge in neonatal nutrition, clinicians should consider adopting feeding strategies to incorporate new evidence into their clinical practice. Health care providers should also be prepared to challenge and debate the long-held beliefs and practices regarding preterm nutrition. This will help develop rational clinical guidelines that can lead to optimal growth, reduced incidence of NEC, and improved long-term neurodevelopmental outcomes.

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Influences of Feeding on Necrotizing Enterocolitis

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Education Gap

Despite the recognition that enteral feeding and some clinical conditions encountered during the management of prematurity may affect the development of necrotizing enterocolitis (NEC) in premature neonates, there is still significant variation in practice. Clinicians should be aware of the current evidence regarding feeding and the development of NEC in premature neonates, specifically relating to the use of breast milk, feeding when a patent ductus arteriosus is present and during its treatment, as well as the potential association of NEC with anemia and red blood cell transfusions.

Abstract

Necrotizing enterocolitis (NEC) remains one of the leading complications of prematurity with an incidence of 5% to 13% and a mortality of up to 30%. Its occurrence is inversely related to gestational age, with the most premature neonates being at highest risk. Despite numerous studies assessing risk factors, the most commonly observed associations remain prematurity and enteral feeding. Furthermore, studies have pointed to receipt of breast milk as a protective factor in decreasing the risk of NEC and formula feeding as potentially increasing the risk. Other potential risk factors and associations in the premature infant include lack of antenatal steroids, receipt of prolonged courses of postnatal antibiotics, presence of anemia, receipt of packed red blood cell transfusions, and presence of a patent ductus arteriosus. Despite the recognition that NEC remains a serious complication of prematurity, there is still no specific prescription for its prevention. Given that enteral feeding is one of the most commonly observed risk factors for the development of NEC, wide variation exists in the enteral feeding recommendations and practices for premature infants. Feeding practices that may contribute to NEC, which remain variable in practice, include feeding strategies used in the presence of a hemodynamically significant patent ductus arteriosus and feeding during packed red blood cell transfusions. Use of breast milk (mother's own milk or donor milk) is recognized as one of the mainstays of NEC prevention. This article explores multiple influences of feeding on the development of NEC.

Objectives After completing this article, readers should be able to:

1. Recognize the impact of breast milk on the occurrence of necrotizing enterocolitis (NEC).

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ABBREVIATIONS

CI	confidence interval
GI	gastrointestinal
NEC	necrotizing enterocolitis
NIRS	near-infrared spectroscopy
NPO	nil per os
OR	odds ratio
PDA	patent ductus arteriosus
PRBC	packed red blood cell
RCT	randomized controlled trial
RR	risk ratio
SMA	superior mesenteric artery
TANEC	transfusion-associated NEC
VLBW	very low birthweight

2. Describe the association between a patent ductus arteriosus, its pharmacologic treatment, and the development of NEC.
3. Explain the possible contribution of anemia, receipt of red blood cell transfusion, and the impact of feeding on NEC.

INTRODUCTION

Necrotizing enterocolitis (NEC) remains one of the leading complications of prematurity, affecting between 5% and 13% of premature infants and is the most common gastrointestinal (GI) emergency in this population. Its occurrence is inversely related to gestational age with the most premature neonates being at highest risk. (1) The most commonly found associations remain prematurity and enteral feeding. Breast milk appears to confer protection from NEC and formula feeding potentially increases the risk. Other potential risk factors and associations include lack of antenatal steroids, receipt of prolonged courses of postnatal antibiotics without bacteremia, presence of anemia, receipt of packed red blood cell (PRBC) transfusions, and presence of a patent ductus arteriosus (PDA). (2)(3)(4)(5)(6)(7)(8)(9)

NEC remains a serious complication of prematurity; however, there is still no specific prescription for its prevention. Although enteral feeding is one of the most commonly observed risk factors for the development of NEC, wide variation still exists in the enteral feeding recommendations and practices for premature infants. This article briefly discusses the pathogenesis of NEC and explores the evidence behind the influences of feeding on the development of NEC.

PATHOGENESIS

The origin of NEC is multifactorial, with intestinal immaturity at its center and genetic susceptibility, inflammation, the altered microbiome of the premature gut, and hemodynamic instability being additional contributory factors. (10) While the pathogenesis of NEC is still being explored, at its core, it is thought to arise from the premature state of the gut. Prematurity portends an impairment of intestinal repair mechanisms, limited mucin production, and other forms of gut protection, leading to a more porous intestinal epithelium. (11) Activation of toll-like receptor 4 and impaired innate immunity lead to a proinflammatory state. These immune factors are genetically determined and may increase or decrease the risk of NEC. (12) A lack of microbial diversity and colonization with predominantly pathogenic bacteria are also established in infants at higher risk of NEC especially when enteral feedings using formula are introduced. (13)(14) The effects of low blood flow states and transient hypoxemia likely cause ischemic injury to an already predisposed gut. Impaired gut motility leads to bacterial stasis, with subsequent bacterial translocation across a leaky, inflamed, and ischemic intestinal epithelium contributing to the pathogenesis of the disorder. (10)(15)

The most commonly described risk factors for NEC are extreme prematurity and enteral feeding. Numerous studies have pointed to the receipt of breast milk as a protective factor in decreasing the risk of NEC. (16) Other potential risk factors and associations include lack of antenatal steroids, receipt of prolonged antibiotics, presence of anemia, receipt of PRBC transfusions, presence of a hemodynamically significant PDA and enteral feeding during its treatment, and other low blood flow states. (2)(3)(4)(5)(6)(7)(8)(9)

DIAGNOSIS AND MANAGEMENT

Symptoms in patients with NEC may include nonspecific metabolic derangements or symptoms specific to the GI tract. GI signs and symptoms may include bilious emesis, hematochezia, abdominal distention, abdominal tenderness, and discolored abdomen. Other signs and symptoms may include lethargy or irritability, cardiorespiratory derangements (apnea, bradycardic episodes, oxygen desaturation, need for increased respiratory support, respiratory acidosis, hypotension), hematologic abnormalities (thrombocytopenia, disseminated intravascular coagulopathy, low or elevated white blood cell count), renal failure (associated electrolyte abnormalities such as hyponatremia, hyperkalemia), metabolic acidosis, bacteremia, and sepsis syndrome.

The hallmark of diagnosis is clinical symptoms coupled with the presence of pneumatosis on abdominal radiography. Abdominal distention, presence of a sentinel intestinal loop, portal venous gas, a paucity of gas, gasless abdomen, and the presence of pneumoperitoneum may also be observed radiographically. The modified Bell staging criteria are used to delineate 3 stages of NEC and the associated signs and symptoms. (17) Because symptoms of stage I NEC can be nonspecific and short-lived, many studies use NEC stage II or higher as their definition of the disorder.

Management includes bowel rest with intestinal decompression, broad-spectrum antibiotics, and supportive care for multisystem organ failure as needed. Serial radiographs are used to monitor for progression of disease. Surgical treatment is warranted in case of a worsening clinical picture or if pneumoperitoneum is noted on abdominal radiography. Approximately 30% of affected neonates require surgical management. NEC has a mortality of up to 30%, with the highest mortality seen in infants who receive surgical management. (15) Short gut, cholestatic liver failure, prolonged hospital stays with increased medical costs, and more significant neurodevelopmental impairment are additional concerning outcomes. (18)(19)

IMPACT OF GENERAL FEEDING PRACTICES ON THE DEVELOPMENT OF NEC

Though enteral feeding is one of the most commonly observed risk factors for the development of NEC, wide variation exists in enteral feeding recommendations and practices for premature infants. (20)(21) Once relative stability has been achieved after the birth of a premature infant, enteral feedings are initiated. Availability and use of an institutional feeding protocol addressing timing of initiation of enteral feedings, use of trophic feedings, use of breast milk versus preterm formula, fortification of feedings, use of continuous versus bolus feedings, and the pace of feeding advancement are some of the variations in practice that are observed and whose evidence is examined further in this article.

Standardized Feeding Protocols

Studies have shown a reduction in NEC rates with the use of institution-specific standardized feeding regimens. A 2017 meta-analysis by Jasani and Patole (22) evaluated 15 observational studies spanning the years 1978 to 2016 and involved 18,160 premature neonates of less than 37 weeks' gestational age. A 78% reduction in NEC stage II or higher was observed with the use of a standardized feeding regimen (risk ratio [RR] 0.22; P=.0001; 95% confidence interval [CI] 0.13-0.36). (22) To account for possible practice changes over time, 2 different epochs were compared, 1978 to 2004 and 2004 to 2016. The results were still significant in both periods, indicating that the use of standardized feeding regimens decreased NEC rates.

Trophic Feedings/Minimal Enteral Nutrition

It was hypothesized that using a strategy of minimal enteral nutrition or trophic feedings for the first few days of enteral feeding shortly after birth for premature infants, compared with keeping the infant nil per os (NPO) would allow the premature gut to be "primed," promoting intestinal maturation and hence a reduction in the incidence of NEC. A Cochrane review in 2013 analyzed 9 trials with 754 study subjects in which trophic feedings with milk volumes up to 24 mL/kg per day were initiated before 96 hours' postnatal age and continued until at least 1 week after birth. (23) There was no statistically significant effect on the incidence of NEC (RR 1.07; 95% CI 0.67-1.70). (23) It is possible that, despite the lack of a statistical effect indicating a decreased incidence of NEC when studies were pooled, there may be sicker, more premature, and more vulnerable populations of premature infants who may benefit from the use of trophic feedings or minimal enteral nutrition.

Delayed versus Early Advancement of Enteral Feedings

It has been postulated that delaying the progressive advancement of feedings for some days after initiation of enteral feedings could reduce the likelihood of NEC. A Cochrane review in 2014 addressed this question, seeking to compare infants who had early (days 1-4 after birth) versus delayed (days 5-7 after birth) advancements of their enteral feedings. (24) Overall, 9 studies were included in the meta-analysis, with 1,106 subjects who were very preterm (<32 weeks' gestational age at birth) or very low birthweight (VLBW; <1,500 g). The NEC analysis included 8 trials with 1,092 subjects. A statistically significant effect on the risk of NEC was not found (RR 0.93; 95% CI 0.64-1.34). This would suggest that it is not beneficial to delay advancement of enteral feedings past 4 days after birth, because it does not portend a reduction in NEC risk. It was noted that most of the study subjects were not extremely premature (few were born at <28 weeks' gestational age); hence, it is unclear that these results are generalizable to this cohort of premature infants who would have the highest risk of NEC. (24)

Slow versus Fast Feeding Advancement

It is hypothesized that advancing enteral feedings in premature neonates at a pace greater than that considered trophic, that is, greater than 20 mL/kg per day, may increase the risk of NEC in premature neonates. In a 2017 Cochrane review, slow (<24 mL/kg per day) versus faster (30-40 mL/kg per day) enteral feeding advancement rate did not result in a statistically significant difference in NEC for very preterm or very low birthweight infants. (25) Included in the meta-analyses were 10 randomized controlled trials (RCTs) with 3,753 subjects (NEC RR 1.07; 95% CI 0.83-1.39). In this meta-analysis, approximately one-third of subjects were extremely premature or extremely low birthweight (<1,000 g), potentially limiting the generalizability of the results to this population subset at the highest risk of NEC. (25)

Breast Milk (Mother's Own Milk and Donor Milk) versus Formula

The benefits of breast milk for premature infants are many and include a reduction in the incidence of NEC, lower rates of retinopathy of prematurity, reduced episodes of late-onset sepsis, improved neurodevelopmental outcomes, and fewer hospital readmission rates during the year after discharge from the NICU. (26)(27)(28)(29)(30) Reduction in rates of bronchopulmonary dysplasia has been demonstrated less consistently. (26)(27)(28)(29)(30) These benefits are observed even with nonexclusive breast milk use. Breast milk contains many protective factors, including bactericidal, immunologic, antioxidant, and anti-inflammatory properties. (31) Maternal white blood cells, lysozymes, secretory immunoglobulin A, various growth factors, lactoferrin, oligosaccharides, and commensal bacteria are among its protective factors. (32)(33)

Although breast milk use has multiple desirable benefits, including reduction in some of the catastrophic comorbidities experienced with prematurity, without fortification, it can be suboptimal for growth and nutritional balance for the rapidly growing premature infant. There are no studies that directly compare, in randomized fashion, mother's own milk to formula. However, one study evaluating a prospective cohort of premature infants grouped by those who received more than 50% of breast milk in the first 14 days of age versus those who received less than 50% of breast milk showed a reduction in NEC. In the high proportion of breast milk (>50%), NEC occurred at a rate of 3.2% versus 10.6% in the low proportion of breast milk (odd ratio [OR] 0.17; 95% CI 0.04-0.68). (34) In an analysis of 1,272 infants enrolled in the National Institute of Child Health and Human Development glutamine study, increasing human milk intake was associated with a decreasing risk of NEC. Of these infants, 13.6% developed NEC after 14 days of age. (35) For each 10% increase in the amount of milk received, risk for NEC (or death) decreased by 0.83 (95% CI 0.72-0.96). (35) It is still unclear, however, what the threshold is for volume or proportion of milk to which a premature neonate would need to be exposed in order to benefit from its use, if that infant is unable to be exclusively fed breast milk.

When exclusive breast milk use is desired and mother's own milk is unavailable, a donor milk option is available, albeit at a significant expense. The processing of donor milk may reduce some of the protective properties. In addition, donor milk is typically pooled from mothers of larger or full-term infants whose milk composition is different from that of the mother of a premature infant. (27) It is, however, recognized that the use of donor milk also reduces the risk of NEC when compared with formula. In a 2014 Cochrane review comparing donor milk to formula, 9 trials were included, with 1,070 subjects. (16) A significant increase was noted in the risk of NEC in infants receiving formula (OR 2.77; 95% CI 1.40-5.46). (16) In a 2016 study by Chowning et al, a retrospective chart review was undertaken of 550 VLBW infants who received some proportion of mother's own milk and donor milk. (36) The results indicated that receipt of human milk, mother's own or donor, for more than or equal to 50% of hospital days was associated with a statistically significant reduction in NEC, from 13.5% to 3.4% ($P<.001$). (36) While donor milk presents a significant opportunity for reduction in rates of NEC, concern exists regarding suboptimal growth. Hence, attention to optimal fortification is warranted. (27)

Fortification

Although breast milk is seen as the most optimal nutrition for premature neonates and is associated with reduced rates of NEC, to meet the needs of the growing premature infant, fortification with protein or fat as well as micronutrients is needed. This need is even more pressing when donor milk is used. (27) It was thought that with the addition of fortification products and other medications to breast milk, there is an increase in osmolality that may warrant caution. On average, the osmolality of fortified breast milk (without protein additive) is similar to that of preterm formula. (37) It is common practice to wait for establishment of at least half of the daily enteral breast milk volume before fortifying. However, given the link between achieving normal or close to normal growth patterns and improved outcomes related to prematurity, it may be beneficial to fortify breast milk feedings earlier. Tillman and colleagues performed a retrospective pre-post study comparing 53 premature infants of less than 31 weeks' gestational age whose feedings were fortified at first feed and 42 others fortified between 50 and 100 mL/kg per day of breast milk feedings. (38) There was no observed effect on NEC incidence. (38) Shah and colleagues performed a randomized study assessing whether early (20 mL/kg per day) versus delayed (100 mL/kg per day) fortification affected feeding tolerance and time to full feedings; NEC was not noted to be different between the 2 groups. (39)

Bovine versus Human Milk Fortifiers

Despite the reduction in NEC that breast milk offers, its use alone may lead to lower postnatal growth rates compared with preterm cow milk formula of equivalent caloric density, necessitating the use of fortifier products. (27) There has

been increased emphasis on minimizing cow milk in the diet of premature infants when possible, including the products available for fortification. An all-human milk diet, including fortifier products, is associated with the lowest risk of NEC. In a study by Sullivan et al, 207 premature infants fed human milk were randomized to 3 groups: 2 groups received pasteurized donor human milk-based human milk fortifier when mother's own milk or donor milk feedings reached 100 and 40 mL/kg per day, respectively, and the third group received bovine-based human milk fortifier and preterm formula if mother's milk was unavailable. (40) They found the groups that received exclusive human milk diets including fortification had significantly lower rates of NEC (P=.02), and "surgical NEC" (P=.007). (40) Other studies have supported this conclusion as well. (30)(41)(42) There is also a suggestion that nonacidified liquid human milk fortifier added to human milk may offer the greatest reduction in NEC. (43)

Continuous versus Bolus Feedings

It has been purported that feedings may be better tolerated by premature infants if administered in a continuous fashion. However, a Cochrane review in 2011, evaluating 7 trials with 511 VLBW subjects, showed no difference in NEC when continuous oro- or nasogastric feedings were compared with bolus feedings given every 2 or 3 hours. (44)

THE INFLUENCE OF A PATENT DUCTUS ARTERIOSUS ON NEC

In utero, a PDA is responsible for the shunting of oxygenated blood into the systemic circulation. Postnatally, for approximately 30% of preterm infants (higher rates with earlier gestational age) there is delayed spontaneous closure of this shunt, leading to increased pulmonary blood flow after pulmonary pressures drop, and "ductal steal" with decreased systemic blood flow. (8) This phenomenon can lead to impaired perfusion of distal organs, including the gut, which has been purported to cause feeding intolerance and possibly NEC. (45)(46)(47) The effects of a hemodynamically significant PDA on superior mesenteric artery (SMA) blood flow have been examined, with some correlation seen in Doppler blood flow velocity parameters. (47)(48) SMA blood flow response has been noted to be blunted in the presence of a PDA in baboons and human infants. (49)(50)

Increasingly conservative management is being practiced for stable premature infants. (51) In cases of a symptomatic PDA, treatment options for closure include cyclooxygenase inhibitors indomethacin and ibuprofen, and more recently, acetaminophen, as well as surgical ligation for symptomatic persistent PDAs. (52)(53)(54) Indomethacin has been associated with vasoconstrictive phenomena affecting distal organs and causing spontaneous intestinal perforation, and in some cases, increased risk of NEC as well as renal insufficiency. (52)

In a large systematic review published in 2018, Mitra et al compared various pharmacologic treatments for PDA closure. (55) They evaluated 68 randomized clinical trials with 4,802 premature and/or low-birthweight subjects. Although the PDA closure rate was 67.4% and was highest with high-dose oral ibuprofen, in a comparison of placebo with all other medical treatment, no differences in NEC were observed. (55)

Indomethacin can be administered via a prolonged or shorter course. However, based on a systematic review done in 2007 evaluating 5 studies with 431 study subjects, the prolonged course (>4 doses) of indomethacin was associated with increased NEC risk (RR 1.87; 95% CI 1.07-3.27). (56) Ibuprofen is associated with less vasoconstrictive effects with a better GI and renal side effect profile, yet has comparable PDA closure rates. (52) A Cochrane review done in 2015 evaluating 33 studies with 2,290 subjects compared treatment of PDA in premature, low-birthweight neonates using indomethacin, ibuprofen, placebo, or no treatment. (57) Results indicated that ibuprofen was just as effective as indomethacin for PDA closure. However, the risk of developing NEC was reduced for ibuprofen (16 studies, 948 infants; RR 0.64; 95% CI 0.45-0.93). (57) In addition, Doppler blood flow studies show less vasoconstrictive effects on mesenteric and renal artery with ibuprofen compared with indomethacin. (58) Acetaminophen has been studied as a relatively newer therapy for PDA closure. In a Cochrane review of 8 randomized studies including 916 infants, acetaminophen was found to be as effective as ibuprofen, but the evidence was considered to be of low quality to assess the effectiveness in comparison with indomethacin. (54) However, concern exists for neurodevelopment impairment, with autism or autism spectrum disorders suggested with pre- and postnatal exposure to the drug. (54) Additional studies with long-term follow-up are ongoing.

FEEDING IN THE PRESENCE OF A PERSISTENT PDA AND ITS PHARMACOLOGIC TREATMENT

Because of the vasoconstrictive effects of pharmacologic treatment of a PDA and its potential increased risk of

NEC, clinicians sometimes reduce or terminate enteral feedings when a hemodynamically significant PDA is discovered; this practice may vary regionally. (59) Jhaveri et al reported a survey on US- and non-US-based neonatologists regarding their beliefs about whether feedings should be withheld when a persistent PDA is suspected. (59) Results indicated that if neonatologists felt that they had to stop feedings, then they would ligate a PDA irrespective of the need for respiratory support. Of the US neonatologists surveyed, 70% believed that enteral feedings need to be stopped in the presence of a hemodynamically significant PDA. (59) Meanwhile, 70% of non-US neonatologists believed that enteral feedings should continue in the presence of a hemodynamically significant PDA. (59) There are few randomized studies to guide practice.

Bellander et al performed a retrospective review to address whether feeding with breast milk within a few hours after birth in neonates who were less than or equal to 29 weeks' gestational age at birth and ultimately received indomethacin treatment for a PDA led to increased GI risks. (60) There was no difference in the outcome of NEC between the 2 groups. Clyman et al assessed enteral feeding during indomethacin and ibuprofen treatment of a PDA. (61) One hundred seventy-seven preterm infants of more than 31 weeks' gestational age at birth were randomized to trophic feedings versus NPO. The results indicated that the time to achievement of 120 mL/kg per day feedings was less in the trophic feeding group and there was no increase in NEC. (61) A retrospective cohort study by Louis et al in 2016 assessed the risk of NEC when neonates were divided into 3 feeding groups: (NPO [n=229], <60 mL/kg per day [n=142], and >60 mL/kg per day [n=44]) and who received indomethacin for PDA treatment. (62) No difference in the primary outcome of NEC was observed. (62)

TRANSFUSION-ASSOCIATED NEC

Recently, clinicians have expressed concern about transfusion-associated NEC (TANEC), also called *transfusion-related acute gut injury* or *transfusion-related NEC*. This condition is most commonly defined as NEC occurring within 48 hours of receiving a PRBC transfusion. (4)(63)(64) Its etiology has been said to be multifactorial and may relate to an increase in proinflammatory cytokines seen after PRBC transfusion in neonates, alterations in vascular adaptability after transfusion (seen on near-infrared spectroscopy [NIRS] as higher intestinal tissue oxygen saturation as well as altered blood flow velocity noted on Doppler studies) and reperfusion injury related to sudden correction of anemia in poorly perfused and oxygenated intestinal tissues. (65)(66)(67)(68) Singh et al, in their retrospective case-control study, found that both a lower hematocrit and PRBC transfusion increased the likelihood of NEC. (3)

Despite the presence of observational studies linking the temporal receipt of PRBC to the development of NEC, there is still strong debate about whether TANEC is an actual pathologic entity, that is, is the receipt of PRBCs simply an association or is it causative in some cases of NEC? Included in this debate are theories as to whether the degree of anemia before transfusion is the factor that predisposes patients to TANEC. (5)(63)(69) Hay et al (70) performed a systematic review and graded the quality of the available evidence around the TANEC phenomenon. Most of the studies evaluated were observational (n=23) with only 3 randomized studies addressing the allocation of PRBC transfusions. When the definition of NEC occurring within 48 hours of PRBC transfusion was used, the results did not show a statistically significant association of NEC with PRBC transfusion. (70) Similarly, Garg et al performed a meta-analysis of 17 observational studies and did not find an independent association between PRBC transfusion and NEC. (71)

FEEDING DURING PRBC TRANSFUSION

Because of the possible association of PRBC transfusion and development of NEC, some neonatal units have developed transfusion guidelines based on consensus within their unit regarding whether to feed during PRBC transfusions, and for how long a duration to maintain NPO, as well as changes in volume of feedings upon reinitiation. Withholding feedings during PRBC transfusion for the smallest and youngest premature infants may mean need for intravenous access, initiation of intravenous fluids, and possible prolongation of the time to acquire full enteral feedings. Despite the adoption of peritransfusion feeding cessation guidelines by many centers in varying forms, there is limited evidence from randomized trials to guide hemoglobin or hematocrit cutoffs as well as the duration of time for which to withhold enteral feedings to protect from TANEC.

In 2014, DeRienzo and colleagues published a retrospective cohort study of VLBW infants comparing outcomes before and after institution of a peritransfusion feeding protocol. (69) The incidence of NEC decreased from 12% to 7% in the pre- to postprotocol interval (P=.01). However, the incidence of TANEC (NEC within 48 hours of a PRBC transfusion) remained the same in both intervals, 41% of the total number of NEC cases. The risk of TANEC was higher with lower pretransfusion hematocrit (OR 0.87; 95% CI 0.79-0.95). (69)

Marin and colleagues published a study in 2014 in which they assessed mesenteric tissue oxygenation measured by NIRS in preterm infants less than 33 weeks' gestation at birth, categorized into 2 groups: those who were fed (n=9) during PRBC transfusion and those not fed (n=8). (72) Mesenteric oxygenation was assessed for up to 48 hours after PRBC transfusion. Upon resuming feedings, they found lower postprandial mesenteric oxygenation trends in infants fed during transfusions, compared with positive trends in those who were not fed during the transfusion interval. This could indicate a risk of mesenteric ischemia that may potentiate the development of TANEC in infants fed during PRBC transfusions. (72)

Pitzele and colleagues explored whether postprandial SMA blood flow velocity would be affected in neonates who were all fed during PRBC transfusion. (73) Infants were VLBW preterm infants, older than 14 days, who received transfusions while being bolus fed every 3 hours. Pre- and postprandial SMA blood flow velocity was assessed, as well as immediately before and after transfusion and at 24 and 48 hours after transfusion. They found that SMA blood flow velocities were blunted immediately after the transfusion and then normalized at 24 hours after transfusion, suggesting that there may be a period of increased risk of ischemia after PRBC transfusion that may potentiate the risk of TANEC. (73) Importantly, they observed normal postprandial responses in the anemia, in the pretransfusion period. (73)

A systematic review undertaken by Jasani et al in 2017 sought to review the effect of withholding feedings during PRBC transfusion on TANEC. (74) In this review, TANEC was defined as NEC stage II or higher occurring within 48 to 72 hours after a PRBC transfusion. No RCTs were available for inclusion in the review; 7 nonrandomized studies with 7,492 study subjects were included. The results indicated that the practice of withholding feedings during PRBC transfusion significantly reduced the incidence of TANEC (RR 0.47; *P*=.005; 95% CI 0.28-0.80). Of note, the feeding protocols used in the included study varied in the amount of time feedings were withheld before transfusion, the total NPO duration, when feedings were restarted, and if feedings were restarted at lower than prior volumes, how fast they were advanced. (74)

DISCUSSION

A 2006 survey assessing nutrition practices in the NICU for 3 different birthweight categories was undertaken by Hans et al to determine how current nutrition practice intentions for preterm infants compare with published recommendations and previous feeding practices. Of the invited participants, 23% responded (N=176). (21) Breast milk was the most common first enteral feeding in all birthweight categories. Enteral feedings were initiated earlier and advanced faster than in the past, especially for infants weighing less than 1,000 g at birth. Even though data support the safety of more rapid feeding advancement, more than 80% of surveyed NICUs had slow feeding advancements of 10 to 20 mL/kg per day across all weight categories. (21) This study highlights that evidence and practice sometimes are not concordant. Those charged with the care of premature infants often do not have strong experimental evidence from RCTs by which to guide management, and instead have to weigh and interpret observational or retrospective data to inform our practice. As such, this leads to significant variability in management for common complications of prematurity. One such common issue faced by premature infants is NEC, the most common GI illness in this population. Although prematurity and enteral feeding are the most common risk factors for NEC, the use of breast milk, even if not exclusive and including donor milk, is highly associated with conferring protection from NEC. However, a host of other variables that may influence the risk of NEC come into play, including the timing of initiation of feedings, use of trophic feedings or minimal enteral nutrition, pace and rate of progressive feed advancement, timing of initiation of enteral feed fortification, and continuous versus bolus feedings. Another clinical issue affecting premature neonates is the presence of a PDA which, if hemodynamically significant, is purported to be a risk factor for NEC. While the trend is toward more conservative management for patients with a PDA, challenges for some still include whether to feed with a PDA. In addition, if a PDA is being treated with cyclooxygenase inhibitors, given their vasoconstrictive properties and effect on mesenteric vessels, is there risk of NEC if feeding occurs during treatment? Another common condition encountered is anemia of prematurity. Its treatment with a PRBC transfusion has been noted as associated with the development of NEC. This has prompted many NICUs to use feed withholding strategies during transfusion to prevent TANEC, despite the evidence of direct causality being marginal.

The influences of certain aspects of feeding on the development of NEC are supported by observational evidence in many cases. (20)(75) The Table provides a summary of the evidence regarding influences of the discussed feeding factors on NEC. The lack of high-quality evidence still leaves wide variation in feeding practices that may affect NEC, with the exception of strong recommendations for the use of breast milk and standardized feeding regimens. No RCTs have been performed to date to assess the practice of withholding feedings during PRBC transfusion. Although

TABLE. **Influence of Feeding Factors on NEC: Summary of the Evidence**

FEEDING FACTOR	DECREASES NEC	INCREASES NEC	NO/MINIMAL IMPACT ON NEC	UNCLEAR
Standardized feeding regimen	+ (meta-analysis - 15 observational studies)			
Trophic feedings/minimal enteral nutrition			+ (meta-analysis – 9 RCTs)[a]	
Delayed vs early advancement of enteral feedings (5-7 d vs 1-4 d)			+ (meta-analysis - 9 RCTs)[a]	
Slow versus fast feeding advancement <24 mL/kg per day vs 30-40 mL/kg per day)			+ (meta-analysis - 10 RCTs)[a]	
Breast milk (mother's own milk and donor milk)	+ (meta-analysis – 9 RCTs)			
Formula		+ (mix of study types)		
Fortification				
Osmolality			+	
Timing of initiation			+ (mix of study types)	
Human milk-based human milk fortifier vs bovine fortifier	+ (mix of study types)			
Continuous vs bolus feedings			+ (meta-analysis - 7 RCTs)	
PDA				
Feeding with a PDA				+ (regional variation in feeding practices; epidemiologic association from observational data and suggestion of risk by SMA blood flow studies)
Feeding during pharmacologic treatment of a PDA			+ (retrospective studies × 2 and 1 RCT; trophic/ minimal enteral feedings; oral ibuprofen associated with less NEC)	
TANEC				
Anemia		+ (observational)		
PRBC transfusion			+ (meta-analysis - 40 observational, 3 RCTs)	
Withholding feedings during PRBC transfusion	+ (meta-analysis - 7 nonrandomized studies)			

NEC=necrotizing enterocolitis; PDA=patent ductus arteriosus; PRBC=packed red blood cells; RCT=randomized controlled trial; SMA=superior mesenteric artery; TANEC=transfusion-associated NEC.

[a]*Overall low proportion of extremely low-birthweight study subjects.*

the available observational data point toward the positive benefit of this practice, this should not yet be considered standard of care. Moreover, the American Academy of Pediatrics has issued no statements or recommendations concerning the practice.

CONCLUSION

Given that enteral feeding is one of the consistently observed risk factors for NEC, neonatologists need to pay close attention to the varying aspects of feeding and how they influence the incidence of the disease. These observations may translate into practice changes despite lack of high-quality experimental evidence to protect the most vulnerable of our pediatric patient population. Of the feeding-related factors that may influence NEC, the evidence regarding the protection that breast milk confers is the most consistently observed along with the use of standardized feeding regimens. We strongly support the future performance of one or more sufficiently powered RCTs to adequately assess whether withholding feedings during PRBC transfusion makes a difference in the incidence of NEC.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the immunologic and anti-infective constituents in human milk and their physiologic effects.
- Know the pathophysiology of NEC.

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New Ventilator Strategies: High-Frequency Oscillatory Ventilation Combined with Volume Guarantee

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Abstract

High-frequency oscillatory ventilation (HFOV) has been proposed as an alternative method of invasive ventilation in immature infants to prevent ventilator lung injury. To better control the size of the high-frequency tidal volume and to prevent large tidal volumes, a new strategy of controlling the tidal volume during HFOV (VThf) has been developed, HFOV–volume guarantee (VG). Data from preclinical, neonatal animal studies in normal and surfactant-depleted lungs have demonstrated the feasibility of this technique to directly control the VThf in the normal compliance and low compliance situations. Different I:E ratios also can modify the effect of CO_2 washout during HFOV combined with VG in a different way as without the VG modality. Finally, clinical use of this technique in newborn infants has demonstrated the possibility of using very high frequency combined with constant very low VThf to decrease the risk of lung trauma related to the ventilator.

Keywords
- high-frequency oscillatory ventilation
- volume guarantee ventilation
- gas exchange
- newborn ventilation
- respiratory distress syndrome

High-frequency oscillatory ventilation (HFOV) has been used for more than three decades, mostly in newborn infants with a severe respiratory failure as a rescue therapy, to improve gas exchange. As it uses a low tidal volume, under the anatomical dead space at supraphysiological respiratory frequencies,[1] it has been proposed as an effective respiratory strategy that can prevent ventilator lung injury.[2]

The use of flow sensors adapted to the new HFOV devices helps to better control the tidal volume sent during high frequency (VThf) and more recently to control this tidal volume using the volume guarantee (VG) modality (HFOV-VG). VG is a well-documented volume target ventilation modality combined to synchronize conventional tidal ventilation,[3] which is now possible to be used during HFOV.

New data from preclinical and clinical studies are available with the use of HFOV combined with VG, representing a promising alternative to protect the immature lung.

High-Frequency Oscillatory Ventilation Combined with Volume Guarantee Strategy

HFOV has been demonstrated to be very effective for CO_2 removal, which is mostly related to the high-frequency tidal volume generated (VThf) and to the ventilator frequency.[4–6]

Therefore, at least in theory, HFOV can reduce the risk of lung injury related to the ventilator and consequently reduce the risk of bronchopulmonary dysplasia (BPD), but clinical studies did not demonstrate that effect when comparing HFOV with conventional mechanical ventilation.[7] It is possible that earlier studies used devices that sent larger VThf than expected, higher than the dead space, 2.4 mL/kg (range: 1–3.6),[8] and even more, most of the standard high-frequency ventilators did not measure the VThf, therefore no information about this could be used during the clinical trials. Also, some investigators demonstrated that when a flow sensor

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was connected to an HFOV, a VThf larger than the dead space were delivered, that is, "conventional tidal ventilation" at very high frequencies.[8]

More recently, new high-frequency ventilators use precise flow sensors, making possible to have this information and then to know how much VThf is used during HFOV; therefore, large VThf can be prevented.[9]

When the VG modality is not in use in HFOV, as the frequency is decreased, $PaCO_2$ decreases as well, and an increase in VThf may probably account for this finding, but some other mechanisms are probably involved, such as a better transmission of the pressure waves through the airways at lower frequencies.

In classic HFOV, when it was needed to increase VThf, it has been used the power of the delta pressure (P) generated by the ventilator, the higher the delta pressure, the higher VThf generated. Also, as the frequency of the ventilator is modified, more or less time the ventilator has to generate larger or lower VThf, and therefore it has been a practical approach to increase or decrease the efficacy of the ventilator to decrease or increase the $PaCO_2$ to modify the frequency. The lower the frequency, the longer the time available for the ventilator and the larger the VThf generated. The efficacy of CO_2 removal during HFOV, described as the diffusion coefficient of CO_2 (DCO_2), is related to the square of the high-frequency tidal volume (VThf) and the frequency (f), expressed as $DCO_2 = VThf^2 \times f$, and depends mostly on the VThf generated and less on the frequency.

Therefore, minimal changes in the VThf will modify more DCO_2 than any change in the frequency.

It has been recommended to use the lowest VThf possible, but to assure this, it is mandatory to know and control it. The delivered tidal volume generated by most of the high-frequency ventilators decreases above 10 Hz; therefore, most of the studies chose this frequency to manage infants. Knowing the VThf generated by the HFOV is key to predict its effect on CO_2 removal,[10] and nowadays, it is possible not only to accurately know the amount of VThf but also to keep it constant using the VG strategy that modifies P to fit the VThf set with the measured expiratory VThf.

Principles of Working of the HFOV Combined with VG

Using the VG modality, the ventilator sends the VThf set continuously by modifications in the proximal P.[9] With this modality, in contrast with the standard HFOV without VG, changes in the frequency by itself do not modify the VThf; therefore, any increase in the frequency now with the VG modality will increase DCO_2, and a decrease in the $PaCO_2$ will be expected. To maintain the VThf as the frequency is increased, an increase in the proximal P is done by the ventilator. Although this proximal P is increased, it is not transmitted distally to the lung (►**Fig. 1**), as we demonstrated this in a testing lung.[11] For any modification in the VThf set, a proportional change in P is done by the ventilator, and therefore VThf is kept constant and controlled.[12]

Preclinical Studies

All the studies were conducted using the Babylog VN500 (Dräger, Lübeck, Germany).

The Babylog VN500 is a high-frequency oscillator that generates a sinusoidal pressure signal around a set mean airway pressure and has an active inspiration and active expiration to allow for this. The VG mode is a volume-targeted ventilation where the microprocessor compares the VThf of the previous breath, using leak compensated VThf, and adjusts delta pressure up or down to achieve the set VThf. After any change in the VThf setting, the ventilator modified ΔP to maintain the VThf.[9]

To better understand the effect of the VG modality using a constant VThf and keeping it constant and controlled, several studies were conducted; first, we analyzed if modifying the VThf alone could modify the $PaCO_2$ in a neonatal animal study.[12]

Using a neonatal animal model of normal lung compliance and low compliance after surfactant removal by a bronchoalveolar lavage (BAL). Animals were ventilated with HFOV combined with VG ventilation. We demonstrated that it was possible, for the first time, to set directly the VThf, instead of P or the frequency, to modify the $PaCO_2$, with a significant decrease in the $PaCO_2$ at any increase in VThf.

After BAL, the ventilator modified P to maintain a constant VThf as needed, and the $PaCO_2$ remained unchanged compared with the presurfactant depletion condition.

In a bench model using HFOV combined with VG ventilation (Babylog VN500) connected to a testing lung with a continuous infusion of CO_2, we demonstrated that the ventilator frequency, in an independent way to the VThf, could modify the CO_2 removal, and after keeping constant the VThf with the VG modality, any increase in the frequency increased the CO_2 washout. We conclude that the frequency, with the VG modality combined with HFOV, has a direct effect on CO_2 elimination. Using a lower delivered tidal volume and higher frequencies may allow for improved ventilation efficacy while minimizing lung injury.[11]

Also, the effect of different I:E ratios was tested during HFOV with the VG strategy (Babylog VN500) and compared with the use of HFOV without VG. The I:E ratio of 1:1 compared with 1:2 in HFOV with VG did not produce a higher CO_2 lavage in contrast to HFOV without the VG modality. Even more, a lower $PaCO_2$ was found when using a lower frequency and 1:2 ratio compared with 1:1. Therefore, in contrast to the non-VG HFOV mode, using a fixed tidal volume, no significant changes on CO_2 elimination are observed during HFOV when the I:E ratios of 1:1 and 1:2 are compared at different frequencies.[13]

Clinical Studies

Only a few clinical studies using HFOV-VG are published,[14] demonstrating a more stable ventilation with better control of the PCO_2 with this modality than without it in preterm infants with severe respiratory distress syndrome.

We wanted to test the hypothesis of using similar DCO_2 at very low VThf and very high frequencies, compared with standard frequencies and VThf, to decrease lung injury.

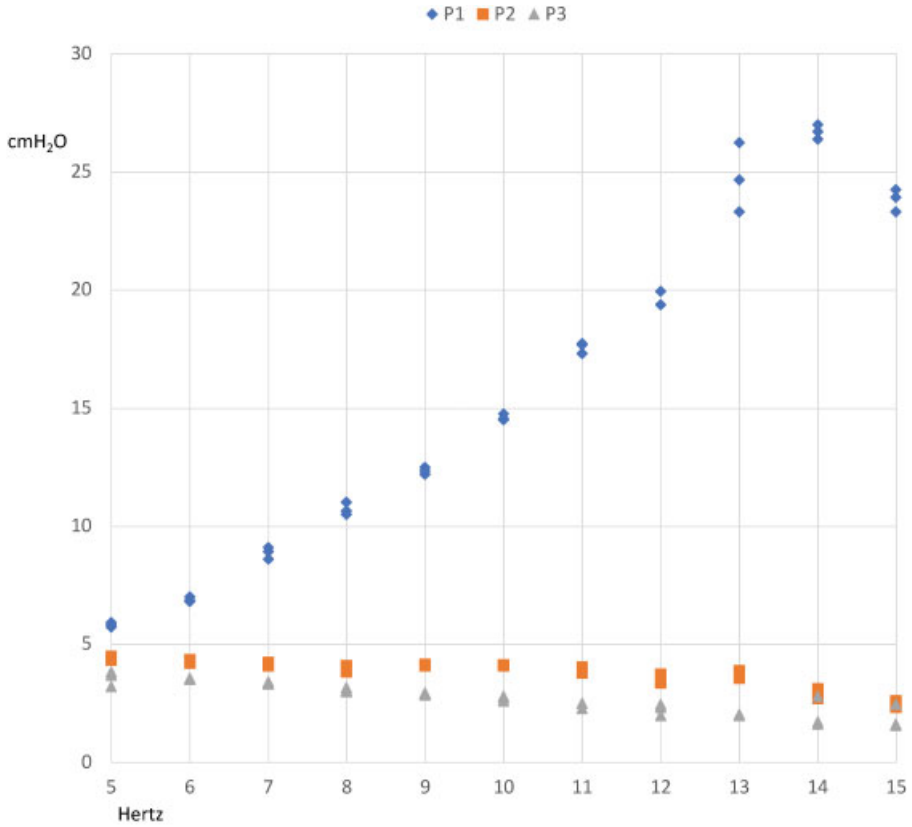

Fig. 1 Changes in P measured at the proximal (P1), medial (P2), and distal (P3) to the ventilator in a testing lung, at frequencies of 5, 10, and 20 Hz, with a fixed tidal volume (VThf), using high-frequency oscillatory ventilation combined with volume guarantee. As frequency increases, only proximal pressure increases, being the medial and distal pressures constant. P1 represents the connection between the ventilator and the endotracheal tube, P2 represents the tip of the endotracheal tube, and P3 represents the distal pressure in a bench model at the testing lung level.[12]

A feasibility study using very high frequencies with very low VThf, with HFOV combined with VG ventilation (Babylog VN500), was conducted in neonates. After reaching the target PCO_2 with the standard frequency of 10 Hz and a VThf of less than the dead space, a reduction in the VThf was done maintaining the DCO_2 similar by increasing the frequency of the ventilator. VThf was decreased from 2.20 ± 0.44 to 1.59 ± 0.36 mL/kg ($p < 0.001$), and therefore a significant reduction of the volume was possible with similar PCO_2 before and after.[15] This study demonstrates that it is possible to maintain a better control of very low VThf in preterm infants of less than 32 weeks of gestation; —this is a new opportunity of decreasing the risk of lung injury during the first days after delivery, when the lung is at more risk, and is possible with similar or even better control of the PCO_2. As lung damage by the ventilator is mostly related to the large tidal volume generated,[16] we speculate that with new modality lung injury could be minimized.

In summary, this promising new strategy, HFOV combined with VG, has been demonstrated to be a potential preventing lung injury strategy, mostly in the more immature infants, and has to be tested in large clinical studies, where a tentative protocol for using a constant very low VThf, at least during the first days after delivery, can reduce the risk of ventilator-induced lung injury and reduce the risk of BPD in the future.

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Conflict of Interest
M.S.L. has received advisory board consulting fees from Dräger. The remaining authors have no conflicts to declare.

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Prevention of bronchopulmonary dysplasia in extremely low gestational age neonates: current evidence

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ABSTRACT

Bronchopulmonary dysplasia (BPD) is one of the most frequent complications in extremely low gestational age neonates, but has remained largely unchanged in rate. We reviewed data on BPD prevention focusing on recent meta-analyses. Interventions with proven effectiveness in reducing BPD include the primary use of non-invasive respiratory support, the application of surfactant without endotracheal ventilation and the use of volume-targeted ventilation in infants requiring endotracheal intubation. Following extubation, synchronised nasal ventilation is more effective than continuous positive airway pressure in reducing BPD. Pharmacologically, commencing caffeine citrate on postnatal day 1 or 2 seems more effective than a later start. Applying intramuscular vitamin A for the first 4 weeks reduces BPD, but is expensive and painful and thus not widely used. Low-dose hydrocortisone for the first 10 days prevents BPD, but was associated with almost twice as many cases of late-onset sepsis in infants born at 24–25 weeks' gestation. Inhaled corticosteroids, despite reducing BPD, were associated with a higher mortality rate. Administering dexamethasone to infants still requiring mechanical ventilation around postnatal weeks 2–3 may represent the best trade-off between restricting steroids to infants at risk of BPD while still affording high efficacy. Finally, identifying infants colonised with ureaplasma and treating those requiring intubation and mechanical ventilation with azithromycin is another promising approach to BPD prevention. Further interventions yet only backed by cohort studies include exclusive breastmilk feeding and a better prevention of nosocomial infections.

INTRODUCTION

Bronchopulmonary dysplasia (BPD) is one of the most frequent complications in extremely low gestational age neonates (ELGANs; gestational age <28 weeks) affecting around 22% to 38% of them.[1 2] It is also an important predictor of neurodevelopmental impairment.[3] Various definitions for BPD exist, the most precise is probably the room-air challenge at 36 weeks postmenstrual age (PMA).[4] The increasing use of high-flow nasal cannulae at fraction of inspired oxygen (FiO_2) 0.21 in recent years might hamper this, so that initiatives at finding a new definition are underway.[5 6] BPD likely results from the effects of non-physiologic stimuli (inflammation, ventilator-induced lung injury, high oxygen levels) on a structurally and functionally immature lung with underdeveloped defence mechanisms.[7] In the past, interventions to avoid BPD mainly focused on reducing inflammation using steroids. This policy was drastically curtailed after data emerged linking dexamethasone use with the subsequent development of cerebral palsy (CP),[8] leading to a resurgence in BPD.[9] Exogenous surfactant, particularly if given soon after intubation, has been another first major step in reducing BPD.[10 11] In recent years, new approaches to respiratory care and steroid use have evolved. This review provides a personal view on strategies likely to reduce death/BPD, or BPD alone (tables 1–3), defined as oxygen requirement at 36 weeks PMA, based on current evidence.

Avoidance of mechanical ventilation via an endotracheal tube

The lungs of ELGANs are uniquely susceptible to injury. Experiments in lambs have shown that already a few large-volume breaths (eg, during bagging) may induce volutrauma leading to long-lasting structural lung injury.[12] It thus seems logical to avoid mechanical ventilation (MV) via an endotracheal tube altogether. This may be achieved by using nasal continuous positive airway pressure (NCPAP) and, if needed, by applying surfactant without MV, for example, through INSURE (intubate, surfactant, extubate) or the less/minimally invasive surfactant administration/therapy (LISA, MIST). The effectiveness of these strategies in preventing BPD has been addressed in several meta-analyses.

The first included four randomised controlled trials (RCT) in infants <32 weeks PMA evaluating the effect of NCPAP compared with MV±surfactant. NCPAP showed a significant benefit for the combined outcome death/BPD, but no effect on BPD alone.[13]

Another meta-analysis compared NCPAP±LISA (LISA used in 3 of 7 studies) vs MV±INSURE in infants <30 weeks PMA. There was a 17% reduction in death/BPD in the NCPAP±LISA group.[14]

A third meta-analysis included *only* studies with NCPAP+LISA in the intervention group in infants <34 weeks PMA. Control group infants received MV and, in four of six RCT, surfactant via INSURE. Death/BPD was reduced by 25%, BPD alone by 28%.[15]

The most comprehensive meta-analysis included 30 trials on different ventilation strategies for spontaneously breathing infants <33 weeks PMA. One study compared LISA with MV; LISA halved the risk of death/BPD.[16] A similar, although smaller,

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Table 1 Summary of randomised controlled trial data on the effects of various respiratory support strategies on death and/or BPD (including selected complications)

Intervention: different modes of respiratory support	Outcome	N studies	N patients	Intervention group	Control group	RR	95% CI
NCPAP vs MV[13]	Death/BPD	4	2782	532/1296	641/1486	0.91	0.84 to 0.99
	BPD	4	2536	383/1182	461/1354	0.91	0.82 to 1.01
NCPAP±LISA vs MV± INSURE[14]	Death/BPD	4	3289	614/1552	737/1737	0.83	0.71 to 0.96
NCPAP+LISA vs MV±INSURE[15]	Death/BPD	6	895	90/447	121/448	0.75	0.59 to 0.94
	BPD	6	814	56/410	77/404	0.72	0.53 to 0.97
NCPAP+LISA vs MV[16]	Death/BPD	1	189	n.p.	n.p.	0.49*	0.30 to 0.79
INSURE vs MV[16]	Death/BPD	2	419	n.p.	n.p.	0.71*	0.50 to 0.98
NCPAP vs MV[16]	Death/BPD	3	2085	n.p.	n.p.	0.58*	0.35 to 0.93
NIPPV vs NCPAP[16]	Death/BPD	5	775	n.p.	n.p.	0.82*	0.53 to 1.24
NIPPV vs NCPAP[17]	BPD	9	899	60/450	77/449	0.78	0.58 to 1.06
sNIPPV vs NCPAP[18]	BPD	3	181	26/93	38/88	0.64	0.44 to 0.95
VTV vs pressure-limited MV[22]	Death/BPD	4	224	53/114	67/110	0.79	0.62 to 1.01
	BPD	9	909	74/325	102/295	0.68	0.53 to 0.87
	PVL/grade 3–4 IVH	6	441	17/227	35/214	0.47	0.27 to 0.80
VTV vs pressure-limited MV[23]	BPD	9	596	58/310	89/286	0.61	0.46 to 0.82
	Grade 3–4 IVH	11	707	n.p.	n.p.	0.55	0.39 to 0.79
HFOV vs pressure-limited MV[25]	Death/BPD	17	3329	678/1659	756/1679	0.90	0.84 to 0.97
	BPD	17	2768	421/1392	485/1394	0.86	0.78 to 0.96
	Air leaks	13	2854	392/1615	337/1439	1.19	1.05 to 1.34
Early vs delayed surfactant for respiratory distress syndrome[10]	Death/BPD	3	3040	447/1519	543/1531	0.83	0.75 to 0.91
	BPD	3	3040	117/1519	170/1531	0.69	0.55 to 0.87

*OR.

BPD, bronchopulmonary dysplasia; HFOV, high frequency oscillatory ventilation; INSURE, intubate, surfactant, extubate; IVH, intraventricular haemorrhage; LISA, less-invasive surfactant administration; MV, mechanical ventilation; NCPAP, nasal continuous positive airway pressure; n.p., not provided ; PVL, periventricular leucomalacia; RR, relative risk; sNIPPV, synchronised nasal intermittent positive pressure ventilation; VTV, volume-targeted ventilation.

effect was seen when INSURE was compared with MV, but not if LISA was compared with NCPAP without surfactant.[16] Comparing individual effects of the different strategies on the various outcomes investigated, the authors concluded that 'LISA was the best strategy among all strategies for all outcomes assessed', and that INSURE ranked second best in this analysis; the quality of the evidence, however, was low.

There are various techniques to provide non-invasive respiratory support and the question arises whether nasal intermittent positive pressure ventilation (NIPPV) is more effective than NCPAP in preventing BPD. For the use of NIPPV vs NCPAP as primary respiratory support, no difference in BPD was seen.[16 17] For postextubation use, results were similar if all NIPPV techniques were analysed together.[18] However, subgroup analysis on synchronised NIPPV (sNIPPV) versus NCPAP did show a reduction in BPD using sNIPPV.[18] Unfortunately, only few commercially available ventilators offer this mode of respiratory support.

Avoiding invasive mechanical ventilation via LISA (or INSURE) with NCPAP, followed by sNIPPV postextubation (if needed), appears to be a promising respiratory support strategy for reducing BPD, although definite data from large well-designed (blinded) trials on the effectiveness of this approach are missing. Nonetheless, in the authors' unit ELGANs receive LISA followed by NCPAP or sNIPPV.

A note of caution must be added here. In a longitudinal follow-up study from Victoria (Australia) comparing respiratory function of ELGANs over three periods (1991/1992, 1997 and 2005), mean duration of NCPAP increased from 5 to 31.5 days, while duration of MV decreased from 21 to 10 days. Despite this increased use of NCPAP, the proportion of infants with BPD increased from 46% to 56% over time. Whether this disappointing trend towards *more* BPD points to an overuse of non-invasive respiratory support, or is due to a 50% reduction in postnatal steroid use or more severely ill infants surviving in recent years remains unanswered.[19]

Alternatives to pressure-limited MV

Despite the increasing use of LISA, many infants with respiratory distress syndrome (RDS) still require MV. What is the best ventilation strategy to avoid BPD in these infants? Given the detrimental effects of volutrauma on the developing lung,[12 20] the volume applied with each breath should be limited. As lung compliance changes rapidly during RDS and its treatment, this is best achieved by using volume-targeted ventilation (VTV).[21] A Cochrane review reported a 21% reduction in death/BPD and a 53% reduction in periventricular leucomalacia/grade 3–4 intraventricular haemorrhage (IVH) for VTV compared with pressure-limited MV.[22] Another meta-analysis found that VTV reduced BPD by 40% and almost halved grade 3–4 IVH.[23] Most studies, however, were small (<50 patients/group), the intervention was not blinded and BPD not the primary outcome. This, combined with recent animal data suggesting that VTV might not eliminate lung injury during spontaneous breaths,[24] raises questions whether the evidence that VTV is superior to other forms of respiratory support can already be regarded conclusive.

An alternative to conventional MV that might also reduce volutrauma is high-frequency oscillatory ventilation (HFOV). A Cochrane review on elective use of HFOV, that is, soon after intubation, showed a significant reduction in death/BPD at 36–37 weeks PMA or discharge and in BPD alone.[25] All but one study applied a high-volume strategy, where mean airway

Table 2 Summary of randomised controlled trial data on the effects of corticosteroids on death and/or BPD (including selected complications)

Intervention: corticosteroids	Outcome	N studies	N patients	Events	Control group	RR	95% CI
Early dexamethasone vs placebo[28]	Death/BPD	15	2481	538/1248	615/1233	0.87	0.80 to 0.94
	BPD	15	2484	247/1249	350/1235	0.70	0.61 to 0.81
	Severe ROP	8	1507	90/762	115/745	0.77	0.60 to 0.99
	GI perforation	9	1936	70/968	40/968	1.73	1.20 to 2.51
	Hypertension	10	1943	211/978	115/965	1.84	1.53 to 2.21
	Hypertrophic cardiomyopathy	1	50	13/25	3/25	4.33	1.40 to 13.37
	Cerebral palsy	7	921	75/472	40/449	1.75	1.20 to 2.55
Early hydrocortisone vs placebo[2]	Survival w/o BPD	1	523	153/256	136/267	1.48*	1.02 to 2.16
	BPD	1	523	55/256	70/267	0.82*	0.58 to 1.16
Late dexamethasone vs placebo[32]	Death/BPD	9	535	159/272	204/263	0.76	0.68 to 0.85
	BPD	9	535	128/272	166/263	0.76	0.66 to 0.88
	Severe ROP	12	558	93/285	65/273	1.38	1.07 to 1.79
	Hypertension	14	1175	58/588	29/587	2.12	1.45 to 3.10
	Hypertrophic cardiomyopathy	4	238	23/119	8/119	2.76	1.33 to 5.74
	Cerebral palsy	14	631	60/322	53/309	1.05	0.75 to 1.47
Early inhaled steroids vs placebo[35]	Death/BPD	6	1285	227/649	256/636	0.86	0.75 to 0.99
	BPD	7	1168	149/581	192/587	0.77	0.65 to 0.91
Inhaled steroids (<2 weeks) vs placebo[36]	Death/BPD	6	1285	227/649	256/636	0.86	0.77 to 0.99
	BPD	5	429	31/212	33/217	0.97	0.62 to 1.52
Inhaled budesonide vs placebo[1 38]	Death/BPD	1	863	175/437	194/419	0.86	0.75 to 1.00
	BPD	1	863	101/363	138/363	0.74	0.60 to 0.91
	Death	1	863	74/437	57/419	1.37	1.01 to 1.86
	Neurodevelopmental disability	1	629	148/308	165/321	0.93	0.80 to 1.09
Intratracheal budesonide+SF vs SF[39]	Death/BPD	1	265	55/131	89/134	0.58	0.44 to 0.77

*OR.
BPD, bronchopulmonary dysplasia; chorio, chorioamnionitis; GI, gastrointestinal; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; SF, surfactant.

pressure is initially set a few cmH_2O above that used with conventional MV, and FiO_2 is reduced first during weaning, before reducing mean airway pressure. Importantly, most studies showing superiority of HFOV are rather old, and the comparison group received pressure-limited MV; thus, the benefits seen with HFOV may not hold up if comparing the latter against VTV. Recent data in adults questioning benefits of lung recruitment strategies might have an impact on ventilation strategies in preterm infants.[26]

Corticosteroids

With inflammation playing a key role in the pathophysiology of BPD, suppressing inflammation is a logical consequence. Traditionally, this has been achieved by systemic corticosteroids using three different approaches: early (postnatal week 1), late (postnatal week 2) and very late administration (after week 3). The last option is used for treating instead of preventing BPD and thus beyond the focus of this review. Early administration of steroids has the advantage that the pathophysiology leading

Table 3 Summary of data from randomised controlled trials and observational studies on the effects of various other strategies for BPD prevention on death and/or BPD (including lung function data)

Intervention: others	Outcome	N studies	N patients	Events	Control group	RR	95% CI
Azithromycin vs placebo[45]	Death/BPD	3	363	106/186	118/177	0.86	0.77 to 0.97
	BPD	3	310	81/161	90/149	0.83	0.71 to 0.97
Vitamin A intramuscular vs placebo[53]	Death/BPD	3	935	222/469	248/466	0.90	0.81 to 1.01
	BPD	4	886	190/442	224/444	0.85	0.74 to 0.98
Caffeine vs placebo[48]	BPD	1	2006	350/1006	447/1000	0.64*	0.52 to 0.78
Caffeine vs placebo[49]	FVC z-score <5th centile	1	142	8/74	19/68	0.31*	0.12 to 0.77
Caffeine vs placebo[50] Early—postnatal days ≤3	BPD	1	822	111/396	190/426	0.48*	0.36 to 0.65
Caffeine vs placebo[50] Late—postnatal days>3	BPD	1	1095	239/567	257/528	0.77*	0.61 to 0.98
Early vs late caffeine[51]	Death/BPD	1	29070	3681/14 535	4591/14 5365	0.74*	0.69 to 0.80
Exclusive formula vs exclusive breastmilk[56]	BPD	1	462	n.p.	n.p.	2.56*	1.33 to 5.04
Exclusive breastmilk[57]	BPD	1	254	n.p.	n.p.	0.91*	0.82 to 0.99

*OR.
BPD, bronchopulmonary dysplasia; FVC, forced vital capacity; n.p., not provided; RR, relative risk.

to BPD is interrupted soon after birth, yet the disadvantage that many infants at low risk of developing BPD are exposed to a toxic drug. Unfortunately, most models for the early prediction of BPD have been assessed as poor,[27] so that targeted prevention remains difficult.

Early administration of systemic corticosteroids

The Cochrane review on early systemic corticosteroids to prevent BPD found a lower risk of death/BPD, patent ductus arteriosus (PDA) and severe retinopathy of prematurity (ROP) using dexamethasone. Short-term side effects included gastrointestinal perforation, hypertension and hypertrophic cardiomyopathy. Most important, however, was an increased risk of CP[28] at 2-year follow-up. Thus, the benefits of early postnatal dexamethasone may not outweigh its adverse effects.

The early use of low-dose hydrocortisone, however, increased survival without BPD with fewer side effects.[2 29] ELGANs with a birth weight ≥3rd percentile were randomised to 2×0.5 mg/kg/day hydrocortisone on days 1–7 followed by 3 days with 1×0.5 mg/kg/day, or placebo. Survival without BPD was present in 60% in the treatment versus 51% in the placebo group; death occurred in 18 vs 23%. There was no difference in pulmonary haemorrhage, insulin treatment, gastrointestinal perforation, sepsis and BPD alone between groups. Post hoc analysis showed a stronger effect of hydrocortisone in infants born in the context of chorioamnionitis and a higher rate of sepsis in the most immature infants (24–25 weeks PMA; 40 vs 23%). The 2-year follow-up, done in 93% of survivors, showed no difference in revised Brunet-Lézine test results or in the proportion of infants with moderate-to-severe neurodevelopmental impairment or CP. Although the data on neurodevelopment are reassuring, it remains unclear whether all ELGANs should be exposed to hydrocortisone early after birth or whether a more selective approach is preferable; this decision may be influenced by an individual centre's BPD rate.[30]

Late (>1 week) systemic corticosteroids

The administration of systemic corticosteroids in the second or third postnatal week may allow for a better identification of infants at risk of BPD. For example, an ELGAN with birth weight <1000 g who still requires MV with FiO_2 ≥0.3 at 14 days of age has a <60% chance of surviving without BPD.[31] In such infants, the beneficial effects of dexamethasone outweigh the potential risk of CP.[30]

In a Cochrane review on late systemic steroids, >75% of infants were started on study drug (almost always dexamethasone) between 1 and 3 weeks of age.[32] Death/BPD was reduced by 24%, as was BPD alone. Adverse events included hypertension, hypertrophic cardiomyopathy and severe ROP, but there was no significant increase in the risk of gastrointestinal perforation or CP. These data suggest that administering dexamethasone to ELGANs who still require MV in their second to third postnatal week may help avoiding BPD without an increased risk of CP.

An important issue with postnatal steroid use is the cumulative dose administered to achieve optimal efficacy with minimal long-term sequelae. A meta-analysis of RCTs comparing different doses of dexamethasone in ventilated infants <30 weeks and >7 days of age found an increased risk of BPD and also of abnormal neurodevelopment with a moderate (2 mg/kg) compared with a high-dose regimen (>4 mg/kg cumulative dose); however, the quality of the evidence was assessed as low or very low.[33] These data are important as they raise the question whether a low cumulative dexamethasone dose, compared with higher doses, although intuitively preferable, is indeed the safest way to prevent BPD. In the author's unit, infants receiving systemic steroids are started on the low dose corticosteroid regime used in the Dexamethasone: A Randomized Trial (DART) study.[34] If extubation after 3 days is unrealistic or unsuccessful, the dose will be increased to 0.3 mg/kg/day for 3 days followed by the DART regime.

Early or late administration of topical corticosteroids

With the emergence of data suggesting an increased risk of CP and gastrointestinal perforation following systemic steroids, interest in topical, for example, inhaled routes of administration resurged. A meta-analysis comparing inhaled steroids versus placebo for the prevention or treatment of BPD found a reduction in death/BPD and BPD alone.[35] The relevant Cochrane analysis focused on inhaled steroids before 14 days of age versus placebo and also found a reduction in death/BPD but not for BPD alone.[36]

A recent large RCT on early (<24 hours) inhaled budesonide for BPD prevention in ELGANs found a reduction in death/BPD.[1 37] Mortality at 2 years of age, however, was increased (19.9% vs 14.5%), while neurodevelopmental disability, which could be assessed in 94% of survivors, was no different.[38] Although no specific cause of death could be identified explaining this mortality signal, prophylactic administration of budesonide to all ELGANs will be difficult to justify.

An alternative to inhalation is the intratracheal administration of budesonide combined with exogenous surfactant. This approach has been investigated in a three-centre study enrolling infants with a birth weight <1500 g with RDS and FiO_2 ≥0.50 within 4 hours of birth.[39] Intervention group infants received 100 mg/kg surfactant (Survanta) mixed with 0.25 mg/kg budesonide, controls received only surfactant; up to five repeat doses were allowed every 8 hours. Primary outcome was death/BPD, which occurred in 42% of intervention and 66% of control group infants. Two-year to three-year follow-up data obtained in 85% of survivors showed no difference in growth, neuromotor dysfunction or Bayley II test results.[32] Given the high baseline rate for death/BPD in this study, these data await confirmation in other settings before this approach can be recommended.

Eradication of ureaplasma urealyticum

Ureaplasma urealyticum is a genitourinary tract commensal in females that can invade the intra-amniotic fluid causing inflammation. It is the most common organism isolated in chorioamnionitis and associated with an increased risk for preterm labour and neonatal morbidity in ELGANs.[40] Its role in developing BPD is controversial.[41 42] Ureaplasma may not by itself cause BPD, but if combined with other stimuli like MV or exposure to high oxygen levels.[43] It still remains unclear if eradication of ureaplasma may prevent BPD. An early Cochrane analysis on erythromycin found no effect on BPD or death.[44] A broader meta-analysis on the effects of macrolides on BPD reported a reduction in death/BPD and BPD alone for azithromycin.[45] Given these data, the approach chosen in the authors' institution is to screen ELGANs for ureaplasma in tracheal aspirates soon after birth and treat those infants still receiving MV and colonised with ureaplama with azithromycin (10 mg/kg/day for 7 days). The dosage used is based on the above-mentioned meta-analysis.[45] Pharmacokinetic data, however, suggest that a 3-day course of 20 mg/kg/day might be more effective in eradicating

ureaplasma.[46] Whichever regime is used, evidence for using macrolides for BPD prevention is rather weak.

Caffeine citrate

Given that caffeine stimulates breathing, reducing the need for MV, and has diuretic effects and exerts anti-inflammatory properties in the developing lung,[47] it is not surprising that its use led to a 36% reduction in BPD in the Caffeine for Apnea of Prematurity (CAP) trial.[48] Encouragingly, this effect on BPD in the neonatal period continued to translate into better lung function results at 11 years of age in Australian former CAP study participants. Expiratory flows were improved by 0.5 SD in children randomised to caffeine, and 11 vs 28% had forced vital capacity values below the fifth centile.[49] Post hoc subgroup analysis of the CAP data showed that postnatal age at onset of treatment influenced the effect of caffeine: BPD was reduced by 52% in those with treatment started on postnatal days 1–3 (early), whereas it was reduced by only 23% if started after day 3 (late).[50] Subsequent cohort studies confirmed this finding: in an analysis of data from the Pediatrix network, death/BPD occurred in 28% of infants with early caffeine start, but in 34% of those started late.[51] Similar data were also reported from the Canadian Neonatal Network.[52] Such post hoc analyses or cohort study data, however, are only hypothesis-generating.

Vitamin A

Vitamin A is important for lung growth and differentiation, and benefits of intramuscular vitamin A administration (usually 3×5000 IE/week intramuscular over 4 weeks) have been confirmed in meta-analysis: BPD was reduced by 13% in infants <1000 g birth weight receiving vitamin A compared with placebo, but there was no effect on the combined outcome death/BPD.[53] Clinical uptake of these data has been limited, possibly because it is costly and intramuscular administration is reported to be painful. One smaller study tested the effect of oral vitamin A showing no effect on BPD.[54]

Exclusive breastmilk feeding and nosocomial infection—cohort studies

Exclusive breastmilk

Breastmilk feeding has been associated with less necrotising enterocolitis and ROP,[55] but there are no RCT data whether it prevents BPD. Data from the German Neonatal Network, however, showed that exclusively formula-fed infants had 2.6-times the risk of developing BPD in multivariate analysis than exclusively breastmilk-fed infants.[56] In another cohort study, multivariable analysis showed a 9.5% reduction in the odds of BPD for every 10% increase in expressed breastmilk.[57] These data further encourage the use of breastmilk instead of formula in ELGANs.

Avoidance of nosocomial infections

Nosocomial infection (NI) has been associated with the development of BPD, but whether BPD can be avoided through better infection control is unknown. In a cohort study from the California Perinatal Quality Care Collaborative database involving 22 967 very low birthweight infants <30 weeks PMA from 129 hospitals, NI rates declined from 25% to 15% between 2006 and 2013, while BPD fell from 35% to 30%. Adjusted individual hospital rates of BPD correlated positively with those for NI. The authors estimated that this 8% fall in BPD rates was attributable to the reductions in NI.[58] Implementing quality improvement bundles for NI prevention may thus be a yet underused approach to reducing BPD.

Box 1 Possible strategies for bronchopulmonary dysplasia prevention in extremely low gestational age neonates (ELGANs)

- Using nasal continuous positive airway pressure (NCPAP) instead of intubation and mechanical ventilation as primary respiratory support.
- Applying exogenous surfactant via less/minimal invasive administration via a thin tracheal catheter/nasogastric tube or via the INSURE method.
- Using volume instead of pressure targeted ventilation in infants requiring mechanical ventilation.
- Using synchronised intermittent positive pressure ventilation instead of NCPAP after extubation
- Starting caffeine on postnatal days 1–3 instead of later.
- Applying vitamin A intramuscularly for the first four postnatal weeks.
- Considering low-dose intravenous hydrocortisone for the first 10 postnatal days in any infant born with a birth weight above the third percentile.
- Considering intravenous dexamethasone in infants who require mechanical ventilation at the end of their second postnatal week.
- Test tracheal aspirates of all ELGANs requiring mechanical ventilation after birth for ureaplasma, consider intravenous azithromycin in those tested positive.

Conclusions and outlook

Effective BPD prevention continues to be challenging. Although meta-analyses of RCTs are considered the highest level of evidence, their results may not be generalisable to other settings. Given the evidence summarised above, some personal recommendations may be given (box 1).

There are also other interventions, such as the use of antenatal steroids, inhaled nitric oxide, cyclooxygenase inhibitors for PDA closure or lower versus higher oxygen target ranges we did not review, as meta-analyses either showed an increased risk[59] or no significant/inconsistent[60] effects on BPD.[10 60–63] The most important approach, however, is to avoid preterm birth. Here, we yet seem far away from an effective intervention, which would likely require closer collaboration with our obstetrical colleagues.

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Prevention of bronchopulmonary dysplasia in extremely low gestational age neonates: current evidence

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Notes

Recomendaciones del VIII Consenso Clínico de SIBEN para la Displasia Broncopulmonar

Augusto Sola, MD,* Diana Fariña, MD,* Ramón Mir, MD,* Sergio Golombek, MD,*† y Miembros del Consenso Clínico de la Sociedad Ibero-Americana de Neonatología (SIBEN)

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AUTHOR DISCLOSURE

Dr Sola has disclosed that he is the Vice President of Medical Affairs with Masimo Corporation. Drs Fariña and Mir have disclosed no financial relationships relevant to the article. Dr Golombek has disclosed that he is on the speakers' bureau with Mallinckrodt and a consultant with Prolacta. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

El Dr Sola es VP de Medical Affairs de Masimo Corporation. Los Dres. Fariña y Mir declaran ausencia de conflicto de interés. El Dr Golombek pertenece al Speakers' Bureau de Mallinckrodt, y es Consultor de Prolacta. Este artículo no contiene una discusión sobre el uso no aprobado / investigativo de un producto / dispositivo comercial.

En este Consenso participaron 48 profesionales de 12 países de Latinoamérica y España. La coordinación y revisión estuvo a cargo de los investigadores principales Dres. Fariña, Mir y Sola quienes han condensado todo el material trabajado.

Los participantes del Consenso por orden alfabético fueron: Amparo del Socorro Acosta Polo, Aldana Ávila, Hernando Baquero, Elizabeth Céspedes, Judith Dachesky, Carmen Dávila, Patricia Fernández, Rosana Fonseca, María del Carmen Fontal, Inés García Fiorini, Flora Josefina García, Larisa Genes, Gustavo Goldsmit, Zandra Grosso, Cecilia Juárez, José Lacarrubba, Gabriel Lara, Lourdes Lemus, Victoria Lima, Irama López, Luciano Macías, Elvira Mendieta, Marcela Montaño, Mónica Morgues, Teresa Murguía, Diego Natta, Francisco Navarro, Sandra Navarrete, Ada Nidia Oviedo Barrantes, Anabel Pereira, Jorge Pleitez, Verónica Puga, Noemí Ruiz Lavado, Alejandro Rossi, Cristina Segovia, Lorena Velandia, María Elena Venegas, Federico Villafañe, Dan Waisman, Alejandro Young.

EDITOR'S NOTE

In 2003, a group of physicians in Latin America noted the painful and regrettable discrepancy between neonatal delivery of care and outcomes in the Latin American region. They formed SIBEN, the Ibero-American Society of Neonatology, a not-for-profit public charitable organization (501[c][3]) committed to advancing positive change for improving the delivery of neonatal care and neonatal health in Latin America. The *NeoReviews* Editorial Board has partnered with SIBEN to publish a few of its clinical consensus statements in Spanish each year, and to provide free open access to the statements. Introductory material appears in both English and Spanish. Please note that the views expressed in this SIBEN statement do not necessarily reflect the views of the American Academy of Pediatrics.

Palabras clave: Displasia broncopulmonar, recién nacido, corticoides, sildenafil

CONTENIDO

RESUMEN

La displasia broncopulmonar (DBP) es una de las secuelas más importantes de la prematurez. Según el grado de severidad, se asocia con hospitalizaciones prolongadas, alteraciones nutricionales y del neurodesarrollo y hasta la muerte por insuficiencia cardio-pulmonar crónica. Ocurre en 25-40% de los recién nacidos (RN) de pretérmino < 32 semanas de edad gestacional. Es una morbilidad que, si bien en la actualidad no puede evitarse, su prevalencia y la incidencia de casos de mayor severidad pueden y deben disminuirse. Este artículo resume la etiología, patogénesis, diagnóstico, estrategias preventivas pre y postnatales y las recomendaciones terapéutico - clínicas realizadas por el VIII Consenso Clínico de la Sociedad Iberoamericana de Neonatología (SIBEN). Entre las medidas preventivas prenatales se encuentran la adecuada nutrición y crecimiento fetal y la prevención y tratamiento óptimo de infecciones uterinas y corioamnionitis. El cuidado neonatal para intentar prevenir la DBP requiere brindar oxigenación no excesiva y utilizar ventilación alveolar óptima con volúmenes corrientes bajos en los RN de riesgo, lo que debe comenzar en la sala de partos y continuar durante toda la fase aguda de la insuficiencia respiratoria. La nutrición debe comenzar en las primeras 12-24 horas de vida. Existen medicamentos que han sido estudiados como preventivos que poseen escaso o nulo beneficio y/o efectos adversos potenciales, como los corticoides postnatales, diuréticos y vitamina A. La cafeína utilizada precozmente se asocia con menos DBP. Los vasodilatadores pulmonares, como el óxido nítrico inhalado y el sildenafil tienen utilidad en el tratamiento de casos severos con hipertensión pulmonar, pero no en la prevención de DBP. La terapia emergente que se estudia actualmente es la terapia celular y es desear que disminuya el impacto sobre la morbilidad a largo plazo de la DBP. El objetivo de esta revisión es, colaborar a que de una manera práctica se continúe mejorando el cuidado de los recién nacidos prematuros (RNPt) en ibero-américa y que haya cada vez menos niños con DBP y que dejen de existir los casos graves con mayor severidad. Sería maravilloso para muchos RNPt que pudiéramos resolver definitivamente esta seria secuela de la prematuridad.

SUMMARY

Bronchopulmonary dysplasia (BPD) is one of the most important sequelae of prematurity. According to the degree of severity, it is associated with prolonged hospitalizations, nutritional and neurodevelopmental abnormalities and even death due to chronic cardiopulmonary insufficiency. It occurs in 25-40% of preterm infants (RN) <32 weeks of gestational age. It is a morbidity that, although at present cannot be avoided, its prevalence and the incidence of cases of greater severity can and should be reduced. This article summarizes the etiology, pathogenesis, diagnosis, pre- and postnatal preventive strategies and therapeutic management-clinical recommendations made by the VIII Clinical Consensus of the Ibero-American Neonatology Society (SIBEN). Adequate nutrition and fetal growth and prevention and optimal treatment of uterine infections and chorioamnionitis are among prenatal preventive measures. Neonatal care to try to prevent BPD requires providing non-excessive oxygenation and using optimal alveolar ventilation with low tidal volumes in at-risk newborns, which should begin in the delivery room and continue throughout the acute phase of respiratory failure. Nutrition must begin in the first 12-24 hours of life. There are medications that have been studied as preventives that have little or no benefit and / or potential adverse effects, such as postnatal corticosteroids, diuretics and vitamin A. Caffeine used early is associated with less BPD. Pulmonary vasodilators, such as inhaled nitric oxide and sildenafil, have utility in the treatment of severe cases with pulmonary hypertension, but not in the prevention of BPD. The emerging therapy that is currently being studied is cell therapy and it is desired to decrease the impact on the long-term morbidity of BPD. The objective of this review is to collaborate in a practical way to continue improving the care of premature newborns (RNPt) in Ibero-America and that there are fewer and fewer children with BPD and that the most severe cases continue to decline. It would be wonderful for many RNPt that we could definitely solve this serious sequela of prematurity.

INTRODUCCIÓN

La displasia broncopulmonar (DBP), descripta por Northway en 1.967, es una de las secuelas más importantes de la prematurez. (1) La DBP es el resultado de un proceso complejo de origen multifactorial en el cual factores prenatales y post natales interfieren con el desarrollo del árbol respiratorio inferior, que a veces conduce a una enfermedad severa para toda la vida. (2) Afecta a los recién nacidos de pretérmino (RNPt), ocurriendo en casi la mitad de los RNPt extremadamente prematuros (<28 semanas) que egresan de las unidades de cuidados intensivos neonatales (UCIN). Anteriormente, la DBP ocurría en los prematuros de mayor edad gestacional debido a que la sobrevida de los más inmaduros era muy baja; a esa DBP se la ha denominado la forma *"clásica"*. Con el avance de los cuidados respiratorios neonatales, la mayor utilización de corticoides prenatales y el aumento de la sobrevida de RNPt pequeñitos, la denominada *"nueva"* DBP se atribuye a un mal desarrollo del pulmón, disminución de la alveolarización y origen multifactorial en el contexto de la prematuridad. (3)(4)(5)(6)

La DBP además, tiene un amplio espectro de severidad. (7)(8)(9)(10)(11)(12) Las formas severas se asocian con mayor frecuencia a un aumento de la mortalidad y a diversas morbilidades, como internaciones prolongadas, insuficiencia respiratoria crónica, alteraciones del crecimiento y del neurodesarrollo. Antes de cumplir el año de vida, los RNPt con DBP tienen dos veces más posibilidades de ser hospitalizados nuevamente luego de ser dados de alta de la UCIN comparados con los prematuros sin DBP. Además, los niños con esta patología duplican la posibilidad de muerte o discapacidad antes de los 5 años de vida y presentan alteraciones de la función pulmonar durante la infancia. Lamentablemente, a pesar de los avances en el manejo de los problemas respiratorios neonatales y de las nuevas técnicas de ventilación no invasiva, la DBP sigue siendo un grave problema.

La patogénesis de la DBP se conoce cada vez mejor, pero queda aún mucho por conocer en relación a los mecanismos que conducen a daño bronco-pulmonar en RNPt. Esto explica por qué, muchos enfoques terapéuticos que en teoría deberían ser efectivos, lo son sólo parcialmente, o directamente no sirven para nada. Peor aún, en algunos casos tienen efectos negativos. Sin embargo, la incidencia de DBP puede disminuirse prestando detallada atención a los aspectos respiratorios y nutricionales en las primeras horas y semanas del cuidado neonatal brindado a RN prematuros. Esto incluye uso óptimo del respirador, evitar exposición supra-fisiológica al oxígeno y la administración de surfactante y cafeína. La nueva medida emergente, fascinante por cierto, es la terapia celular. Sería maravilloso para muchos RNPt que los estudios en curso, den resultado positivo para resolver definitivamente este serio problema clínico, económico y social.

Esta publicación está basada en el extenso trabajo del grupo del VIII Consenso Clínico de SIBEN (13) liderado por Fariña y Mir, y publicado por EDISIBEN en un manual de 160 páginas y más de 350 citas bibliográficas. A continuación, se presentan aspectos fundamentales de relevancia clínica descritos en ese Consenso y se actualizan conceptos fundamentados presentados en publicaciones de los últimos 3 años.

DEFINICIÓN Y GRADOS DE SEVERIDAD DE DBP

La definición de DBP ha evolucionado de una basada solamente en la duración de O_2 (edad postnatal de 28 días o edad postmenstrual de 36 semanas o al alta) a una que incorpora una evaluación estandarizada de la necesidad de O_2. (7)(8)(9)(10)(11)(12) La primera definición incluye una clasificación de grados de severidad (leve, moderada, grave) que se resumen en la Tabla 1. Esta definición de DBP puede ocasionar cierto grado de subjetividad y explica las diferentes incidencias de DBP reportadas en diversos estudios.

Teniendo en cuenta esta clasificación uno puede darse cuenta que hay margen para diferentes grados de severidad dentro de cada categoría. Por ejemplo, no es lo mismo que un RN de 24 semanas deje de tener oxígeno suplementario a los 29 o 30 días de vida que otro que tolere estar sin O_2 suplementario recién después de 8-9 semanas de vida. En el otro extremo, el de los casos "graves", se pueden observar al menos tres estadíos diferentes, según la FiO_2 requerida, la necesidad o no de Presión Positiva Continua en Vía Área (CPAP) o Asistencia Respiratoria Mecánica (ARM) y la presión requerida. Así mismo, es muy diferente la severidad si existe asociación con hipertensión pulmonar, hipertrofia ventricular derecha y cor pulmonale.

DISPLASIA BRONCOPULMONAR FISIOLÓGICA

La definición de DBP fisiológica fue descrita por Walsh en 2003 (7)(9) y se realiza por medio de la prueba de reducción de FiO_2. Esta prueba se ha validado en diferentes estudios, y reduce la variabilidad en el diagnóstico de DBP. Se emplea en RNPt que están recibiendo O_2 suplementario en la semana 36 pos menstrual.

La ventaja de esta definición estaría, en que todos los niños se evalúan en forma más objetiva, independiente de las diferentes prácticas clínicas que ocurren en los diversos centros neonatales. Con ella se confirma o no el diagnóstico

TABLA 1. **Grados de severidad según edad postnatal, necesidad de oxígeno y edad gestacional al nacer**

GRADO - SEVERIDAD	NECESIDAD DE O_2 SEGÚN EDAD GESTACIONAL AL NACER
1 - Leve	RNPt < 32 semanas al nacer: Necesidad de O_2 suplementario > 28 días, pero en aire ambiente a las 36 semanas de edad pos menstrual o al alta, lo que ocurra antes. RNPt > 32 semanas al nacer: Necesidad de O_2 suplementario a los 56 días de edad posnatal o al alta, lo que ocurra antes.
2 - Moderado	RNPt < 32 semanas al nacer: Necesidad de O_2 suplementario > 28 días y FiO_2 <0.3 las 36 semanas de edad pos menstrual o al alta, lo que ocurra antes. RNPt > 32 semanas al nacer: Necesidad de FiO_2 <0.3 a los 56 días de edad posnatal o al alta, lo que ocurra antes.
3 - Grave	RNPt < 32 semanas al nacer: Necesidad de O_2 durante >28 días yFiO_2 >0.3 y/o CPAP nasal o ventilación mecánica a las 36 semanas de edad pos menstrual o al alta, lo que ocurra antes. RNPt > 32 semanas al nacer: Necesidad de FiO_2 > 0.3 a los 56 días de edad posnatal o al alta, lo que ocurra antes.

de DBP según la variación de la SpO_2 al disminuir progresivamente la FiO_2 y/o llegar a aire ambiente (FiO_2 de 0.21). También se califica la gravedad de la DBP según la necesidad de O_2.

Los trabajos de investigación, para ser "bien sólidos" y no dejar la evaluación a la discreción clínica, usaron una FiO_2 arbitraria (mayor o menor a 0.30) para definir gravedad de DBP. Redujeron la FiO_2 en RN con FiO_2 <0.30 con SpO_2 > 90% y en RN con FiO_2> 0.3 con SpO_2 > 96%.

Para la definición de "NO DBP" eligieron, también en forma arbitraria, valores de SpO_2 de 88% o de 90% en aire ambiente o un valor de corte de SpO_2> 90%. Esta prueba permite identificar a los RNPt que no necesitan O_2 y que lo están recibiendo innecesariamente. Sin embargo, un RN en aire ambiente que posea SpO_2 de 88% - 90% no es normal y de hecho puede ser muy anormal. Estos RNPt que no estén recibiendo O_2 lo deberían estar recibiendo para evitar las complicaciones serias de la hipoxia en DBP.

Como se menciona, los estudios utilizaron valores arbitrarios de FiO_2 y de SpO_2 e hicieron la prueba disminuyendo la FiO_2 en forma progresiva hasta llegar a aire ambiente si el RN lo toleraba. Si el RN está en respirador, CPAP o halo cefálico se desciende la FiO_2 de a 2% cada vez y se observa si disminuye la SpO_2. Si está respirando con cánulas nasales se va disminuyendo el flujo. Con flujos de 1–2 L/min o más, se reduce 0.5 L/min cada vez; si el flujo es bajo, 0.1-0.99 L/min, las reducciones pueden ser de 0.1 L/min cada vez, hasta llegar a "no flujo" (aire ambiente) y retirar la cánula nasal si el RNPt lo tolera. La FiO_2 se desciende progresivamente de a 20% del valor previo en el mezclador o blender,

En las publicaciones esta prueba de reducción de FiO_2 fue dividida en 4 fases:

a) fase basal (evaluación de FiO_2 y SpO_2)
b) fase de reducción de FiO_2
c) fase de aire ambiente si se toleraba la reducción progresiva de FiO_2 hasta 0.21%
d) fase de vuelta a la FiO_2 inicial, para no influir con el cuidado clínico

La interpretación de la prueba tiene varias posibilidades:

1. Un RNPt en ventilador o en CPAP o con FiO_2 > 0.30 con SpO_2 entre 90% y 96% se define como DBP fisiológica y no se hace la prueba
2. Con FiO_2 > 0.30 y SpO_2 > 96% se hace la prueba
3. Con FiO_2 < 0.30 y SpO_2 > 90% se hace la prueba

Mientras el RN tolere los descensos progresivos de FiO_2 se la sigue descendiendo cada 30 minutos en forma gradual.

Para los estudios de investigación se consideró que la prueba era positiva (o sea: DBP fisiológica con fracaso al "destete") si por 5 minutos continuos la SpO_2 se mantenía entre 80-89% o si la SpO_2 caía por debajo de 80%. Si el RN no tolera el "destete" queda establecido el diagnóstico de DBP. Por otro lado, en forma arbitraria se define como "NO DBP" cuando la SpO_2 se mantiene > 90% en aire ambiente por 30 minutos. Sin embargo, recordemos que la SpO_2 de 91-94% en aire ambiente NO es normal. En los estudios, al concluir estos 30 minutos, y con diagnóstico de "NO DBP", los RNPt volvieron a recibir la FiO_2 basal. Analizando bien lo descrito, pueden verse claramente entonces situaciones en las cuales realmente hay necesidad de O_2 (SpO_2 de 91-94% o menos en aire ambiente) y otras en las que se da O_2 innecesariamente (SpO_2 de 95% o más en aire ambiente).

TABLA 2. **Clasificación según definición fisiológica y prueba de reducción del oxígeno**

1. Fisiológica leve	RNPt < 32 semanas al nacer: Necesidad de O_2 suplementario > 28 días, pero en aire ambiente SpO_2>90% a las 36 semanas de edad pos menstrual o al alta, lo que ocurra antes RNPt > 32 semanas al nacer: igual, pero a los 56 días o al alta, lo que ocurra antes
2. Fisiológica moderada	RNPt < 32 semanas al nacer: Necesidad de O_2 suplementario > 28 días y necesidad documentada de FiO_2 <0.3 basada en el fallo para mantener SpO_2> 90% en la prueba de reducción de oxígeno a las 36 semanas de edad pos menstrual o al alta, lo que ocurra antes RNPt > 32 semanas al nacer: igual, pero a los 56 días o al alta, lo que ocurra antes
3. Fisiológica grave	RNPt < 32 semanas al nacer: Necesidad de O_2 suplementario > 28 días y necesidad documentada de CPAP nasal o ventilación o FiO_2> 0.3 basada en el fallo para mantener SpO_2> 90% en la prueba de reducción de oxígeno a las 36 semanas de edad pos menstrual o al alta, lo que ocurra antes RNPt > 32 semanas al nacer: igual, pero a los 56 días o al alta, lo que ocurra antes

La Tabla 2 resume la definición fisiológica y prueba de reducción del O_2 como fue hecha en las publicaciones. Sin embargo, teniendo en cuenta todo lo involucrado y descrito aquí, los clínicos tenemos que estar bien informados y ser bien conscientes en nuestra práctica clínica.

Para finalizar esta sección, el diagnóstico de DBP basado en el requerimiento de O_2 a las 36 semanas, no es bueno para predecir morbilidad respiratoria a largo plazo. La necesidad de O_2 o de presión positiva a las 40 semanas de edad postmenstrual sí lo es. Por lo tanto, la variabilidad en criterios diagnósticos y en la severidad de DBP, nos deben llevar a pensar y re-pensar y volver a reflexionar al interpretar estudios publicados y al decidir usar medicamentos en los RNPt que tenemos la responsabilidad de cuidar. En la sección de fármacos, drogas y medicamentos, más adelante, se presentan recomendaciones de qué usar y cuándo y qué no utilizar

INCIDENCIA

Si bien la incidencia o prevalencia de DBP no se conoce en detalle, se pueden hacer ciertas estimaciones, reconociendo que existe gran variabilidad. Una dificultad es obviamente que hay definiciones variables de DBP, como se menciona antes. Pero la variabilidad también se explica por varios otros factores, siendo uno principal qué se utiliza como denominador y por ello hay que estar atento a quién es la población reportada. ¿A qué edad postnatal se hace el análisis (al alta hospitalaria, al año de edad, otra)? ¿Se incluyen los fallecidos? ¿Se usan para el denominador todos los RNPt o solamente los ventilados? ¿Cuál es el grado de inmadurez, edad gestacional, género y raza de los bebés incluidos en el denominador? Por supuesto, también se relacionan con la variabilidad la severidad de la enfermedad respiratoria al nacer, el cuidado clínico postnatal, y las tasas de supervivencia en las diferentes UCIN. Debe resultar obvio que las UCIN con elevadas tasas de mortalidad en RNPt < 32 semanas de gestación tendrán menor frecuencia de DBP en los niños dados de alta, ya que la DBP es una enfermedad en RNPt que sobreviven. Teniendo en cuenta todo lo anterior, si se toma como denominador 'general' a RNPt ventilados, la incidencia es muy variable, alrededor del 10-15% para RNPt de 28 a 31 semanas de gestación y 40-66% en RNPt < 28 semanas de gestación. En 15 centros de la base de datos de la RED SIBEN la incidencia en RNPt < 32 semanas y < 1.500 g en el año 2017 fue de 28,5% utilizando la definición de dependencia al oxígeno a las 36 semanas, con gran variabilidad inter-centros y por edad gestacional. Entre 24 a 28 semanas la incidencia fue de 44% y entre 28 a 32 semanas fue de 15%. De todos los RN con DBP, 35% tuvo DBP grave.

PATOGENIA

Los mecanismos involucrados en la patogénesis de la DBP son multifactoriales (14)(15)(16)(17)(18)(19)(20)(21)(22)(23)(24)(25)(26)(27)(28) y pueden ser prenatales (factores intrínsecos) y post natales o extrínsecos (Tabla 3). La prematuridad es el principal determinante para desarrollar DBP. El riesgo se incrementa en los RNPt ventilados, debido a un desarrollo pulmonar incompleto, así como al déficit de factores protectores contra la lesión o injuria producida por el ventilador y el daño oxidativo.

Los mecanismos fisiopatológicos son múltiples y complejos y aún no se conocen en su totalidad. Tampoco se conoce completamente la interacción entre la expresión de genes protectores con los injuriantes o potencialmente nocivos. No hay una causa precisa o definida de DBP, sino que se trata de una condición de origen multifactorial con alteración del balance de mecanismos injuriosos con mecanismos reparadores.

FACTORES PRENATALES

Inflamación e infección fetal: Una revisión sistemática sobre asociación entre corioamnionitis y desarrollo de

TABLA 3. **Patogénesis de DBP**

FACTORES PRENATALES	FACTORES POSTNATALES
Intrínsecos	Extrínsecos
Genética	Oxígeno / estrés oxidativo
Inflamación e infección fetal	Ventilación mecánica
Carencias Nutricionales	Déficit Nutricional
Corticoides	Infección e inflamación Líquidos Ductus Insuficiencia adrenal

DBP (59 estudios con aproximadamente 15.000 RNPt) comprueba una asociación entre corioamnionitis y DBP, (16) aun controlado por varios factores como edad de gestación, peso al nacer y otros. También se correlacionan con la presencia de DBP los niveles elevados de inter-leucina (IL) 1β en muestras obtenidas de lavados de tráquea de neonatos y la presencia en el líquido amniótico de mediadores inflamatorios 5 días antes del parto (IL-6, 1β u 8 y factor de necrosis tumoral). Finalmente, los niveles elevados de citoquinas en sangre fetal y neonatal se asocian con más DBP. (17)(18)

El Ureaplasma es un organismo comensal de baja virulencia del tracto genital urinario femenino y masculino bajo. Puede infectar en forma ascendente al líquido amniótico y es el microorganismo más comúnmente aislado en mujeres con corioamnionitis y más frecuentemente asociados con nacimiento prematuro. Sin embargo, la contribución del Ureaplasma para el desarrollo de la DBP no es tan clara. (19)(20)(21)(22)

Uso de corticoides prenatales y DBP

Los esteroides antenatales son muy beneficiosos en los nacimientos prematuros entre las 23 y 34 semanas de edad gestacional(23)(29)(30)(31)(32) ya que reducen en aproximadamente un 50% las muertes neonatales y el síndrome de dificultad respiratoria (SDR), hemorragia intraventricular, enterocolitis necrosante, sepsis y el retraso madurativo a largo plazo. (31) Lamentablemente, los esteroides antenatales no disminuyen la DBP. El uso de corticoides antenatales disminuye la severidad de la DBP, pero no la frecuencia de aparición. Por otro lado, al mejorar las tasas de sobrevida de los RNPt más pequeños aumenta el número absoluto de niños que sobreviven con DBP.

Nutrición intra uterina

La restricción del crecimiento intrauterino es un factor de riesgo independiente para desarrollar DBP (24)(25) y, por ello, los RNPt que nacen pequeños para su edad gestacional tienen más incidencia DBP.

Predisposición genética

Se conoce que los factores genéticos influyen en la susceptibilidad de los neonatos pretérmino para desarrollar DBP. (26)(27)(28) Si el primer gemelo presenta DBP, la probabilidad de que el segundo gemelo la presente también es del 65% y cuando no se diagnostica DBP en el primer gemelo, la probabilidad de que ocurra en el segundo gemelo es de sólo 8%. (33) Así mismo, los neonatos que tienen antecedentes familiares de hiperreactividad de las vías aéreas son más susceptibles a desarrollar DBP, lo cual podría interpretarse como cierta predisposición genética y la interacción con factores ambientales. (34)

Los niveles elevados de citocinas proinflamatorias tales como IL-6, glicoproteína 130, también conocida como transductor de señal de IL-6, en sangre de cordón umbilical y la expresión reducida de IL-10 en la placenta se asocian con alto riesgo de desarrollar DBP. Estudios de asociación del genoma ampliado (GWAS, whole genome association study, por sus siglas en inglés,), se han convertido en un método popular para la investigación de patologías complejas y ofrecen la posibilidad de identificar características específicas en los portadores de una determinada patología. En otras palabras; el estudio del GWAS define perfiles de expresión de vías genéticas afectadas en pulmones de niños con DBP. (28) En los pulmones de estos niños, se han identificado 159 genes con expresión diferente a lo encontrado en tejido pulmonar de necropsias de niños sin DBP. Se ha encontrado una expresión alterada de genes relacionados con vías bioquímicas y moleculares del desarrollo y la morfogénesis pulmonar y una expresión disminuida de factores de crecimiento relacionados con la vasculogénesis, como el factor de crecimiento vascular endotelial (VEGF) y la enzima óxido nítrico sintasa endotelial. Todos ellos están involucrados en la patogénesis de la DBP. (35)

Los genes que están relacionados con apoproteínas del surfactante y genes pro-inflamatorios, como el 6A6 de la proteína del surfactante A-1, se han asociado con mayor incidencia de DBP. (36) También se han identificado genes que podrían ser responsables de un mayor daño oxidativo, independientemente del nivel de FiO_2. El factor de transcripción NrF2 (factor nuclear eritroide 2) activa el sistema antioxidante enzimático pulmonar y es fundamental ante la exposición a oxígeno. Existen deleciones en el gen NrF2 que altera la transcripción de factores protectores contra el estrés

oxidativo. Así mismo podrían alterarse los efectores de NrF2. La expresión génica de los diferentes factores de transcripción, depende de características genéticas individuales y, por lo tanto, la respuesta a similares concentraciones de FiO_2 puede variar. (37)(38)

Estudios en gemelos homocigotos comparados con dicigotos, han demostrado mayor susceptibilidad a desarrollar DBP y ductus arterioso permeable, cuyo impacto es atribuible a componente genético de un 53 a un 79% y hasta un 82% respectivamente(39)

En resumen, el factor genético puede ser la causa de gran parte de la variación en el riesgo y severidad de la DBP. Sin duda la DBP es una muestra clara de la interacción entre los genes y el medio ambiente, lo que se conoce como epigenética. Las interacciones entre los genes pueden ser la explicación de por qué algunos RNPt con mínimas injurias extrínsecas desarrollan DBP moderada severa y otros con una multitud de factores ambientales extrínsecos (volutrauma, hiperoxia, sobre hidratación, y otras) no desarrollan DBP.

FACTORES POSTNATALES O EXTRÍNSECOS

Oxígeno

El oxígeno suplementario es esencial para la sobrevida de los RNPt con falla respiratoria hipóxica. Pero no por ello hay que usarlo de más ni administrar FiO_2 elevadas innecesariamente. Los RNPt tienen disminuida la función del sistema de defensa antioxidante y por ello el oxígeno en exceso es muy peligroso. La injuria se debe al estrés oxidativo causado por la producción de especies reactivas del oxígeno y/o radicales libres de oxígeno. El daño celular ocurre, por la sobreproducción de estos metabolitos citotóxicos que lesionan a los ácidos nucleicos, lípidos, proteínas y carbohidratos y directamente inducen alteración y remodelación estructural pulmonar. Escapa a esta publicación describir en detalle los efectos deletéreos del oxígeno, lo que se narra minuciosamente en una de nuestras publicaciones en Neoreviews. (40) Basta con recordar que la concentración elevada y el tiempo de exposición, se asocian con DBP y que el oxígeno acumulado precozmente predice DBP, en RNPt de extremada baja edad gestacional. (41) Por ello, se debe usar la mínima FiO_2 posible y por el menor tiempo posible, desde el nacimiento. (42)(43)

Ventilación mecánica

La ventilación mecánica favorece el barotrauma, el volutrauma y también el biotrauma, que es la respuesta inflamatoria en el tejido pulmonar que ocasiona más daño pulmonar. Para disminuir la incidencia de DBP, es esencial calentar y humidificar los gases y ventilar adecuadamente. Las recomendaciones clínicas al respecto se describen más adelante.

INFECCIÓN - INFLAMACIÓN

La sepsis hospitalaria incrementa el riesgo de desarrollar DBP, debido a que desencadena respuestas inflamatorias. (44) En ocasiones esta situación se asocia a la presencia del ductus arterioso permeable (DAP) aumentando la incidencia de DBP.

LÍQUIDOS Y DUCTUS ARTERIOSO PERSISTENTE (DAP)

Los recién nacidos con SDR que reciben exceso de líquido, o no tienen una adecuada diuresis en los primeros días de vida, tienen una mayor incidencia de DBP y muerte. (45)(46)(47) Por ello, es de importancia que el balance hídrico sea negativo en los primeros días de vida de los RNPt.

Además, el exceso de líquido favorece la persistencia o reapertura del DAP, el cual produce un aumento del flujo sanguíneo hacia los pulmones, predisponiendo a edema pulmonar, con deterioro en la mecánica respiratoria, mayor tiempo de oxígeno suplementario y/o ventilación mecánica, que son importantes factores para el desarrollo de DBP. (48)(49)

APORTE NUTRICIONAL

La malnutrición se asocia con disrupción de la formación alveolar (50) y DBP. (51)(52)(53) En el primer mes de vida los RNPt que desarrollan DBP reciben menor aporte energético que los que no desarrollan DBP. (51)(53) La inadecuada nutrición neonatal interfiere con el crecimiento corporal, la maduración del pulmón y la reparación de las lesiones pulmonares, potenciando el efecto deletéreo del oxígeno y el volutrauma y la falta de mejoría en RNPt con DBP. (33) En corderos pretérmino tratados con apoyo ventilatorio no invasivo la escasa nutrición altera la formación de alvéolos. (50) Además, la desnutrición interfiere en la defensa pulmonar contra la inflamación y la infección, lo cual también afecta el proceso de desarrollo y de reparación pulmonar. (53)

INTERACCIÓN MULTIFACTORIAL

En la Tabla 4, presentamos en forma simplificada y resumida, múltiples factores que intervienen de una u otra manera en la patogenia de DBP. La interacción entre ellos es compleja y en muchos casos no se conoce completamente. Los factores predominantes no son constantes y

varían entre diferentes RNPt. El desequilibrio entre factores potenciadores y protectores de daño, es muchas veces un elemento determinante. El resultado final, es una alveolarización alterada (número reducido de alvéolos) y una vascularización alterada (densidad de vasos reducida) que producen alteración de la estructura y la función.

CUADRO CLÍNICO Y RADIOLÓGICO

El cuadro clínico de los pacientes con DBP es variable, en general los RN son de baja edad gestacional y bajo peso al nacer. En la fase aguda la enfermedad no tiene características propias, por lo que no se puede establecer un diagnóstico.

En la fase crónica se encuentran alteraciones en la funcionalidad y/o morfología pulmonar; a veces la única manifestación es una dependencia absoluta y persistente del oxígeno. La taquicardia y taquipnea, con retracciones o tiraje y aleteo nasal son comunes, debido a que hay una alteración en la relación ventilación-perfusión y un incremento en el espacio muerto. Por todo esto, suele haber hipoxemia o episodios frecuentes de desaturación e hipercapnia. Las sibilancias y estertores pueden estar presentes. El tórax puede tener el diámetro anteroposterior aumentado por atrapamiento aéreo. Los RNPt con formas moderadas a severas presentan irritabilidad, dificultad para alimentarse, un patrón de sueño irregular o interrumpido, fallo en el crecimiento, episodios de cianosis recurrentes causados por obstrucción laringo traqueal y en algunos casos severos se acompaña de hipertensión pulmonar, lo que se describe más adelante.

La radiografía es muy variable y depende de la etapa en curso y de la severidad. En fases iniciales puede existir leve opacidad difusa y uniforme en ambos campos pulmonares, lo que también se observa en la nueva DBP. En etapas más tardías puede haber híper-expansión y hasta lesiones compatibles con fibrosis y quistes pulmonares que expresan ausencia de parénquima pulmonar. Sin embargo, no es buena la correlación entre la radiografía de tórax y el estado clínico del RNPt. La Figura muestra tres imágenes radiológicas muy diferentes en tres RNPt con DBP.

TABLA 4. Factores involucrados en patogenia de DBP

➢ Vida fetal
➢ Genes, nutrición, restricción de crecimiento, infección, inflamación
➢ Prematuridad - en todos los casos
➢ Mayor riesgo en < 28 semanas y < 1.000 gramos
➢ Factores de crecimiento y transcripción (NF-KB; IL-1beta; TGF; VEGF, otros)
➢ Factores angiogénicos y antiangiogénicos
➢ Toxicidad de oxígeno - Estrés oxidativo
➢ Infección / Inflamación
➢ Ventilación Mecánica; volutrauma, biotrauma, gases secos y fríos
➢ Enfisema intersticial; neumotórax
➢ Malnutrición
➢ Ductus con repercusión hemodinámica
➢ Exceso hídrico

DIAGNÓSTICOS DIFERENCIALES

Las neumonías infecciosas causadas por Citomegalovirus, Chlamydia, Pneumocystis, Cándida, Ureaplasma y Herpes, pueden tener una evolución prolongada y originar cuadros pulmonares crónicos semejante a la DBP. Algo similar puede suceder con micro aspiraciones recurrentes y crónicas.

PREVENCIÓN DE DBP

Obviamente, la medida preventiva más efectiva para reducir la prevalencia de DBP sería poder disminuir o evitar la prematuridad. Lamentablemente esto no es posible en la actualidad, pero deben intentarse las medidas conocidas para los mejores cuidados en la amenaza de parto prematuro. Entre otros se encuentran evitar la exposición al tabaco y alcohol, usar suplementos de progesterona, el cerclaje cervical, y otros. Prevenir y tratar los cuadros infecciosos o inflamatorios materno-fetales es esencial, al igual que la adecuada y óptima nutrición y el crecimiento fetal junto con administración de corticoides antenatales, para mejorar la maduración pulmonar fetal, factores mencionados antes.

Los cuidados inmediatos al nacer son de suma importancia, debido a que las primeras intervenciones de soporte respiratorio, pueden determinar la predisposición a daño que puede ocurrir a corto y largo plazo. (54)

PREVENCIÓN DE DBP CON ADECUADA REANIMACIÓN DEL RNPT EN SALA DE RECEPCIÓN

La recomendación actual de la Asociación Americana de Cardiología (AHA), el Consejo Europeo de Reanimación (ERC) y el Comité Internacional de Enlace en Reanimación (ILCOR) sugieren no dar oxígeno a menos que sea imprescindible, utilizar un monitor de SpO_2, e iniciar la reanimación con una FiO_2 baja (21% -30%) en los RN <35 semanas de edad gestacional. (55)(56)

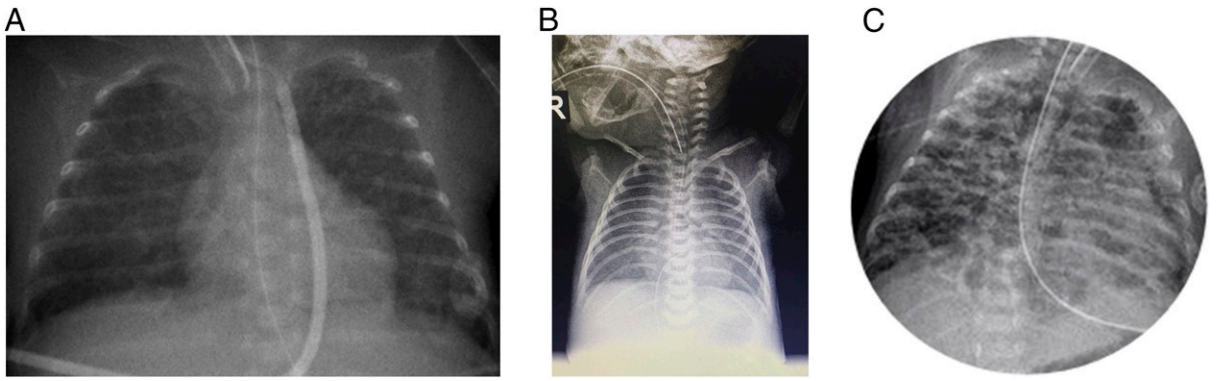

Figura. Variabilidad radiológica en tres RNPt con DBP

Para los RNPt que respiran espontáneamente con dificultad respiratoria que requieren apoyo respiratorio, la Asociación Americana de Cardiología (AHA), el Consejo Europeo de Reanimación (ERC) y el Comité Internacional de Enlace en Reanimación (ILCOR), sugieren el uso inicial de CPAP en lugar de intubación y ventilación mecánica en la sala de parto. (57)(58)

Si el RN en la sala de partos requiere ventilación artificial lo ideal es usar un respirador, con gases calientes y húmedos y con mezclador, para conocer en detalle la FiO_2. Si hubiera que brindar respiración manual con bolsa auto inflable y máscara o tubo endotraqueal, también se debe administrar gas caliente y húmedo y con FiO_2 conocida. No se deben usar gases fríos y secos ni oxígeno puro (100%). Tampoco deben usarse volúmenes corrientes (Vt) amplios. No hay que ver expandir el tórax, ya que casi con seguridad cuando eso sucede se está administrado un Vt >5-6 ml/kg. Esto no solamente predispone a DBP, sino que aumenta significativamente el riesgo de hemorragia intraventricular grados III o IV de 6% a 27% en los RNPt con Vt >6 mL/kg. (54) Lo ideal y óptimo es medir el Vt y no administrar Vt > 6 ml/kg. No usar la bolsa a menos que sea realmente imprescindible.

Una medida promisoria descrita recientemente es la instilación intratraqueal de corticoides (budesonida, 0.25 mg/kg) junto con surfactante (100 mg/kg) en las primeras 4 horas de vida en RNPt de extremado bajo peso y enfermedad respiratoria severa. (59)(60)(61) Esta medida redujo en 43% el riesgo de DBP (RR: 0.57; 95%CI: 0.43-0.76, NNT = 5) pero no modificó la mortalidad (OR: 0.61; 95%CI: 0.34-1.04). No se puede recomendar su utilización como estándar de cuidado ya que lo publicado hasta el momento adolece de algunos problemas metodológicos y muchos RN con DBP, no están severamente enfermos en las primeras horas o días de vida. Es necesario que los hallazgos recientes se repitan en estudios con mayor tamaño muestral y en situaciones clínicas diferentes para poder conocer mejor, a quién beneficia y si no hay efectos a largo plazo.

MEDIDAS PREVENTIVAS DE DBP EN UCIN

Las siguientes intervenciones son generalmente utilizadas en forma combinada para la prevención o mejoría del resultado final en los RNPt con riesgo de desarrollar DBP

- Prevenir el parto prematuro.
- Surfactante exógeno precoz (no profiláctico).
  - En RNPt que respiran espontáneamente y no tienen insuficiencia respiratoria severa, usar CPAP precoz.
  - Si fracasa el CPAP, intubar y dar surfactante precoz. Dos dosis.
  - Aumenta la sobrevida
  - Modifica las características de la DBP
  - Reduce el riesgo de desarrollar DBP
  - No recomendamos el método "InSurE" (intubar dar surfactante y extubar). Si el RNPt requirió intubación, es más beneficioso observarlo en ventilación. Si en las 2-4 horas siguientes hubiera franca mejoría de la insuficiencia respiratoria y no requiere más ventilación, entonces extubar a CPAP o ventilación nasal no invasiva. Si no fuera así, dar la segunda dosis de surfactante y luego decidir extubación lo más precozmente posible. (62)
  - Más efectivo parece ser el denominado método "LIST" (siglas del inglés), que significa terapia con surfactante menos invasiva. En RNPt que respiran espontáneamente se instila el surfactante por medio de un catéter intratraqueal delgado y no con un tubo endotraqueal. Hay 6 estudios comparativos; en 4 de ellos se comparó "LIST" vs "InSurE"(63). Se encontró que con "LIST" hubo menos prevalencia de DBP (pero con inconsistencia entre los estudios), menos fracaso de CPAP y menos ventilación

invasiva. No se encontró mejoría en otras morbilidades ni en mortalidad. Lamentablemente, no hay estudios a largo plazo. (63)
  - Como se menciona anteriormente, no recomendamos en la actualidad la instilación intratraqueal de corticoides junto con surfactante.
- Restricción de fluidos los primeros días de vida. Balance hídrico negativo.
- Evitar hiperoxia e hipoxia.
- Tolerar valores de CO_2 entre 45-55 mmHg.
- Evitar la hipocapnia.
- Estrategias de soporte ventilatorio que minimicen el barotrauma, volutrauma y atelectrauma durante la enfermedad pulmonar aguda. Esto incluye lo siguiente:
  - Usar gases mezclados y bien acondicionados (humidificados y calentados)
  - CPAP precoz
  - Tiempos inspiratorios de 0,2 a 0,3 segundos
  - PEEP óptimo (5-7 cmH_2O) para que haya suficiente reclutamiento pulmonar sin sobredistensión
  - Mantener Vt no mayor de 4 a 5 ml/kg
  - Destete precoz del soporte respiratorio
  - Intención de tratamiento de SpO_2 en RNPt con O_2 suplementario en las primeras semanas de vida: SpO_2 entre 86%-94%, con alarma mínima de 85% y máxima de 95%.
  - Intención de tratamiento de $PaCO_2$ en RNPt con ventilación mecánica en las primeras semanas de vida: 45-55 mmHg (sin sobrepasar 55 mmHg)
- **Cafeína:** Droga muy bien estudiada en neonatología. Se recomienda su uso de rutina en forma temprana en los RNPt < 1.500g dentro de las primeras 12 a 48 horas de vida. (64)(65)(66)(67)
  - Marcada reducción de DBP (OR 0,69; 95% IC 0,58-0,82, p < 0,001)
  - Disminuye alteraciones del neurodesarrollo a largo plazo
  - (Algunos se preocupan por estudios de cohorte done se ha reportado aumento de enterocolitis necrosante, pero no es un efecto adverso comprobado)
  - Mecanismo de acción: antiinflamatorio, antioxidante, disminuye necesidad de ventilación asistida y períodos de hipoxemia.
- Otros fármacos (ver más adelante).
- Tratamiento oportuno del DAP hemodinámicamente significativo.
- Evitar las infecciones asociadas a los agentes de salud.

TRATAMIENTO DE LA DBP SEVERA (INJURIA PULMONAR ESTABLECIDA)

Una vez establecida, la DBP es una enfermedad crónica en la cual es importante esperar mejoras paulatinas y no agudas. Estos RN requieren una atención cuidadosa y paciente. Citaremos alguno de los tratamientos más importante para la DBP establecida y severa, que resumimos en la Tabla 5.

Objetivos de SpO_2 y de $PaCO_2$

- El requerimiento de oxígeno y su saturación ideal no se conoce en RNPt con DBP.
- La intención de tratamiento de SpO_2 en RNPt con DBP debe tratar de mantener la SpO_2 en no menos de 89% y no más de 96%, tal vez poniendo las alarmas en esos valores para intentar que el RN este la mayor parte del tiempo posible con una SpO_2 entre 90-95% y mejor 92%-96%.
- Si bien la hiperoxemia es nociva, en los RNPt con DBP es esencial evitar hipoxemia persistente (SpO_2 <90%) y los episodios frecuentes o recurrentes de desaturación o hipoxemia. Permitir esto aumenta la resistencia vascular pulmonar y el riesgo de hipertensión pulmonar ulterior, a veces muy grave.
- No permitir hipoxemia ni episodios frecuentes de desaturación.
- Descender la FiO_2 con cautela siempre que el niño se encuentre más o menos estable con SpO_2> 94-95%

TABLA 5. **Enfoque terapéutico para DBP**

➢ Oxígeno y objetivos de SpO_2 y de $PaCO_2$
➢ Aporte hídrico y nutricional
➢ Ventilación mecánica
➢ Fármacos, drogas y medicamentos
➢ § corticoides postnatales sistémicos e inhalatorios
➢ § broncodilatadores
➢ § diuréticos
➢ § antioxidantes e Isoprostane
➢ § óxido nítrico inhalado (ONi), Sildenafil, antagonistas de la endotelina, análogos de la prostaciclina (Bosentan, Treprostinil, Iloprost)
➢ Tratamiento de alcalosis metabólica y acidosis respiratoria
➢ Kinesiología respiratoria
➢ Estimulación del tono muscular y del neurodesarrollo
➢ Cuidado de la familia
➢ Posibilidades terapéuticas futuras

- Con cánula nasal (alto o bajo flujo). Si la SpO_2 es > 95%, descender la FiO_2 progresivamente hasta llegar a aire ambiente (FiO_2 0.21)
- En niños con respirador o CPAP, no usar 100% de O_2 (FiO_2 1.0)
- Siempre usar gases mezclados, humidificados y calentados
- En DBP, se pueden tolerar niveles de $PaCO_2$ entre 50 y 60 mmHg para poder descender parámetros, mientras el pH no sea < 7.28.
- La $PaCO_2$ elevada disminuye la presión parcial alveolar de oxígeno y por lo tanto se asocia con más requerimiento de FiO_2.
- La hipercarbia puede aumentar la resistencia vascular pulmonar y producir hipertensión pulmonar, sobrecarga e hipertrofia ventricular derecha y hasta cor pulmonale

La Tabla 6, extraída del VIII CONSENSO CLINICO de SIBEN sobre DBP, resume los conceptos anteriores.

HIDRATACIÓN PARENTERAL Y NUTRICIÓN

La restricción hídrica los primeros días de vida (con balance de agua negativo) es un factor preventivo. Varios trabajos demuestran que volúmenes iniciales mayores a 150 ml/kg/día son dañinos. (45)(46)(47) Los niños con DBP reciben mayores cantidades de cristaloides y coloides por kilogramo en los primeros 4 días de vida y suelen tener aumento de peso, comparado con los controles que mantienen el descenso de peso esperado en los primeros 4 días de vida. De las observaciones y estudios se infiere que los fenómenos postnatales tempranos tales como la terapia con exceso de fluidos, la falta de descenso de peso y el uso de furosemida son importantes en la patogénesis de DBP.

Los niños con DBP tienen también un crecimiento óseo subóptimo y una mayor incidencia de enfermedad metabólica ósea u osteopenia. (51) El inicio precoz de nutrición parenteral con aporte proteico de 3-4 g/kg/día, la estimulación trófica gastrointestinal y la alimentación exclusiva con leche de la propia madre o de donante también son factores preventivos. (68)

La investigación de nutrientes que puedan ser de utilidad en la prevención o tratamiento de DBP, incluyen glutamina, cisteína y N-acetil cisteína, L-arginina y L-citrulina, ácidos grasos poli- insaturados de cadena larga ("PUFA"), inositol, selenio, y algunas vitaminas antioxidantes como la vitamina A. La evidencia muestra, que la vitamina A y los "PUFA" pueden prevenir DBP, y que la L-citrulina, puede convertirse en un nuevo método para tratar la hipertensión pulmonar (HP) crónica asociada con DBP. (52) Los efectos de otros nutrientes en prevención o tratamiento de DBP siguen siendo estudiados. Mientras tanto hay que hacer el máximo esfuerzo para lograr brindar aporte energético suficiente, ya que los RNPt presentan reservas calóricas no proteicas mínimas, que rápidamente se consumen y provocan estado catabólico. Lamentablemente, la mayoría de los RNPt graves suele recibir escaso aporte nutricional durante el periodo agudo y esto debe modificarse en la práctica cotidiana.

Los niños con DBP ya establecida tienen aumento del estado catabólico y del trabajo muscular y requieren 15 a 25%

TABLA 6. **FiO_2, SpO_2 y $PaCO_2$ en RNPt con DBP**

ASPECTOS CLÍNICOS	VALORES DE SpO_2 y $PaCO_2$
SpO_2 normal (con o sin DBP) en aire ambiente (FiO_2 0.21)	SpO_2 95-100%
Recién nacido con DBP	NO tolerar SpO_2 <90% por períodos prolongados (con FiO_2 0.21 o con cualquier FiO_2)
Alarmas respirando FiO_2> 0.21	Mínima 88%; Máxima 96% (97% en casos más graves)
	SpO_2 91-96%
Objetivo de SpO_2 en DBP severa	No usar FiO_2 1.0 (100%)
Siempre con mezclador y gases calientes y humidificados	
Disminuir progresivamente la FiO_2	Con SpO_2>95%
Rango "normal" de $PaCO_2$ en DBP	$PaCO_2$ 42-50 mmHg
Intención de tratamiento para $PaCO_2$	$PaCO_2$ 45-55 mmHg ("destetar")
Aceptar $PaCO_2$ sin aumentar	$PaCO_2$ 55-60 mmHg

más calorías que un RNPt sano. Para evitar sobrecarga de líquidos se recomienda no sobrepasar 150 ml/kg/día con un aporte calórico de 120 a 140 kcal/ kg/ día. Esto se logra utilizando leche humana más fortificadores que garanticen el aumento proteico, energético y de minerales o mediante fórmula para prematuros de 22 o 24 kcal/oz (0.8 cal/ml).

El aporte proteico varia con la edad gestacional apuntando a 4 g/kg/día para RNPt con peso al nacer < 1.000 g, y entre 3,5 a 4 g/kg/día en RN <1.800 gramos. Los lípidos son importantes para proveer ácidos grasos esenciales y poliinsaturados, favorecer la absorción de vitaminas liposolubles y logar el objetivo calórico. En RNPt con DBP, es necesaria la suplementación con calcio 150-200 mg/kg/día, fósforo 60-90 mg/kg/día y vitamina D 800 a 1.000 UI /día, para evitar la osteopenia del prematuro.

Por lo tanto, restringir aporte hídrico, optimizar el aporte nutricional y monitorizar el crecimiento y el estado metabólico óseo puede disminuir la incidencia de DBP y además es esencial para mejorar el proceso de reparación pulmonar en los RN con DBP.

ASISTENCIA RESPIRATORIA MECÁNICA

Una orientación meticulosa de la ventilación mecánica puede minimizar el daño pulmonar y la toxicidad por oxígeno. Como se menciona antes, en la fase respiratoria aguda, la ventilación del RNPt debe realizarse con los parámetros mínimos posibles para intentar mantener pH de 7.20-7.30, $PaCO_2$ 45-55 mmHg, y PaO_2 45-70 mmHg con SpO_2 86-94%. En general esto se logra sin dificultades con tiempos inspiratorios de 0,2 a 0,3 segundos, PEEP 5-7 cmH_2O, Vt no mayor de 4 a 5 ml/kg y destete precoz del soporte respiratorio. Teniendo en cuenta en todo momento los principios fisiológicos básicos, evitando hipocarbia y optimizando el reclutamiento pulmonar puede disminuirse el riesgo de DBP.

Uso del respirador en DBP severa

El enfoque de la ventilación mecánica debe modificarse una vez que RNPt ha desarrollado DBP. Los siguientes son conceptos a considerar en los RNPt con DBP severa.

- Vt 'amplios' (10-12 ml/kg)
- Ti más largos (≥0.6 segundos)
- PEEP suficiente y hasta 8-10 cm H_2O si hay colapso dinámico de la vía aérea
- Soporte de presión
- Frecuencia respiratoria (FR) baja (FR de 10-20 por minuto), para disminuir atrapamiento y mejorar intercambio de gas, especialmente cuando se usan Vt amplios y Ti largos
- Por todo lo anterior usar sincronización, pero NO ventilación asistida y controlada
- Toda estrategia ventilatoria tiene efectos interactivos
- Modificaciones en FR, Vt, tiempo inspiratorio, PEEP y soporte de presión son muy interdependientes
- La sobredistensión puede aumentar la agitación y empeorar la ventilación alveolar
- Si se toman en cuenta las medidas anteriores, pocas veces es necesario usar ventilación de alta frecuencia por hipoventilación alveolar e hipercarbia refractaria.

PUNTOS CLAVE *Para RNPt con DBP moderada a severa que requieren ventilador*

-Asignación de enfermería sin muchos cambios de profesionales a lo largo de los días (o sea, "cuidado continuo de enfermería").

- Nutrición con adecuada ingesta proteica (3.5-4.0 g/kg/día) y calórica (130-140 cal/kg/día) pero sin exceso hídrico, no más de 140-150 ml/kg/d.
- Emplear los principios conocidos de la fisiología respiratoria y su aplicación continua (también son de utilidad para el destete).
- Emplear suficiente PEEP (5-8 cm H_2O)
- Intentar descender los parámetros del respirador en forma gradual y progresiva todos los días. Bajar la FiO_2 de a 1-3% siempre que la SpO_2 sea > 92-94%
- Hacer una prueba de extubación a ventilación nasal no invasiva o a CPAP (6-8 cm H_2O) en cuanto se pueda. Como ejemplo, pero no para universalizar, cuando la frecuencia respiratoria del respirador es baja (20-25 por minuto) y la FiO_2 < 0.5
- Administrar cafeína

FÁRMACOS, DROGAS Y MEDICAMENTOS

Los fármacos empleados con intención de prevenir o tratar DBP no constituyen el tratamiento; son solamente coadyuvantes que no se deben emplear de rutina.

Hasta el año 2014 había más de 60 estudios aleatorizados o de fase temprana con 24 fármacos estudiados en más de 24.000 RNPt. (69)

La inmensa mayoría de esos medicamentos no demostró efectividad y fracasó para reducir la incidencia de DBP y/o mejorar los resultados a largo plazo (Tabla 7).

Desde aquel momento y hasta marzo de 2018 hemos encontrado 24 estudios más, pero escapa a esta revisión hacer un análisis de cada uno de ellos. Ya hemos comentado de la cafeína y el surfactante. Nos enfocaremos a continuación en, diuréticos, broncodilatadores, corticoides postnatales, instilación intra-traqueal de budesonida con

TABLA 7. Resumen de fármacos estudiados en DBP con y sin efecto beneficioso

CON BENEFICIOS	SIN BENEFICIOS
Cafeína , Vitamina A, Corticoides parenterales, Vasodilatadores pulmonares, Inositol, Claritromicina, Instilación de budesonida + surfactante	Diuréticos; corticoides inhalados; salbutamol inhalado y nebulizado, vitaminas E y C, Selenio, Alopurinol, N-acetil cisteína, Azitromicina, Estrógeno/ progesterona, Superóxido dismutasa, Zinc, Tiroxina, Alfa-1-anti-tripsina, Cromoglicato de Na

surfactante, vitamina A y el uso de vasodilatadores para niños con DBP severa e hipertensión pulmonar.

Diuréticos

El diurético de asa más utilizado y mejor estudiado en el tratamiento de DBP es la furosemida. No es de ninguna utilidad en la prevención de DBP ni en el curso agudo de una enfermedad respiratoria en el RNPt. A la inversa, un diagnóstico clínico de conducto arterioso persistente o ductus arterioso permeable (DAP) y recibir furosemida en los días 3 y 4 de vida se asocian con más propensión a DBP. (70) La furosemida aumenta la producción de prostaglandina y por ello puede asociarse con DAP. (71) Aunque el tratamiento diurético puede mejorar la mecánica pulmonar a corto plazo en algunos RNPt, hay poca evidencia de que su empleo a largo plazo mejore el resultado clínico de los bebés con DBP. (72) En el tratamiento de la DBP establecida, no tiene beneficios en resultados clínicos, necesidad de asistencia respiratoria, duración de la estancia hospitalaria, supervivencia o evolución a largo plazo. Si usa furosemida en el tratamiento de DBP establecida, sólo debe ser empleada por tiempos cortos en aquellos niños con mal manejo de líquidos. Hay que monitorizar el calcio y el sodio. Por otro lado, los efectos adversos y la injuria potencial de la furosemida son serios y se resumen en la Tabla 8. La hipocloremia y alcalosis metabólica suelen ser serias y conducen a hipoventilación, lo que es contraproducente en DBP (ver más adelante).

La administración aguda y crónica de diuréticos que actúan sobre el túbulo renal distal (tiazidas y/o espironolactona) produce una mejora a corto plazo en la mecánica pulmonar en algunos RNPt con DBP. (73) Sin embargo, no hay mejoría persistente de la mecánica pulmonar ni de la oxigenación. No son efectivos en DBP. Por lo tanto, la

TABLA 8. Efectos fisiológicos y adversos de la furosemida

EFECTOS FISIOLÓGICOS	EFECTOS ADVERSOS
• Mejora mecánica y función pulmonar y oxigenación	• Hipocloremia • Hiponatremia
• Disminuye resistencia en la via aérea	• Hipokalemia
• Mejora distensibilidad (compliance)	• Alcalosis metabólica
Dinámica	• Hipoventilación
• Aumenta capacitancia venosa	• Hipovolemia
• Disminuye Filtración transvascular pulmonar	• Arritmias • Agrava función cardíaca al elevar niveles
• Facilita destete de apoyo respiratorio y O_2	de angiotensina-II en plasma
• Anti-Inflamación	• Más incidencia de ductus arterioso
• Broncodilatación	permeable por inhibir un inhibidor de
• Puede mejorar la sensibilidad de las células a los esteroides endógenos	Prostaglandina • Inadecuada mielinización (por hiponatremia)
• No beneficios en resultados clínicos, necesidad de asistencia respiratoria, duración de la estancia hospitalaria, supervivencia o evolución a largo plazo	y peores resultados del neurodesarrollo • Hipoacusia • Osteopenia • Hipercalciuria; nefrocalcinosis • Hipocalcemia, hipofosfatemia

TABLA 9. **Resumen de recomendaciones en relación a los corticoides**

✓ No usar corticoides sistémicos o inhalatorios para prevención de DBP
✓ Como potencial preventivo, tal vez considerar HC endovenosa (1 mg/kg/d) en RN 24-25 semanas que estén muy enfermos al nacer y en ventilación mecánica con altos parámetros en las primeras 24 horas de vida
✓ Para el tratamiento de DBP establecida no usar de rutina. Seleccionar con extrema cautela el uso de corticoides sistémicos (dexametasona <0,2 mg/kg/día o HC 3-6 mg/kg/d)
✓ No usar corticoides inhalatorios ni agonistas beta-2 para tratamiento de DBP

recomendación es limitar el uso de diuréticos a casos muy bien seleccionados. Si se utilizan debe evaluarse individualmente si hay algún efecto agudo positivo de la medicación, que no debe usarse en forma prolongada.

Broncodilatadores

No se recomienda el uso rutinario o crónico de los broncodilatadores inhalados Beta2 en bebés con DBP por falta de pruebas de la eficacia a largo plazo y sus efectos adversos conocidos. Sin embargo, algunos niños con DBP grave y lactantes que son dependientes del respirador tienen episodios agudos de broncoconstricción. En este contexto, la utilización de beta-2 agonistas inhalados (por ejemplo, albuterol o levalbuterol) pueden mejorar la función respiratoria a corto plazo.

Corticoesteroides

En la práctica, no se recomienda utilizar rutinariamente dexametasona ni otro corticoide para tratar la DBP establecida ni para prevenirla (Tabla 9). La dificultad es que tanto la dexametasona como los corticoides inhalados no han sido evaluados en estudios con gran tamaño muestral que incluyan seguimiento a largo plazo. Se reserva el tratamiento con corticoides para el niño excepcional con DBP severa que no puede ser destetado del respirador con parámetros elevados o con alto apoyo de oxígeno. A continuación, se resumen los aspectos sobresalientes basados en la literatura publicada sobre corticoides en DBP en los últimos años hasta marzo del 2.018. (51)(74)(75)(76)(77)(78)(79)(80)(81) Un meta-análisis de 47 estudios con 6.747 niños (76) sugiere que la dexametasona utilizada precozmente como prevención, puede reducir algo el riesgo de DBP a las 36 semanas de edad post-menstrual; pero las dosis elevadas y por tiempos más prolongados, se asocian con elevado riesgo de parálisis cerebral y peor neurodesarrollo.

- El uso rutinario de altas dosis de dexametasona (alrededor de 0,5 mg/kg/día) no pueden recomendarse en el manejo y prevención de la DBP.
- Los datos son insuficientes para hacer una recomendación en el uso de dosis bajas de dexametasona (<0,2 mg / kg por día) en el tratamiento de DBP
- Los datos son insuficientes para recomendar el uso de hidrocortisona (1 mg/kg/día), en las dos primeras semanas de vida aunque, puede haber una sub población de RN que pueden beneficiarse de dicha terapia.
- El tratamiento con glucocorticoides inhalados no es beneficioso en el tratamiento de niños con DBP.
- El estudio llamado "NEUROSIS" evaluó budesonida inhalada comenzando antes de 12 horas en RN de 23 a 28 semanas con ventilación mecánica. Budesonida 2 "puffs" (200 μg por "puff") cada 12 horas por 14 días y un "puff" cada 12 horas desde el día 15 hasta que el RN no requiriera O_2 y presión positiva o hasta las 32 de edad post-menstrual. (77) ¿Qué pasó en la evaluación a los 2 años? ¡Más mortalidad! A los 2 años de edad no hubo beneficios, hubo más mortalidad en el grupo con budesonida con riesgo relativo de 1.37, p=0.04.)
- En relación a corticoides inhalados, la revisión de Cochrane de fines del 2017 (78) muestra la gran variabilidad entre las escasas publicaciones existentes, con diferentes dosis y edad de inicio y otros factores como el escasísimo número de bebés estudiados en algunas de las publicaciones. No hay beneficios. No se recomienda utilizar.
- En un estudio aleatorizado, controlado, enmascarado, efectuado en Francia (denominado "PREMILOC") se comparó Hidrocortisona (HC) versus placebo EV en RN de 24-27 semanas. La dosis fue 1 mg/kg/d (c/12h) comenzando en las primeras 24 horas y por durante una semana, seguido de 0.5 mg/kg/d tres días más. La dosis acumulativa total fue de 8,5 mg/kg. La variable de resultado primario es una variable "combinada o compuesta" (sobrevida sin DBP a las 36 semanas). Ya va la tercera publicación con los mismos recién nacidos estudiados. (79)(80)(81) En la primera publicación se reportó que la sobrevida sin DBP en el grupo con HC fue de 60% mientras que en el grupo placebo fue de 51%, o sea una mejora del 9% con el esquema terapéutico de HC mencionado. En el grupo de 24-25 semanas la incidencia de sepsis fue casi el doble que en el grupo tratado (40% vs 23%). En análisis post-hoc se encontró

que el efecto positivo sólo ocurre en RNPt de sexo femenino y que no hay efectos beneficiosos si no hay antecedentes de corioamnionitis. A los 2 años la segunda publicación reportó que no hay evidencia de daño. La tercera publicación publica el análisis dividiendo a los grupos por edad gestacional y muestra que para los RNPt de 24–25 semanas hay mejoría en la evaluación neurológica en el grupo tratado con HC, pero no en los RN 26-27 semanas. En resumen, en RNPt de 24-25 semanas, muy enfermos al nacer y en ventilación mecánica con altos parámetros, la HC precoz puede disminuir DBP a las 36 semanas y parece no afectar negativamente (o quizás mejora) el resultado neurológico a los 2 años en esos RN. Antes de utilizar de rutina HC en estos RNPt ¿Cuál es la mortalidad de estos RNPt en su centro? ¿Porcentaje de infecciones en su centro? ¿Candidiasis? ¿Eje hipotálamo hipofisario neonatal? ¿Crecimiento? ¿Nutrición? Preguntas que cada uno debe hacerse para evaluar relación riesgo/beneficio y que no pueden ser respondidas en esta publicación.

VITAMINA A Y VITAMINA D

La evidencia muestra que la vitamina A puede prevenir DBP. (52) La vitamina A se considera dentro de los muy pocos medicamentos que han demostrado impacto positivo en la prevención de la DBP. Sin embargo, en la actualidad no hay suficientes estudios que justifiquen la recomendación en cuanto a la administración de la vitamina A como rutina a todos los RNPt con extremo bajo peso al nacer. La vitamina A es uno de los principales antioxidantes en RNPt, ya que protege contra el daño oxidativo pulmonar inducido por la administración de oxígeno suplementario e inflamación. (82)(83)(84) En los RNPt extremos los niveles de vitamina A son bajos al nacer y disminuyen aún más en las 2 primeras semanas de vida alcanzando el nadir a las 5 semanas. (84) Una revisión sistemática de 9 estudios con 1291 RNPt, muestra una tendencia a la reducción de la mortalidad o necesidad de oxígeno a las 36 semanas corregidas, sin afectar los parámetros estudiados en cuanto al neurodesarrollo a los 18-22 meses (RR 0.93; IC 95% 0.88 -0.99; NNT 20). El único estudio de los nueve que exploró diferentes dosis de vitamina A, no encontró diferencias de resultados entre los diferentes grupos. (85) Dar inyecciones intramusculares tres veces por semana tiene poca aceptación por el personal de salud por ser dolorosas. Podría considerarse no justificable dar 12 o más inyecciones a cada RNPt para un resultado modesto en cuanto a beneficio posible. Podría ser de utilidad para algunos bien seleccionados, como por ejemplo RNPt de <800 g con enfermedad pulmonar severa. Todavía hay que evaluar desde varios puntos de vista el valor de la vitamina A para su uso en prevención de DPB, sobre todo por su asociación con sepsis y enterocolitis y porque cuando hubo escasa disponibilidad de Vitamina A en el mercado de USA no aumentó la incidencia de DBP. (86)(87)

La Vitamina D desempeña un papel fundamental en el desarrollo pulmonar fetal, particularmente como factor de crecimiento de las células epiteliales tipo II. Además, participa en la regulación de la inmunidad, inflamación y reparación del daño. Se ha descrito que el polimorfismo del receptor de vitamina D (Fok 1 RVD), representa un factor de riesgo significativo para el desarrollo de DBP. (88)(89) Siempre debe aportarse la cantidad recomendada de vitamina D (600-1000 Unidades) a todo RNPt y más aún a aquellos niños con DBP.

ALTERACIONES ELECTROLÍTICAS Y ALCALOSIS METABÓLICA

El uso indiscriminado y exagerado de furosemida se asocia con alcalosis metabólica hipoclorémica e hipokalemia y muchas veces con hiponatremia. Además, puede conducir a hipocalcemia y osteopenia. La hipercarbia ($PaCO_2$ > 55-60 mmHg) con pH normal o alto (alcalosis metabólica) requiere tratar el componente metabólico. (3)(4)(5)(6)(13) Esto incluye mantener el potasio en el límite superior de lo normal. La respuesta fisiológica normal en la alcalosis metabólica es la hipoventilación para aumentar la $PaCO_2$ y esto es perjudicial en RNPt con DBP a quienes hay que sacarlos del respirador lo antes posible. La hipokalemia puede disminuir aún más la respuesta del centro respiratorio. Por ello, hay que aumentar el aporte de cloruro, aportando suficiente KCl (> 4-5 mEq/kg/día) y no usar diuréticos innecesariamente, que muchas veces no mejoran absolutamente nada la función pulmonar. En algunas ocasiones se requiere la administración de una sustancia acidificante con cloruros (como Cloruro de Arginina) para combatir la alcalosis metabólica secundaria.

HIPERCARBIA

La $PaCO_2$ elevada ocasiona respuestas fisiológicas importantes en todo el cuerpo que no son inconsecuentes y tienen efectos deletéreos potencialmente muy serios que pueden afectar pulmón, cerebro, corazón, circulación periférica, ojos, la expresión de genes y otros. Escapa a esta revisión describir en detalle cada uno de los efectos adversos y citar toda la bibliografía correspondiente. La Tabla 10 presenta los efectos deletéreos y resumimos algunos de ellos; las referencias al respecto se encuentran en el VII Consenso Clínico (13) y en otro material publicado por nosotros. (13)(90) La

$PaCO_2$ elevada, puede actuar como un aditivo anestésicos, causar alteraciones de la conciencia y ser analgésico y anestésico ($PaCO_2$ > 100 mmHg). En adultos, la hipercarbia reduce las capacidades intelectuales y empeora la capacidad para resolver problemas complejos y para el pensamiento estratégico. Asimismo, la $PaCO_2$ elevada en forma prolongada puede producir alteraciones en el sistema inmunitario por supresión de expresión de genes de la inmunidad innata. En un modelo animal con hipoxia-hiperoxia intermitente combinada con hipercapnia se demostró peor estrés oxidativo y aumento de muerte neuronal por disfunción mitocondrial. La hipercapnia produce también importantes alteraciones metabólicas. Entre ellas, a nivel renal hay aumento de la reabsorción de bicarbonato y de la excreción de iones hidrógeno y cloro. El bicarbonato plasmático aumenta alrededor de 3.5 mEq/L por cada 10 mmHg de aumento de $PaCO_2$. La hipercapnia produce una desviación a la derecha de la curva de saturación de la hemoglobina (efecto Bohr) y disminución de la afinidad de la Hb por el O_2, y, por lo tanto, menor saturación y menor contenido de O_2 a igual PaO_2. Además, ocasiona vasoconstricción pulmonar y descenso de la presión alveolar de O_2. Finalmente, produce efectos renales y hormonales y que impactan el estado metabólico del organismo. Entre ellos, disminución del flujo sanguíneo renal, activación del sistema renina-angiotensina-aldosterona, degradación de proteínas, generación de radicales libres y peroxidación lipídica. En RNPt la hipercarbia se asocia con peor desarrollo de la sustancia blanca a la edad corregida de término y con déficits persistentes del aprendizaje y es un predictor independiente de hemorragia intracraneana severa, muerte y alteración del neurodesarrollo. La denominada "ventilación mínima no disminuye la tasa de DBP o muerte y no confiere beneficios. En definitiva, no se puede apoyar una recomendación general de ventilar RN induciendo hipercarbia. Lo que importa al cuidar un RNPt enfermo es individualizar el cuidado y definir el nivel "óptimo o "aceptable" de $PaCO_2$ para ese bebé en ese momento. A la vez, hay que determinar el nivel de $PaCO_2$ al cual habrá que intervenir con el objetivo de mejorar la ventilación alveolar y disminuir o evitar la posibilidad de daño. En RNPt con DBP la $PaCO_2$ de 56 mmHg NO es normal y se debe a disminución de la ventilación alveolar, pero esto no quiere decir que haya que intubar o aumentar parámetros de ventilación. Los efectos deletéreos potenciales de hipercarbia se resumen en Tabla 10. (6)(13)(91)

HIPERTENSIÓN PULMONAR (HP) POR DBP

La mayoría de los niños con DBP mejoran con el tiempo. Sin embargo, cuando hay enfermedad vascular, la morbilidad y mortalidad asociada con BPD aumenta considerablemente. La incidencia de hipertensión pulmonar (HP) por DBP ha sido descrita en un meta-análisis, (92) que sugiere que la HP ocurre en uno de cada 4-5 niños con DBP.

Es recomendable que todos los RN con DBP tengan un ecocardiograma (ECO) antes del alta de la UCIN para evaluar si tienen HP. El ECO también debe evaluar la presencia de estenosis de las venas pulmonares que está presenta en alrededor del 5% de RNPt con DBP severa. Si esta condición queda sin diagnóstico, los resultados son peores que en los niños con DBP severa con HP, pero sin estenosis adquirida de las venas pulmonares. (93)

Como posibles marcadores de HP en DBP podrían ser de utilidad encontrar elevación de niveles del péptido natriurético alto y niveles bajos de citrulina, un precursor del óxido nítrico. (94) Y un tratamiento podría ser dar L-citrulina, como se menciona antes. (52) El tratamiento con sildenafil de niños con DBP complicada por HP mejora parámetros hemodinámicos y la sobrevida. (95) Vemos brevemente las drogas que pueden utilizarse.

Óxido nítrico inhalado (ONi) en DBP:

Cuatro publicaciones recientes (96)(97)(98)(99) van confirmando lo que han sostenido otros autores. En 37.909 RNPt de 22-29 semanas 2,6% (993) recibieron ONi. No hubo mejoría de mortalidad ni morbilidad. (96) En RNPt de muy alto riesgo para DBP, el ONi a 20 ppm iniciado entre los 5 y 14 días de edad postnatal y continuado por 24 días, no mejoró la sobrevida sin DBP a las 36 semanas de edad postmenstrual, ni los resultados respiratorios y del neurodesarrollo a los 18-24 meses de vida. Un análisis en Cochrane (99) describe que ONi no previene DBP ni daño neurológico y que la administración de ONi de rescate para el RNPt extremadamente enfermo no parece ser efectivo y requiere de más estudios. Con toda esta evidencia, y pese a que puede disminuir tasas de DBP y mejorar resultados neurológicos en algún grupo de RNPt no podemos recomendar ONi para el tratamiento de SDR en RNPt ni para prevención de DBP. En casos individualizados de DBP con HP puede ser de utilidad, pero considerando su uso con mucha cautela, ya que los estudios realizados no demuestran mejoras estadísticas de la supervivencia de RNPt con falla respiratoria hipóxica.

Sildenafil en DBP:

En el 2006 publicamos por primera que el Sildenafil por vía oral produce vasodilatación pulmonar y mejora RN con HP (100) En los último 5 años el Sildenafil ha mostrado, en estudios randomizados y controlados, (101)(102) en

TABLA 10. Potenciales efectos deletéreos de la hipercarbia

POTENCIALES EFECTOS DELETÉREOS DE LA $PACO_2$ ELEVADA SOBRE EL APARATO RESPIRATORIO	
Fisiopatología y Clínica	**Bases celulares y moleculares**
• ↓de perfusión pulmonar • Alteración de la relación ventilación perfusión	Múltiples y complejas que escapan al contenido de esta sección.
• ↑ de resistencia vascular pulmonar (shunt D I) • ↓ de presión alveolar de oxígeno (PAO_2) • Lo anterior: conduce a hipoxemia o a >FiO_2 • Potente estimulación de la ventilación con aumento de 'respuesta ventilatoría' y taquipnea resultante • Broncoconstricción	Quimiorreceptores centrales y periféricos
Potenciales efectos deletéreos de la $PaCO_2$ elevada sobre el sistema cardiovascular	
Fisiopatología y Clínica	**Bases celulares y moleculares**
• Vasoconstricción sistémica, Mala perfusión	Liberación de catecolaminas
• resistencia vascular sistémica y post-carga	
• Alteración de la variabilidad de frecuencia cardiaca	Modificación de respuesta de receptores
• Hipertensión arterial sistémica	
• ↓ del gasto cardíaco	
• Hipertrofia ventricular derecha	
• Corpulmonale	
• Disritmias	
Potenciales efectos deletéreos de la $PaCO_2$ elevada sobre el sistema nervioso	
Fisiopatología y Clínica	**Bases celulares y moleculares**
• ↓ del metabolismo energético cerebral	Fosforilación de la Proteína CREB
• Vasodilatación en la Resistencia Vascular del Sistema Nervioso Central	Expresión de proteínas (genes) apoptóticas
• Predisposición a hemorragia intra-craneana	
• Factor predictivo independiente de hemorragia	Aumento de calcio intranuclear
severa/muerte, DBP/muerte y desarrollo/muerte • ↑ del volumen sanguíneo cerebral • ↑de la presión intra-craneana • Descenso de umbral convulsivo • Agitación • Irritabilidad • Alteración de la plasticidad sináptica del hipocampo (área CA1): puede contribuir a alteraclones del aprendizaje.	Activación de neuronas GABA-minérgicas en el tronco cerebral Modificaciones de la función neuronal de la corteza Altera sintesis de neuropéptidos y sus receptores orexin y orexin-A
Potenciales efectos deletéreos dede $PaCO_2$ sobre el sistema auditivo y oftalmológico	
Fisiopatología y Clínica	**Bases celulares y moleculares**
• Respuestas anomnales de Potenciales Evocados Auditivos • Vasodilatación retiniana • Variabilidad regional en la sensibilidad de los campos visuales • Retinopatia del prematuro	Trasmisión neuronal Estimulación de la sintasa de oxido nítrico (NOS): retarda la vascularización retiniana; estimula neovascularización, con más alteración proliferativa

revisiones sistemáticas (103) y en Cochrane, (104) que en forma oral produce vasodilatación pulmonar y es útil en DBP con HP. Lo hace al inhibir la PDE5, aumentando el GMPc, dando lugar a vasodilatación y mejorando la oxigenación en la HP, sin producir hipotensión. El sildenafil puede ser administrado por la vía oral y por largo tiempo, con baja toxicidad. La administración oral diaria cada 6-8 h de 0.5-3 mg /kg, hasta un máximo de 8 mg/kg/día, es efectiva y bien tolerada en DBP con HP. Esta droga no debe ser utilizada en la práctica clínica para la prevención de DBP ni para tratamiento de niños con DBP, salvo en niños con DBP-HP severa. Existe cierta evidencia que, si el sildenafil se continúa hasta la resolución de la HP, puede reducirse la mortalidad en esta enfermedad tan debilitante. (101)(102)

Prostaciclina y derivados análogos

El Iloprost y el beraprost de sodio son derivados análogos de la prostaciclina que no se usan de rutina en DBP y se necesitan más estudios para recomendar su empleo.

Bosentan y Treprostinil

Bosentan es antagonista de la endotelina-1 con eficacia en la HP en pediatría, (105)(106) más aún en combinación con sildenafil, pero no se usa de rutina en DBP.

KINESIOLOGÍA RESPIRATORIA

La terapia kinésica respiratoria neonatal se debe considerar con suma cautela, ya que tiene beneficio, pero también riesgos y por ello no debe hacerse de rutina en forma diaria y menos cada 6-8 horas en RNPt.

En los casos en que se realice algún procedimiento es fundamental lo siguiente:

- Establecer límites físicos con ayuda de rollos, cojines, y/o pañales.
- La posición preferente es el decúbito prono, facilita la ventilación.
- Realizar cambios posturales.
- Decúbitos laterales: el aire inspirado y el flujo de sangre mejoran en el pulmón no dependiente, restringiéndose en el dependiente.
- La cabeza no debe quedar siempre al mismo lado.

Cuidado de la Familia

Algunos aspectos relevantes relacionados al cuidado de la familia.

- Los padres no son visitas, estos niños tienen internación prolongada a veces de hasta 3-4 meses o más.
- Es perjudicial no facilitar en forma permanente o el mayor tiempo posible el contacto entre madre e hijo.
- Contacto piel a piel desde el inicio y aún con el RN en asistencia respiratoria (favorece el aumento de producción de leche materna, contribuye a regular la temperatura y el ritmo cardíaco y respiratorio, mejora la posición, facilita el masaje y la estimulación para el neurodesarrollo.)
- La aplicación de técnicas de masaje que además de ayudar a mantener el vínculo con los padres provee otros beneficios.
- Entrevistarse con los padres para orientarlos y educarlos en el manejo postural y la estimulación, motivando su participación como principales estimuladores .
- Preparar a los padres para el alta y la vida en su domicilio.

TERAPIAS EMERGENTES

La alteración de células madres o progenitoras favorece el desarrollo de DBP. (107)(108)(109) Estudios experimentales publicados en los últimos 18 meses muestran, en forma muy promisoria que el uso de estas células exógenas podría proteger o aún regenerar un pulmón dañado. (110)(111)(112)(113)(114)(115)(116)(117) Las células mesenquimatosas derivadas de la médula ósea, del cordón umbilical y del líquido amniótico mejoran la morfometría alveolar y vascular, la función pulmonar y la inflamación. Los efectos terapéuticos parecen estar mediados por modulación paracrina de inflamación, fibrosis y angiogénesis. Los hallazgos sugieren que la terapia celular intravenosa o intra-traqueal puede convertirse en una alternativa atractiva para el futuro. No hay publicaciones de estudios aleatorizados prospectivos para prevención o tratamiento con células mesenquimáticas y por lo tanto no se conoce su eficacia ni seguridad. Hay dos estudios en marcha actualmente y sería maravilloso para muchos RNPt que los estudios en curso den resultado positivo para resolver así definitivamente este serio problema clínico, económico y social.

METABOLÓMICA

La metabolómica es la ciencia que estudia el contenido de metabolitos de una célula, y por lo tanto puede identificar el conjunto de metabolitos presentes en un sistema biológico. De esta manera, la ciencia metabolómica permite identificar cambios en la composición de metabolitos, ocasionados por la interacción entre estados fisiopatológicos específicos, la expresión génica y el ambiente. La comprensión de las vías moleculares que subyacen la patogenia de la DBP, es fundamental para la caracterización

de estos biomarcadores, los cuales podrían favorecer el desarrollo de nuevas estrategias preventivas y terapéuticas. Todo esto es de significativa importancia futura, pero una detallada descripción escapa al objetivo de este artículo. Referimos al lector con mayor interés a revisar el texto, las referencias y los cuatro cuadros que describimos en las páginas 36-48 en el Consenso original. (13)

CONDICIONES PARA EL ALTA Y SEGUIMIENTO DE NIÑOS CON DBP.

Citamos las condiciones más relevantes para decidir el alta de un niño con DBP.

- Respiratorio: Ausencia de episodios de apnea y bradicardia en las últimas 2 semanas. Lo normal es SpO_2 > 95% en aire ambiental. Con FiO_2 suplementaria, mantener SpO_2 92-96% ante signos de compromiso pulmonar crónico. Obviamente hay RN que requieren O_2 domiciliario.
- Nutricional: Grado de desarrollo y situación clínica, junto con curva pondo-estatural adecuada, con ganancia de peso en las últimas semanas en el rango de 15-20 g/kg/día con buena capacidad de coordinar succión con deglución y respiración.
- Lactancia materna: En general es necesario el apoyo nutricional con fortificadores de leche humana o fórmulas de prematuros.
- Regulación térmica: en un ambiente de 20-25°C.
- Cardiovascular: Estabilidad de la función cardiovascular.
- Control audiológico y metabólico realizados.
- Inmunizaciones: adecuadas según edad cronológica.
- Inmunoprofilaxis pasiva: con anticuerpo monoclonal contra virus sincicial respiratorio (palivizumab) según recomendaciones locales.
- Oftalmológica: Evaluaciones oftalmológicas adecuadas para detección de ROP con citación acordada para seguimiento en forma ambulatoria (hasta vascularización completa de retina: 41-44 semanas edad postmenstrual).
- Neurológica: Evaluación neurológica con derivación ambulatoria a neurología infantil y servicios de estimulación temprana si es necesario.
- Monitorización de saturación en silla de automóvil.
- Entrenamiento y capacitación de los padres: como se menciona antes.
- Aspectos sociales: Valoración familiar por parte del servicio social, gestionar la asistencia económica necesaria (asegurar provisión de vitaminas, hierro y otros medicamentos, y de fórmulas lácteas si es necesario) y programar visitas domiciliarias para garantizar los cuidados en el hogar, así como sus desplazamientos a las consultas de seguimiento.
- Asegurar cita con Programa de Seguimiento de Prematuros.

En resumen, la DBP es la secuela crónica más frecuente en los RN en el periodo neonatal y postneonatal, no existe un agente efectivo para la prevención o el tratamiento de DBP. Hasta que esto se aclare lo más importante en la práctica son los conceptos fisiológicos para obtener los mejores resultados en muchos recién nacido con riesgo de DBP o con DBP establecida.

Los 12 puntos a continuación enfatizan conceptos de relevancia clínica que hay que tener siempre presentes en el cuidado cotidiano de RN con DBP establecida.

1. Cuidado interdisciplinario - importancia y necesidad
2. **Respiratorio en DBP establecida y severa**: Vt y Ti "más altos que lo habitual" en (6-12 ml/kg y 0,5-0,8 segundos), con FR "más bajas". (14-20 x min). PEEP nunca bajo. 5-6 y hasta 8 cmH_2O según el grado de colapso de vías aéreas. Intentar mantener SpO_2 91-96%. Cuando la FiO_2 < 40% intentar pasar a CPAP o ventilación no invasiva. No realizar traqueostomía precozmente. Gases siempre húmedos y calientes, aún en cánula nasal.
3. **Hipertensión pulmonar (HP)**: sucede en 25% de los RNPt con DBP. Evaluar con ecocardiograma a todos. Si la hay, no dejar que SpO_2 sea < 91-92%. En casos severos: sildenafil 0.5 mg/kg cada 8h hasta 2 mg/kg cada 6h. Puede intentarse iNO a 20 ppm.
4. **Nutrición**: minimizar estrés para reducir consumo calórico y de O_2. Dar suficientes calorías y energía (130-150 cal/kg y 3,5-4.0 g de proteína por kg/día. En la medida posible, usar leche materna exclusiva, con fortificadores. Alternativa: Fórmulas hipercalóricas (hasta 1 cal/ml) y no dar más líquidos que 120-140 ml/kg/d (o máximo de 150 ml/kg/d). Prevenir osteopenia.
5. **Vía aérea alta:** algunos RN tienen broncomalacia o traqueomalacia o ambos. Otros tienen estenosis subglótica o traqueal. PEEP es útil. Broncodilatadores como el salbutamol empeoran este problema.
6. **Vía aérea baja:** No sirven mucho los broncodilatadores. Cuidado con efectos adversos que son muchos y muy variados. Guardar para exacerbaciones o deterioros agudos. Corticoides (sistémicos o inhalados) tienen muchísimos efectos adversos en todos los órganos incluyendo el cerebro. No usar innecesariamente. Y los inhalados casi no sirven.
7. **Diuréticos**: Si lo usan, ¿qué efecto beneficioso demuestran? Pero la alcalosis metabólica y la hiponatremia

son muy deletéreos, además de la calciuria, nefrocalcinosis, osteopenia, hipoacusia y otros.

8. **Hipertensión arterial**: ¿Cuánto será por uso indebido de corticoides? Descartar hipertrofia ventricular izquierda y también hipertrofia septal asimétrica. Medicamentos antihipertensivos pueden ser requeridos, en general mejora con el tiempo.
9. **Medicamentos Anti-reflujo:** Una lista larga…. Eritromicina, Metoclopramida, Omeprazol, Ranitidina, etc. ¡Su uso es claramente innecesario y potencialmente dañino!
10. **Cuidado transicional y post-alta**: Interdisciplina. No usar medicamentos no efectivos. Variable complejidad según la severidad. Definir claramente si el RN necesitará oxígeno domiciliario. Para ello, intentar destetar progresivamente la FiO_2 con $SpO_2 > 95\%$ disminuyendo la FiO_2, y no el flujo durante la estancia hospitalaria.
11. **O_2 domiciliario.** Se puede usar 100% con cánula nasal. Es recomendable usar bajos flujos y con 20 ml/kg o menos se puede iniciar intentos con aire ambiente. Mantener SpO_2 >91-92% cuando reciben FiO_2 y SpO_2 no hipoxémica en aire ambiente. Cuidar el crecimiento y la posibilidad de hipertensión pulmonar. A veces se requiere FiO_2 solamente de noche o con la alimentación. Documentar con monitor de SpO_2.
12. **Palivizumab profilaxis** sin omitir ninguna dosis. La bronquiolitis (VSR, metaneumovirus, rinovirus) puede ser muy severa.
13. **Neurodesarrollo**: clínicas especializadas de seguimiento. Estimulación temprana. Los RN con DBP en respirador a las 36 semanas de edad corregida tienen 6 veces más probabilidad de presentar cuadriparesias que los RN que reciben solamente O_2 a las 36 semanas. La mayoría de los RN sin dependencia al O_2 en domicilio, están con neurodesarrollo normal a los 2 años de vida.

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Recomendaciones del VIII Consenso Clínico de SIBEN para la Displasia Broncopulmonar

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Current Strategies to Prevent Maternal-To-Child Transmission of Human Immunodeficiency Virus

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KEYWORDS

• HIV • Maternal-to-child transmission • Prevention • Perinatal transmission

KEY POINTS

- Early diagnosis and treatment of human immunodeficiency virus (HIV) is the most effective prevention strategy to reduce maternal-to-child transmission.
- Combined antiretroviral therapy should ideally be initiated before pregnancy or as early as tolerated in pregnancy to achieve maximal suppression of viral load.
- Prevention of maternal-to-child transmission of HIV requires a multidisciplinary approach.

EPIDEMIC

The Centers for Disease Control and Prevention (CDC) estimates that more than 1.2 million people are living with human immunodeficiency virus (HIV) in the United States today. Of these 1.2 million, an estimated 19% to 24% are women.[1] In 2010, it was estimated that 9500 women were newly infected with HIV; most (84%) were infected through heterosexual sex. Approximately 64% of women living with HIV are African American, making them disproportionately affected.[1] Advances in antepartum care and combined antiretroviral treatment (cART) have led to a dramatic reduction in the maternal-to-child transmission of HIV. By the end of 2014, there were 1995 children in the United States living with perinatal HIV.[1] In the United States between 2009 and 2014, almost 22,000 cases of potential perinatally acquired HIV infections were prevented.[1] In contrast, globally in 2009, 370,000 children became newly infected with HIV.[2] *The cumulative in utero, intrapartum, and postpartum HIV transmission rate without intervention is estimated to be 35% to 40%.*[3] Advances in

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antiretroviral therapy have led to a great reduction in mortality attributed to HIV and a dramatic reduction in maternal-to-child transmission of HIV in resource-rich settings. *Utilization of* the *current recommendations for the management of HIV-positive pregnant women has led to an average maternal-to-child transmission rate of less than 1% in many US states.*[3] However, we still have work to do in improving maternal-to-child transmission rates. The CDC developed a new framework with the goal of eliminating maternal-to-child transmission in the United States. The key components of the framework include comprehensive care; case review to identify and address missed opportunities for prevention; research and long-term monitoring, which allows for the development of safe and efficacious interventions; and data reporting for HIV surveillance and evaluation of elimination of maternal-to-child transmission treatment programs.[4]

Prevention of maternal-to-child transmission is a multifaceted, multidisciplinary approach that encompasses the entirety of a woman's reproductive life. Given the many needs in resource-limited settings, the scope of this review focuses on the prevention of maternal-to-child transmission in resource-rich settings. A study in 2015 analyzed missed opportunities for prevention of maternal-to-child transmission between the years of 2005 and 2012 in the state of Georgia. This study identified 27 perinatally infected infants. They found that in 24 of the 27 cases, limitations in health care delivery and uptake were significant risk factors for the HIV-infected women. They also noted that 74% of women knew their HIV status before pregnancy, but only 50% received prenatal care. This study identified several risk factors to a lack of adherence to maternal-to-child transmission of HIV, including illicit drug use, lack of prenatal care, and lack of antepartum cART.[5]

PRECONCEPTION COUNSELING

Preconception counseling is an important aspect of women's health and is especially important for HIV-infected women. *One of the most important components of preconception counseling is* the *prevention of unintended pregnancies.* For HIV-infected women, this discussion should include initiation or continuation of cART; compliance with medication and prenatal appointments antepartum and post partum; addressing potential barriers to care and treatment throughout pregnancy and post partum; and, ultimately, prevention of maternal-to-child transmission.[3] Women infected with HIV should be optimized on their cART to ensure maximal viral suppression. In addition, any other medical comorbidities should be optimized. A thorough review of her prior obstetric history should be performed, and any previous poor obstetric outcomes should be addressed and appropriate referrals to maternal-fetal medicine colleagues should be placed. They should also receive any indicated vaccinations and appropriate prophylaxis or treatment of opportunistic infections. Women should undergo screening and treatment of any concomitant sexually transmitted infections. Importantly, screening for psychosocial factors that may impact pregnancy outcomes (eg, psychological and substance use disorders) should be completed and treatment initiated as appropriate. Lastly, couples should be counseled on the how to optimize conception while minimizing the risk of transmission of HIV to an uninfected male partner or transmission of a more resistant strain to an HIV-infected partner.[3,6,7]

DIAGNOSIS

The first step in preventing maternal-to-child transmission is establishing the diagnosis of HIV. *The earlier the diagnosis is known in a pregnancy, the sooner*

treatment can be started to prevent transmission to the fetus. It was found that almost a quarter of the perinatal HIV transmissions reported by the CDC between 2008 and 2012 were due to maternal HIV infections that remained undiagnosed until the intrapartum or postpartum periods.[8] In order to achieve the goal of elimination of maternal-to-child transmission, the World Health Organization (WHO), the American Academy of Pediatrics, and the American College of Obstetricians and Gynecologists (ACOG) recommend using a universal opt-out approach for HIV testing as early as possible during pregnancy. Rapid HIV testing should be performed on labor and delivery for those whose status is undocumented and if positive antiretroviral prophylaxis should be started immediately without waiting for confirmatory testing results.[8,9] To date, all but 2 states, Nebraska and New York, have laws that are consistent with the CDC's opt-out HIV testing recommendations.[10] Studies have shown an opt-out approach can increase testing rates among pregnant women and, therefore, increase the number of pregnant women who know their status and can ultimately increase the number of HIV-infected women who are offered treatment and, thus, reduce maternal-to-child transmission.[10,11]

The CDC and ACOG also recommend repeat testing in the third trimester in certain geographic areas or for women who are known to be at high risk of becoming infected while pregnant. This population includes injection-drug users, women who have sex partners that are injection-drug users, women who exchange sex for money or drugs, women who are sex partners of HIV-infected persons, and women who have had a new or more than one sex partner throughout the pregnancy.[8–11] The geographic areas include settings where there is an elevated HIV incidence, more than 17 cases per 1000,000 person-years, or where prenatal screening identified at least 1 pregnant woman infected with HIV per 1000 women screened.[8–11] Universal opt-out HIV retesting for all pregnant women is recommended based on a 2005 CDC-sponsored study that reported *all women who seroconverted* during pregnancy denied new sexual partners, alcohol, or illicit drug use.[8]

Rapid HIV testing has a sensitivity and specificity close to 100%; however, the positive predictive value depends on the prevalence of the disease. After a positive screening test, either a positive HIV 1/2 antigen/antibody fourth-generation test or detectable HIV viral load establishes an HIV diagnosis. The window period for diagnosis for fourth-generation tests and the antigen tests is 11 days to 1 month, and they take 2 days to 2 weeks to get results. In comparison, the rapid test has a window period of 3 months, and the results are available within 20 minutes.[3] Once an established diagnosis of HIV is made during pregnancy, the focus is prevention of maternal-to-child transmission and treatment of the woman in a multidisciplinary fashion. Please see **Box 1** for key features of care of HIV-infected pregnant patients.

Box 1
Key principles when considering screening for human immunodeficiency virus during pregnancy

1. Universal screening for HIV is recommended at the first prenatal visit for all women.
2. Opt-out HIV screening is recommended.
3. Repeat HIV screening in the third trimester is recommended for all high-risk women.
4. For women who present in active labor with unknown HIV status, a rapid HIV test should be performed on arrival.

ANTEPARTUM TREATMENT

Once a diagnosis of HIV infection is established in a pregnant woman, multidisciplinary care should begin immediately. There should be close collaboration between HIV care providers, obstetric providers, pediatric providers, and social service providers. *The goal of treatment of HIV in pregnancy is to maximally suppress viral replication and viral load as well as providing pre-exposure prophylaxis to the fetus*[6,7,12] (**Box 2**).

Aneuploidy screening should be routinely offered to all HIV-infected pregnant women. Invasive testing, such as an amniocentesis, chorionic villus sampling, and cordocentesis, may place the fetus at increased risk of transmission of HIV.[6,7,13] However, to date no transmission of HIV has been reported after amniocentesis in women taking cART with suppressed viral loads. If an amniocentesis is determined to be necessary, then it should be ideally performed after initiation of cART and when the viral load is undetectable.[7]

In addition, case managers and social workers should be readily available for HIV-infected women throughout their pregnancy in order to enhance compliance

Box 2
Initial prenatal evaluation

Complete medical, obstetric, and gynecologic history

Evaluation for symptoms of AIDS

- Fever, night sweats, weight loss, a new and persistent cough, diarrhea, refractory vaginal candidiasis, oral candidiasis, and new outbreaks of herpes

Complete physical examination, including evaluation for disease progression

- In women with CD4 count <200 cells/mm^3, should include evaluation of thrush, herpes simplex virus, lymphadenopathy, or rash

Detailed HIV history, including suspected transmission route, previous antiretroviral use, previous AIDS-defining illnesses, current prophylaxis regimen

Assessment of need for prophylaxis against opportunistic infections

Assess psychosocial supportive care needs, mental health services, substance abuse treatment, and smoking cessation

Baseline laboratory evaluation

CD4 cell count

- Initial visit & every 3 mo throughout pregnancy

Resistance testing before starting cART

- HLA-B5701 if abacavir use is anticipated

Complete blood count with differential, complete metabolic panel

- Repeat each trimester

Tuberculosis screening

Early diabetes screening of patients with a history of gestational diabetes, family history of diabetes, or those with prolonged use of protease inhibitor exposure

Plasma HIV RNA levels (viral load)

- Initial visit, 2–4 wk after initiating or changing cART regimen, monthly, and then again at 34–36 wk gestation
- Recommendations regardless of starting viral load

Hepatitis B surface antigen and antibody

Hepatitis C antibody

Concomitant sexually transmitted disease testing, including syphilis, gonorrhea, chlamydia, trichomoniasis

Evaluation of immunization status of rubella, varicella, hepatitis B, and pneumococci

Papanicolaou test and high-risk HPV testing

with medical visits and cART adherence. Women should be educated about HIV and prevention of maternal-to-child transmission and the importance of cART.[12] This discussion should include the risk of transmission and factors that modify that risk, the risks and benefits of cART, and safe sex practices with condoms.[7]

Given the gravity of the diagnosis of HIV, there is a significant risk of development of depression in these women. When left untreated, depression can lead to poor cART adherence and ultimately a shortened life span and increased risk of maternal-to-child transmission. Many HIV-infected women are also victims of trauma and intimate-partner violence, which contributes to the increased risk of posttraumatic stress disorder, depression, anxiety, and substance use disorder.[14]

ANTIRETROVIRAL DRUGS DURING PREGNANCY

Current recommendations are that antiretroviral treatment should be initiated for all HIV-infected pregnant women at their initial prenatal visit or as early as possible in pregnancy. The earlier a women can be started on a highly effective cART regimen that will decrease her HIV viral load to undetectable levels, the sooner the risk of perinatal transmission can be reduced and the likelihood of cesarean delivery can be reduced.[6,13] Antepartum and intrapartum antiretroviral treatment and prophylaxis, as well as infant prophylaxis, are recommended in combination because antiretroviral medications reduce perinatal transmission by several mechanisms, including lowering the viral load and providing pre-exposure and postexposure prophylaxis to the infant.[13]

The importance of adherence to the cART regimen needs to be discussed at length and emphasized when counseling HIV-infected pregnant women.[13] A recent series of systematic reviews identified individual and contextual factors and health system barriers affecting cART initiation, adherence, and retention in HIV-infected pregnant women. They identified lower age, lower education level, HIV denial, concern cART will harm the child, misplacing/forgetting medication, use of drugs or alcohol, transportation problems, and negative attitudes of health workers as barriers to cART adherence. They also identified that lack of knowledge regarding prevention of maternal-to-child transmission was a barrier to initiation of cART.[15]

When selecting medications, the known benefits and known and unknown risks of antiretroviral medications in pregnancy should be discussed and considered carefully. The regimens in pregnancy typically contain at least 3 medications and are individualized to patients based on comorbidities, convenience, side effects, drug interactions, resistance testing, and potential teratogenic effects.[6,13] The goal of cART is to produce at least a 1-log drop in viral load over 4 to 8 weeks. If such a response is not seen, then initial or repeat resistance testing should be performed as well as a thorough investigation of medication adherence and a search for potential drug interactions.[13,16] cART regimens in pregnancy typically consist of 2 nucleoside reverse transcriptase inhibitors and either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor.[6] The US Department of Health and Human Services (HHS) has a multidisciplinary panel of experts in HIV care who are responsible for updating the HIV guidelines. The HHS Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission publishes: *Recommendations for Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in The United States*.[13]

The Panel categorizes antiretroviral medications for use in pregnancy as follows: preferred, alternative, use in special circumstances, not recommended, or insufficient data to recommend. Please see **Table 1** for the antiretroviral regimens recommended in pregnancy.

Table 1
Antiretroviral regimen recommendations in pregnancy

Drug	Comments	Dosing
Preferred 2-NRTI backbones		
ABC/3TC Epzicom	• Available as FDC • ABC not used in women who test positive for HLA-B*5701 because of risk of hypersensitivity reaction • High placental transfer	ABC (Ziagen): 300 mg twice daily or 600 mg once daily ABC/3TC: 1 tablet twice daily (600 mg ABC, 300 mg 3TC)
TDF/FTC Truvada Or TDF/3TC Viread & Epivir	• TDF/FTC available as FDC • TDF/FTC or TDF with separate 3TC can be administered once daily • TDF has potential renal toxicity, take caution in patients with renal insufficiency	TDF/FTC: 1 tablet once daily TDF & 3TC: 2 tablets once daily (300 mg each)
Preferred PI regimens		
ATV/RTV Reyataz + Norvir + 2-NRTI preferred backbone	• Once-daily administration • Extensively used in pregnancy • Can lead to maternal hyperbilirubinemia, no reports of clinically significant neonatal hyperbilirubinemia • RTV boosting in pregnancy recommended	ATV: 300 mg daily + RTV: 100 mg daily
Preferred integrase inhibitor regimen		
RAL Isentress + 2-NRTI preferred backbone	• Rapid viral load reduction • Potential role in treatment of women who present late to care for initial therapy • Twice-daily dosing • If concerns of compliance, a PI regimen preferred to minimize risk of resistance	RAL: 400 mg twice daily
Alternative initial regimens in pregnancy: regimens with efficacy in adults but with limited use in pregnancy, incomplete teratogenicity data, or associated with dosing, formulation, toxicity, or interaction issues		
Alternative 2-NRTI backbones		
ZDV/3TC Combivir	• Available as FDC • Most experience with use in pregnancy • Twice-daily dosing • Increased potential for hematologic toxicity	ZDV/3TC: 1 tablet twice daily
PI regimens		
LPV/RTV Kaletra	• Abundant use in pregnancy • More nausea than with preferred regimens • Twice-daily dosing • Recommend dose increase in third trimester	LPV/RTV: 400 mg LPV and 100 mg RTV twice daily Recommend increasing to 600 mg LPV plus 150 mg RTV twice daily during third trimester

(*continued on next page*)

Table 1
(*continued*)

Drug	Comments	Dosing
NNRTI regimen		
EFV Sustiva OR (EFV/FTC/TDF) Atripla + preferred 2-NRTI backbone	• Concern regarding possible increase in birth defects in primate studies • Recommended in women who require drugs with significant interactions with PIs • Screen carefully for antenatal and postpartum depression • To be continued in women who begin pregnancy with good viral suppression on EFV	EFV: 600-mg tablet once daily at bedtime EFV/FTC/TDF: 1 tablet once daily at bedtime

The preferred regimens and drug combinations are designated as such for initiation of ART in ART-naïve pregnant women based on clinical data that show optimal safety and efficacy profiles in adults and are not associated with teratogenicity.

Abbreviations: ABC, abacavir; ART, antiretroviral treatment; EFV, efavirenz; FDC, fixed-drug combination; FTC, emtricitabine; LPV, lopinavir; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RAL, Raltegravir; RTV, ritonavir; TDF, tenofovir disoproxil fumarate; 3TC, lamivudine; ZDV, zidovudine.

Data from Refs.[6,13,17]

An example of a preferred cART regimen to initiate in HIV-infected pregnant women is emtricitabine/tenofovir, atazanavir, and ritonavir.[13] The main difference in cART regimens in pregnant women compared with nonpregnant women is the lack of recommendation for integrase inhibitor–based regimens for pregnant women. There is increasing literature about the safety of raltegravir in pregnancy, especially in women with a high viral load because of its ability to rapidly suppress viremia.[6] Because of the increasing body of literature and safety profile, raltegravir is the preferred integrase inhibitor for use in antiretroviral-naïve pregnant women. In addition, recent case series have reported rapid declines in viral load with the use of raltegravir late in pregnancy to achieve viral suppression and reduce the risk of perinatal transmission.[13] More data on the use of newer integrase inhibitors (many of which are administered once daily and/or part of a single combination pill) in pregnancy are needed. Lamivudine/zidovudine was the mainstay for nucleoside reverse transcriptase inhibitor regimens in pregnancy; although it is still highly efficacious, especially in antiretroviral-naïve women, it requires twice-daily dosing and has higher rates of side effects (nausea, headache, and neutropenia) and, therefore, is now considered an alternative regimen.[13,17]

Because of an ongoing debate regarding efavirenz, it is still categorized as an alternative NNRTI medication. There was significant concern regarding the potential teratogenicity of efavirenz. Previous studies linked efavirenz use with increased risks of neural tube defects. A recent large meta-analysis did not find an increased risk of neural tube defects in women who used efavirenz in the first trimester. Therefore, the current perinatal guidelines, as written by the panel, do not include a restriction of use of this medication before 8 weeks' gestation, despite the insert in the packaging saying otherwise.[18] Both the British HIV Association and the WHO support the use of efavirenz throughout pregnancy.[13,17]

The newest recommendations are that cART should be initiated as soon as possible in pregnant women even if the antiretroviral resistance testing results are not yet

available.[13] Clinicians may consider starting a protease inhibitor–based cART regimen when resistance-testing results are not available because resistance to protease inhibitors is less common than resistance to NNRTIs in antiretroviral-naïve women.[6,13]

In general, HIV-infected women who enter pregnancy on a stable cART regimen should continue the cART regimen without adjustment. Discontinuation or disruption of cART can lead to viremia and increase the risk of HIV transmission.[6] With the advent of new antiretroviral medications, women may enter pregnancy on cART regimens that include antiretroviral medication with a paucity of data with regard to use in pregnancy. Viral suppression in pregnancy is of the utmost importance for both maternal health and prevention of perinatal transmission; therefore, continuation of these regimens is generally recommended. Consultation with an HIV perinatal specialist is recommended when considering altering cART regimens in pregnancy.[13]

Lastly, clinicians should inform HIV-infected pregnant women that there may be a small increased risk of preterm birth in those women who receive cART.[13] However, HIV treatment should not be withheld because of this possible complication. In addition, recent studies have found that certain cART regimens may be associated with low-birth-weight and small-for-gestational-age infants.[13] The panel compiled 27 studies from around the world that investigated the associated preterm delivery risk with cART regimens. They found that 13 of the 27 studies found an association between preterm delivery and protease inhibitor–based cART regimens. Specifically, the use of ritonavir to boost a protease inhibitor–based cART regimen was associated with preterm delivery.[13] Although clinicians and women should be aware of these possible increased risks, the benefits of cART regimens in pregnancy far outweigh these risks and, therefore, should be initiated and continued as recommended earlier.

INTRAPARTUM TREATMENT

Antiretroviral Management

It is well established that intravenous zidovudine given intrapartum significantly prevents the transmission of HIV to the fetus during delivery in a women with HIV viremia.[13] However, newer guidelines suggest that intravenous zidovudine may not be required for all HIV-infected women. The most recent guidelines published by the Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission reports that intravenous zidovudine is not required for HIV-infected women with a viral load less than 1000 copies per milliliter in late pregnancy or near delivery (typically between 34–36 weeks) and for whom there are no concerns about adherence to their cART, as further reduction in perinatal transmission is unlikely.[13] However, intravenous zidovudine should be administered to HIV-infected women with a viral load greater than 1000 copies per milliliter regardless of adherence to cART.[13] Irrespective of viral load, a clinician may elect to use intravenous zidovudine intrapartum based on their clinical judgment. In addition, the most recent viral load should drive the decision for mode of delivery. Despite whether an HIV-infected woman has been shown to have resistance to zidovudine, it should still be used intrapartum, as it has unique properties that prevent perinatal transmission.[7,13]

Route of Delivery

Women with a viral load greater than 1000 copies per milliliter should be counseled on the benefit of a scheduled cesarean delivery to prevent transmission. In this case, intravenous zidovudine should be started 3 hours before cesarean delivery. The ACOG recommends that scheduled cesarean delivery for viral load greater than 1000 should be performed at 38 weeks' gestation to reduce the risk of onset of labor

before delivery.[19] In women with a viral load less than 1000 copies per milliliter, the trial of labor and vaginal delivery do not significantly increase the risk of transmission. All antepartum cART should be continued on schedule throughout labor and delivery.[7,13]

In contrast, induction and scheduled cesarean delivery for obstetric reasons should be performed at standard times for these obstetric indications in women with a viral load less than 1000 copies per milliliter. In women with a known viral load greater than 1000 copies per milliliter or unknown viral load who present in active labor or with ruptured membranes, there is not enough evidence to determine whether cesarean delivery reduces perinatal HIV transmission; thus, the management of these patients should be individualized. In a woman who presents in active labor with unknown HIV status and then is found to be positive on rapid HIV testing, intravenous zidovudine should be promptly started and cesarean delivery should be considered.[6,7,13] Please see **Table 2** for a summary of these recommendations.

During labor or induction of labor, it is recommended to avoid any interventions that may increase maternal-to-fetal blood exchange unless there is a clear obstetric indication, including the use of a fetal scalp electrode, assisted delivery with forceps or vacuum extractor, and/or episiotomy.[6] New data suggest that the duration of rupture of membranes in women with a viral load less than 1000 copies per milliliter may not be associated with an increased risk of perinatal transmission. Therefore, in women on cART with viral suppression at term with ruptured membranes, obstetric care should be normalized. This recommendation also applies to artificial rupture of membranes, as new studies have determined that in the setting of cART and viral suppression, there is no increased risk of perinatal transmission. Therefore, artificial rupture of membranes can be safely performed for obstetric indications in those women with a viral load less than 1000 copies per milliliter who have been adherent with cART.[13] *When the infant is delivered, the infant should immediately be bulb suctioned and all maternal secretions should we washed off as soon as possible*.[7]

Table 2
Summary of intrapartum antiretroviral recommendations

Clinical Situation	Mode of Delivery	IV AZT	Timing of Delivery	cART
VL <1000, no obstetric indication for cesarean delivery, no antepartum cART adherence concerns	Vaginal delivery	Not required	Spontaneous or earlier for maternal/fetal indications	Continue oral cART during labor and delivery
VL <1000, no antepartum cART adherence concerns, obstetric indication for cesarean delivery	Cesarean delivery	Not required	≥39 wk or earlier for maternal/fetal indications	Continue oral cART during delivery
VL >1000	Cesarean delivery	Required	38 wk or earlier for maternal/fetal indications	Continue cART during delivery
VL unknown	Cesarean delivery	Required	38 wk or earlier for maternal/fetal indications	Continue cART during delivery if previously started

Abbreviations: ARV, antiretroviral; AZT, zidovudine; IV, intravenous; VL, viral load.

In challenging clinical scenarios regarding the perinatal care of HIV-infected women, such as preterm premature rupture of membranes, the National Perinatal HIV Hotline is available to provide evidence-based expert advice.[7,13] The National Perinatal HIV Hotline (888-448-8765) is a federally funded service and provides free clinical consultations to providers caring for HIV-infected pregnant women and their infants, especially for difficult cases.[13]

NEONATAL AND POSTPARTUM TREATMENT

The postpartum period is crucial for maternal and infant health, especially the ongoing prevention of HIV transmission to the infant. It is recommended that all HIV-exposed infants should receive postpartum antiretroviral prophylaxis to further reduce the risk of HIV transmission. *Infants should begin antiretroviral prophylaxis as soon as possible following delivery, ideally within 6 to 12 hours of birth*.[6,7,13] The standard of care for term infants born to mothers who received cART during pregnancy and maintained a viral suppression includes 4 weeks of oral zidovudine.[13] In all other situations, a 6-week course of oral zidovudine is recommended.[6,13] Based on several maternal and infant factors, some infants are at higher risk of HIV transmission after birth; in these cases, combination prophylaxis is recommended for at least 6 weeks. These risk factors include a lack of maternal antepartum or intrapartum antiretroviral treatment, only intrapartum zidovudine treatment received, or in women who received both antepartum and intrapartum antiretroviral treatment but had a detectable viral load, especially in those who underwent a vaginal delivery, women with known antiretroviral-drug resistance, or unknown HIV status at delivery.[6,13] Currently, there is no consensus on the ideal antiretroviral regimen for high-risk infants; however, several clinical trials are currently underway to address this issue. *The current recommendations for high-risk infants are as follows: 6 weeks of oral zidovudine plus 3 doses of nevirapine at prophylactic doses given during the first week of life, first dose at birth to 48 hours, the second dose at 48 hours after the first dose, and the third dose 96 hours after the second dose.* Additionally, some providers recommend a 3-drug infant antiretroviral regimen using a treatment dose of zidovudine, lamivudine, and nevirapine. This regimen is currently under investigation.[13] In infants born to mothers who were adherent to their cART regimen but did not achieve viral suppression, a discussion with the family and a pediatric HIV specialist to decide whether combination antiretroviral prophylaxis is appropriate. Additionally, in infants born to women with an unknown HIV status, if rapid testing is positive, antiretroviral prophylaxis should be started until the results of confirmatory testing are obtained.[13] *Again, the National Perinatal HIV Hotline* (888-448-8765) *can provide free clinical consultations to providers caring for at-risk HIV-exposed infants, especially for difficult cases.* They can also provide referrals to local or regional pediatric HIV specialists.[13] See **Table 3** for a summary of these recommendations. Please see the recommendations produced by the Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission for additional dosing regimens based on weight and gestational age.[13]

Breastfeeding is contraindicated in women with HIV in the United States because of the high potential for HIV transmission through breast milk.[3,7,13] However, in resource-limited settings where a safe alternative to breastfeeding is not available to sufficiently replace breastfeeding, exclusive breastfeeding is preferable.[7] In resource-rich settings, such as the United States, exclusive formula feeding is the recommendation for all HIV-infected women and infants. Choosing not to breastfeed can be met with social, familial, and cultural barriers for many women; therefore, clinicians should be cognizant of this and be sure to provide adequate support to these women. It is

Table 3
Recommendations for antiretroviral prophylaxis for high-risk infants

Clinical Scenario	Recommendations
Infant born to a woman who did not receive antepartum cART or only received intrapartum AZT prophylaxis	6-wk oral AZT + 3 doses of nevirapine (at birth, 48 h after first dose, and 96 h after second dose), consultation with pediatric HIV specialist
Infant born to a woman who received antepartum cART but did not achieve optimal viral suppression	6-wk oral AZT + consider combination prophylaxis after consultation with parents and pediatric HIV specialist
Infant born to a woman with ARV-resistant virus	Unknown optimal prophylactic regimen, consult pediatric HIV specialist, 6-wk oral AZT + consider combination prophylaxis based on maternal ARV-resistance pattern

Abbreviations: ARV, antiretroviral; AZT, zidovudine.

also important to address recommendations against breastfeeding antenatally so that any possible barriers to formula feeding can be addressed at that time.[13]

CONTRACEPTION

Following delivery, women infected with HIV should be connected with an HIV specialist for ongoing care. In addition, these women need to receive counseling regarding contraception and how to effectively prevent unintended pregnancies and ongoing transmission to sexual partners. The CDC and ACOG recommend that all women with HIV be offered effective and appropriate contraception to prevent undesired pregnancies. Long-acting reversible contraceptives (LARCs), including implants and intrauterine devices, serve as excellent contraceptive options for HIV-infected women. LARC devices should be offered in the immediate postpartum period or in conjunction with a bridge to their postpartum visit. LARC devices can aid in pregnancy spacing and optimization of maternal health and cART adherence.[13] No contraceptive methods are contraindicated in HIV-positive women; however, special considerations about drug interactions with antiretroviral regimens should be discussed. For specific safety profiles and additional information, please reference the CDC's medical eligibility criteria.[20] Additionally, patients should be counseled regarding the importance of dual protection, concomitant use of condoms, and additional contraception methods.[21]

SUMMARY

Eliminating maternal-to-child transmission of HIV is a top priority for the WHO, CDC, ACOG and many other humanitarian and medical associations. Current recommendations for treatment of pregnant women who are HIV infected can reduce the rate of maternal-to-child transmission to less than 1%. Continued research is needed to optimize cART during pregnancy and to reach a goal of zero maternal-to-child HIV transmissions.

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