Targeting Inflammation to Prevent Bronchopulmonary Dysplasia: Can New Insights Be Translated Into Therapies?

AUTHORS: Clyde J. Wright, MD,^{a,b} and Haresh Kirpalani, BM, MSc^{a,b,c}

^a*Division of Neonatology, Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania;*

^b*Department of Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; and* ^c*Department of Clinical Epidemiology, McMaster University, Hamilton, Ontario, Canada*

KEY WORDS

infant, newborn, bronchopulmonary dysplasia, inflammation, NF- κ B, randomized controlled trials, postnatal steroid therapy, mechanical ventilation

ABBREVIATIONS

BPD—bronchopulmonary dysplasia

CI—confidence interval

NF- κ B—nuclear factor κ B

LPS—lipopolysaccharide

IL—interleukin

NO—nitric oxide

SNP—single-nucleotide polymorphism

TNF—tumor necrosis factor

OR—odds ratio

RR—relative risk

RCT—randomized controlled trial

MSC—mesenchymal stem cell

PEEP—positive end-expiratory pressure

Drs Wright and Kirpalani contributed substantially to the conception and design of the article, were involved in the drafting and revising of the article, and have given final approval of the version to be published.

www.pediatrics.org/cgi/doi/10.1542/peds.2010-3875

doi:10.1542/peds.2010-3875

Accepted for publication Mar 9, 2011

Address correspondence to Clyde J. Wright, MD, Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA 19104. E-mail: wrightcl@email.chop.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2011 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: *The authors have indicated they have no financial relationships relevant to this article to disclose.*

Funded by the National Institutes of Health (NIH).

abstract

Bronchopulmonary dysplasia (BPD) frequently complicates preterm birth and leads to significant long-term morbidity. Unfortunately, few therapies are known to effectively prevent or treat BPD. Ongoing research has been focusing on potential therapies to limit inflammation in the preterm lung. In this review we highlight recent bench and clinical research aimed at understanding the role of inflammation in the pathogenesis of BPD. We also critically assess currently used therapies and promising developments in the field. *Pediatrics* 2011;128:111–126

Preterm birth affects 12.5% of pregnancies in the United States, and this rate continues to increase.¹ The common corollary, bronchopulmonary dysplasia (BPD), affects up to 43% of infants born at <1500 g.² BPD has long-lasting effects including poor neurodevelopmental outcomes and long-term pulmonary dysfunction.^{3,4} Unfortunately, few interventions currently used to prevent or treat BPD do so with certain benefit that outweighs harm. Only caffeine has a narrow confidence interval (CI) around estimates of efficacy, whereas those for postnatal steroids and vitamin A are wide.⁵ Because inflammation is central to the pathogenesis of BPD, it is disappointing that this understanding has not translated into useful therapies. Here we review recent concepts on inflammation that might help identify potential new therapeutic targets and highlight specific mediators with human correlates in the pathogenesis of BPD. The transcription factor nuclear factor κ B (NF- κ B) is a central cellular mediator of inflammation and is linked to the pathogenesis of many pulmonary diseases including acute respiratory distress syndrome, asthma, and chronic obstructive pulmonary disease.⁶ Here we discuss its potential pathogenic role in BPD. Finally, we critically evaluate whether common clinical interven-

tions, including mechanical ventilation, administration of glucocorticoids, and emerging therapies, affect the impact of inflammation on the preterm lung. Despite an enormous body of bench work that has identified key molecular components of the inflammatory cascade, we conclude that much of this work has not yet been translated into evidence-based therapies.^{5,7}

ADVANCES IN SCIENCE AND TECHNOLOGY: INFLAMMATION AND BPD

General and Methodologic Considerations

In 1975, Philip⁸ proposed that the etiology of BPD was multifactorial, largely composed of external forces: the duration of exposure to oxygen and pressure. As inflammation entered this paradigm, it included external sources (chorioamnionitis, postnatal infections), iatrogenic sources (ventilation, oxygen), and the internal host response.^{9–15} In 1999, Jobe¹⁶ amended Philip's model to incorporate multiple dimensions of inflammation and created a unified model of "new BPD." However, even as this paradigm was confirmed by experimental data, few innovative therapies have proven efficacious. Is it useful to ask "why not?"

Several methodologic issues complicate moving potential therapies from

bench to bedside for the treatment of BPD. One issue is the obvious difficulty of extrapolating animal data to human preterm infants. This issue is especially evident when the animal studies use 1 insult (eg, hyperoxia, lipopolysaccharide [LPS]) of limited duration, which is an infrequent occurrence in human newborns. However, single-hit models do carry explanatory power and generate hypotheses relevant to human disease (Table 1). However, the molecular redundancy within the complex inflammatory process complicates the translation of experimental interventions into treatments. The multiple stimuli and pathways that lead to NF- κ B activation illustrate this complexity (Fig 1). Finally, human studies remain of small size. For example, of the nearly 30 studies that have attempted to predict BPD from proinflammatory biomarkers in tracheal aspirate, blood, and urine samples,^{17–19} only 2 were of "reasonable size" to address population risks.^{20,21} Ambavalan et al²⁰ examined 1067 preterm infants in a prospective cohort study, of which 606 infants developed BPD. An early (<3 days of life) increase in serum levels of interleukin 8 (IL-8) and IL-10 or early decreases in levels of RANTES (regulated on activation normal t-cell expressed and secreted) protein and (at days of life 14–21) increases in the level of IL-6 pre-

TABLE 1 Inflammatory Mediators With Animal and Human Data That Suggest a Role in the Pathogenesis of BPD

Factor	Animal Data				Human Data, Tracheal Aspirate Levels in Infants Who Develop BPD
	Regulated by NF- κ B	Intervention	Insult	Effect	
CINC-1 (rat)	Yes ²²⁸	Neutralizing antibody	O ₂	Blocks pulmonary PMN influx ²²⁹	↑ ^{20,230,231}
IL-8 (human)					
IL-1 β	Yes ²³²	IL-1R antagonist	O ₂	Inhibits PMN influx and improved alveolar number ²³³	↑ ^{20,233}
IL-6	Yes ²³⁴	Pulmonary overexpression	O ₂	Increases mortality rate ²³⁵	↑ ^{20,235,237}
MMP-9	Yes ²³⁸	MMP-9 ^{-/-} mice	O ₂	Improves lung morphology ²³⁸	↑ ²³⁹
MCP-1	Yes ²⁴⁰	Neutralizing antibody	O ₂	Blocks pulmonary PMN influx ²⁴¹	↑ ²⁴²
CCSP	Unknown	CCSP ^{-/-} mice	O ₂	Increases mortality rate ²⁴³	↓ ²⁴⁴
					Intratracheal administration of recombinant protein ↓ lung PMN ²⁴⁵
MIF	Unknown	MIF ^{-/-} mice	Preterm delivery	Increases mortality rate ²⁴⁶	↓ ²⁴⁶

CINC-1 indicates cytokine-induced neutrophil chemoattractant 1; ↑, increase; ↓, decrease; MMP-9, matrix metalloproteinase 9; MCP-1, monocyte chemoattractant protein 1; CCSP, Clara cell secretory protein; MIF, macrophage migration inhibitory factor; PMN, polymorphonuclear leukocyte.

FIGURE 1

The transcription factor NF- κ B regulates the cellular response to inflammatory and oxidant stress, as well as stretch. Normally, NF- κ B remains sequestered in the cytoplasm bound to members of a family of inhibitory proteins: I κ B. The canonical pathway, active after inflammatory stress (TNF α , LPS, etc) results in activation of IKK (I κ B kinase), which phosphorylates (p) the inhibitory protein I κ B α on 2 N-terminal serine residues. With hyperoxia, a tyrosine kinase phosphorylates (p) the inhibitory protein I κ B α on tyrosine 42. The pathway that leads to NF- κ B activation after stretch has not been described. Phosphorylation of I κ B α results in the ubiquitination (u) and subsequent degradation of I κ B α , which allows for dissociation and nuclear translocation of the active NF- κ B dimer (the p65 and p50 subunits are used as examples here), binding to specific nucleotide sequences on promoter genes and transcriptional activation or repression of gene expression. Known inhibitors of NF- κ B activation, including NO, dexamethasone, azithromycin, and pentoxifylline, are shown where they affect the activation cascade. Multiple genes with a purported role in the pathogenesis of BPD are controlled by NF- κ B. IFN γ indicates interferon γ ; MIP-2, macrophage inflammatory protein 2; RANTES, regulated on activation, normal T-cell expressed and secreted; ELAM-1, endothelial-leukocyte adhesion molecule 1; ICAM-1, intracellular adhesion molecule 1; VCAM, vascular cell adhesion molecule; HGF, hepatocyte growth factor; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; SOD, superoxide dismutase; MMP-9, matrix metalloproteinase 9; iNOS, inducible NO synthase; EGR-1, early growth response 1.

dicted BPD (Table 2). Bose et al²¹ studied 1506 infants but excluded 38% of the original cohort secondary to death or lack of follow-up.²¹ They found that the protective effect of an elevated RANTES level (at <7 days of life) was lost after adjusting for mechanical ventilation. These 2 large studies need replication to better characterize timing and the importance of such markers.

NF- κ B: A Potential Link Between Oxidant and Inflammatory Stress and BPD

The transcription factor NF- κ B regulates the cellular response to inflam-

TABLE 2 Estimates of Risk Conferred by Selected Predisposing Factors for BPD

Factor Associated With Development of BPD	BPD Definition (28 Days of Life vs 36 wk postmenstrual age)	OR or RR (95% CI)
Serum cytokines		
IL-8, early ²⁰	36 wk	14.98 (1.29–173.90) ^a
IL-10, early ²⁰	36 wk	2.03 (1.11–3.72) ^a
RANTES, early ²⁰	36 wk	0.72 (0.56–0.91) ^a
IL-6, late ²⁰	36 wk	2.42 (1.11–5.29) ^a
SNP association		
TNF-308 ⁶⁶	36 wk	1.03 (0.85–1.25) ^b
<i>Urealyticum</i> (tracheal) ⁷⁹	28 d	2.834 (2.288–3.512) ^b
	36 wk	1.620 (1.129–2.325) ^b

RANTES indicates regulated on activation normal T-cell expressed and secreted.

^a OR.

^b RR.

matory and oxidant stress.²² Activation of this ubiquitous transcription factor potentially determines the net cellular

response to inflammatory and oxidant insult in the lung. In the “oxygen radical disease” model, Saugstad^{23–25} pro-

posed an intracellular abundance of reactive oxygen species contributed to the pathogenesis of BPD. Inflammatory and oxidant insults stimulate NF- κ B via discrete signaling pathways, which fine-tune the cellular response.²² In a quiescent cell, NF- κ B remains sequestered in the cytoplasm bound to a member of the I κ B family of inhibitory proteins (α , β , ϵ).²⁶ After phosphorylation and degradation of the inhibitory proteins, NF- κ B translocates to the nucleus. The dimeric NF- κ B complex is composed of different combinations of 5 subunits: p50, p52, p65, c-Rel, and RelB. Once in the nucleus, specific subunit dimer combinations bind to unique DNA oligonucleotide sequences.²⁷ Adding further control, some dimeric complexes contain transactivation domains (p65–p50 heterodimers) that increase gene transcription, whereas others (p50–p50 homodimers) repress gene transcription.²⁸ Many proinflammatory mediators associated with BPD are direct targets of NF- κ B (Fig 1). After activation, NF- κ B increases expression of its inhibitory protein I κ B α , which shuttles NF- κ B dimers out of the nucleus and results in a tightly regulated negative feedback loop.²⁹ Finally, each of the 3 inhibitory proteins (I κ B α , I κ B β , and I κ B ϵ) have unique characteristics, and their presence determines a complex oscillatory pattern of NF- κ B–regulated gene expression.³⁰ Together, this complexity enables NF- κ B to tightly control the transcription of genes.

NF- κ B displays maturational differences in response to oxidant and inflammatory stress. For example, neonatal lymphocytes show increased NF- κ B activation in response to various stimuli when compared with their adult counterparts.^{31,32} Similarly, fetal lung fibroblasts, in contrast to adult cells, demonstrate hyperoxia-induced NF- κ B activation.³³ In vivo, hyperoxia-induced NF- κ B activation is enhanced

in alveolar epithelium and endothelium of neonatal mice but not in adults.³⁴ Both inflammatory and oxidant stress-induced activation of NF- κ B impairs branching morphogenesis in the developing lung,^{35,36} which suggests that NF- κ B not only controls the expression of proinflammatory genes but also controls the expression of growth factors and proapoptotic and antiapoptotic proteins.³⁷ Therefore, there may be unintended consequences of modulating NF- κ B activation in the developing lung.

Some human data link NF- κ B to BPD. It is unclear yet whether the presence of activated NF- κ B indicates its pathologic role or merely represents a response to injury. Nevertheless, if tracheal aspirates from preterm infants contain leukocytes demonstrating NF- κ B activation, there is an increased risk of developing BPD³⁸ and an association with severity of RDS,³⁹ duration of mechanical ventilation, *Ureaplasma urealyticum* colonization, and exposure to chorioamnionitis.⁴⁰ Agents that inhibit NF- κ B activation have shown promise in clinical trials aimed at preventing BPD. These agents include dexamethasone, azithromycin, nitric oxide (NO), and pentoxifylline.^{41–44}

Prenatal and Fetal Modulators of Inflammation

Genetics of the Host Responses to Inflammation

The genetic predisposition for BPD was recently reviewed comprehensively.^{12,45–47} Parker et al⁴⁸ first proposed a genetic susceptibility to BPD when they found that the BPD status of 1 twin predicted BPD in the second twin. Subsequent studies of 450 and 318 preterm twins characterized a risk for BPD from both genetic and environmental factors.^{49,50} Beyond these twin-birth association studies, specific nucleotide polymorphisms (SNPs) have been investigated. However, the excitement

that this has generated is tempered by the methodologic constraints on the validity of some studies, which sometimes include less-than-stringent levels of statistical significance, given the issue of multiple testing.^{51–53} Thirty-three studies have linked BPD to specific SNPs.^{12,53–72} These studies enrolled between 33 and 1209 patients. Many of these studies focused on SNPs in proinflammatory and anti-inflammatory mediators including tumor necrosis factor α (TNF α), IL-4, IL-10, IL-12, monocyte chemoattractant protein 1 (MCP-1), surfactant protein A (SPA), surfactant protein D (SPD), transforming growth factor β (TGF β), mannose-binding lectin, matrix metalloproteinase 16 (MMP-16), and interferon γ (IFN γ). Note that although small studies have suggested a link between TNF-308 SNPs and the risk of developing BPD, a recent meta-analysis that included a total of 804 infants failed to show statistical significance for this relationship (Table 2).⁶⁶ Although small studies are hypothesis-generating, only larger studies can address the methodologic and statistical criteria outlined by Attia et al^{51–53} to provide robust validation of previous findings.

Ureaplasma Infection and Chorioamnionitis: Causal Agents or Prevalent Bystanders?

The old neonatal obsession with the potential role of *U urealyticum* was reviewed recently⁷³ but with new twists. Although *U urealyticum* colonization in preterm sheep does not result in BPD, in nonhuman primate models it does.^{74–78} One meta-analysis of 23 studies that included 751 infants revealed a significant association between *U urealyticum* colonization and BPD at 36 weeks (Table 2).⁷⁹ However, the authors urged caution, because the included studies demonstrated large heterogeneity, and the greatest association was present in the smallest studies. Results of more recent research have been con-

flicting; some studies have shown an association of *U urealyticum* colonization with BPD,^{80,81} whereas others have shown no association.^{82,83} Because *U urealyticum* causes intra-amniotic bacterial infection, its role in BPD may have been exaggerated.

Similar considerations apply to chorioamnionitis. Although clinical chorioamnionitis (defined as maternal fever and uterine-abdominal wall tenderness) occurs in 40% of preterm pregnancies at <28 weeks,⁸⁴ histologic chorioamnionitis occurs in up to 80% of these pregnancies.⁸⁵ In 1996, Watterberg et al⁸⁶ proposed a causal link between histologic chorioamnionitis and BPD. However, receipt of antenatal steroids was an exclusion criterion in that study. Studies performed since the widespread administration of antenatal steroids to pregnant mothers threatening preterm birth have shown either a protective effect or no association between chorioamnionitis and BPD.^{87–100} In a large population-based study of 798 premature infants with a 90% rate of exposure to antenatal steroids, histologic chorioamnionitis protected against BPD.¹⁰¹ Moreover, evidence of a fetal response to inflammation, evidenced by umbilical vasculitis, conferred more protection than chorioamnionitis alone.⁹⁹ Future studies should not only discern the presence of chorioamnionitis but also the fetal response to it.

Because NF- κ B has a central role in regulating the cellular response to inflammation, does it play a role in the fetal response to chorioamnionitis? Animal models of the fetal inflammatory response syndrome (FIRS) suggest that it does. Exposure to intra-amniotic LPS increases NF- κ B activation in bronchoalveolar lavage-derived neutrophils and monocytes of lambs.¹⁰² In a murine model of LPS chorioamnionitis, NF- κ B activation led to an enhanced type II cell maturation.¹⁰³

Furthermore, human preterm amnion cells show a more pronounced NF- κ B response to LPS compared with term controls.¹⁰⁴ Similarly, NF- κ B activation is seen in fetal capillaries of human infants with funisitis and chorioamnionitis.¹⁰⁵ These findings suggest that NF- κ B may mediate inflammation in the fetal lung.

Postnatal Modulators

Bacterial Sepsis in the Neonate

The term systemic inflammatory response syndrome (SIRS) has been adapted to children and newborns.¹⁰⁶ However, it may not be sensitive and, thus, may miss bacterial infections¹⁰⁷; here we discuss data only in which positive growth identifies an organism. Stoll et al¹⁰⁸ demonstrated that rates of BPD increased from 35% to 62% in a cohort of 5447 very low birth weight infants from the Neonatal Research Network after early-onset sepsis (odds ratio [OR]: 2.4 [95% CI: 1.2–4.7]). This relationship was confirmed recently in a population study from Israel of 15 839 infants (OR: 1.74 [95% CI: 1.24–2.43]).¹⁰⁹ It is interesting to note that the protective effect of chorioamnionitis and funisitis on the development of BPD was lost if the infant experienced early-onset sepsis (OR: 1.98 [95% CI: 1.15–3.39]).¹⁰¹ In fact, Lahra et al¹⁰¹ found that the infants at highest risk for BPD were born to mothers without histologic chorioamnionitis but who had experienced sepsis (OR: 2.71 [95% CI: 1.64–4.51]). Late-onset sepsis also increases the risk of BPD (relative risk [RR]: 2.32 [95% CI: 1.95–2.77]).^{110,111} These data suggest that irrespective of the timing, inflammatory exposure from sepsis plays an important role in the development of BPD.

Oxygen Toxicity

Hyperoxia is a powerful proinflammatory stimulus, and its role in the pathogenesis of BPD was reviewed re-

cently.^{112,113} Although a full discussion of hyperoxia-induced pulmonary inflammation is beyond the scope of this review, recent clinical studies are relevant. Even short-term exposure to hyperoxia affects the developing lung. When infants born at 24 to 28 weeks' gestation were randomly assigned to resuscitation in the delivery room with either 90% or 30% oxygen, the incidence of BPD at 36 weeks' gestation was reduced from 31.7% to 15.4% (RR: 0.51 [95% CI: 0.21–1.21]).¹¹⁴ Infants exposed to 90% oxygen had significantly elevated serum TNF α and IL-8 levels. In addition, a recent meta-analysis revealed that limiting oxygen exposure in the NICU by adopting lower pulse-oximetry goals could reduce the incidence of BPD in premature infants from 40.8% to 29.7% (OR: 0.73 [95% CI: 0.63–0.86]).¹¹⁵ This meta-analysis was validated by the Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT) which showed that infants who were randomly assigned to lower pulse-oximetry goals less frequently developed BPD (RR: 0.82 [95% CI: 0.72–0.93]) and retinopathy of prematurity (RR: 0.52 [95% CI: 0.37–0.73]).¹¹⁶ However, concerns about lowering oxygen-saturation ranges have arisen. Specifically, infants enrolled in the SUPPORT-NICHD trial and randomly assigned to lower pulse-oximetry goals had a higher mortality rate by discharge (number needed to harm: 27) (RR: 1.27 [95% CI: 1.01–1.60]).¹¹⁶ However, this was only 1 of 4 separate ways of assessing mortality (at 7 days, 14 days, 36 weeks' postmenstrual age, or by discharge) that was statistically significant. Results from 3 similar large, randomized controlled trials (RCTs) (Canadian Oxygenation Trial [COT] and Benefits of Oxygen Saturation Targeting II [BOOST II], and BOOST-UK) are pending.^{117,118} We advise that neonatologists retain equipoise while these trials answer whether adopting lower pulse-oximetry goals will

improve outcomes at 18 to 22 months, which is the a priori primary outcome of all 4 of these trials.

Molecular Mechanisms Signaling Stretch: Understanding Barotrauma/Volutrauma in Animal Models

Excessive lung stretching results in barotrauma/volutrauma and is a powerful proinflammatory force.¹¹⁹ Multiple signaling pathways, including NF- κ B, translate stretch into a proinflammatory signal,^{120,125} and the degree of stretch determines unique cytokine-expression profiles. Preterm lambs subjected to large-tidal-volume ventilation show upregulation of multiple proinflammatory mediators including IL-1 β , IL-6, IL-8, and Toll-like receptors 2 (TLR-2) and 4 (TLR-4).¹²⁶ In addition, systemic inflammation occurs, indicated by a hepatic acute-phase response.¹²² There are strong developmental differences in the pulmonary cytokine response to excessive stretch.^{127,128} For example, acute exposure to high-tidal-volume ventilation and hyperoxia induces a pulmonary cytokine response (IL-1 β , IL-6, and TNF α) in adult mice, which is attenuated in neonates. Even then, chronic exposure to hyperoxia and high-tidal-volume ventilation will induce pulmonary cytokine release (TNF α and IL-6) in the newborn lung.¹²⁸

Animal data suggest that the inflammatory response to stretch can be prevented. Lung injury induced in mice exposed to hyperoxia and high-tidal-volume ventilation is reversed by NF- κ B inhibition.¹²⁹ Dexamethasone inhibits NF- κ B activation and prevents lung cytokine expression in mice exposed to high-tidal-volume ventilation.¹³⁰ It is significant that IL-6 elevation in ventilated preterm lambs is attenuated by gentle ventilation (lower tidal volumes).¹³¹ The mode of ventilation also plays a role, as indicated by the fact that intubated piglets had markedly differing

cytokine responses compared with animals ventilated with high-frequency nasal ventilation.¹³² These data suggest that modification of current practices could decrease inflammation and injury in the preterm lung.

CRITICAL ASSESSMENT: ANTI-INFLAMMATORY THERAPIES, OLD AND NEW

Therapies that may decrease inflammation in the preterm lung are vitiated by uncertainty (wide CIs around estimates of efficacy or harm) and fraught with potential undesired serious adverse effects (eg, cerebral palsy after postnatal steroids). Because the search for efficacious anti-inflammatory agents continues, we highlight emerging therapies for preventing or treating BPD.

Interruption of Key Components of the Inflammatory Cascade

The commonest paradigm for inflammation is not BPD but, rather, severe sepsis.¹³³ Superficially, it might be logical to ask whether cytokine cascades integral to inflammation could be blocked by antibody therapy. Several large adult trials have investigated this avenue for treating severe sepsis. By 2000, 60 trials that used various monoclonal antibodies directed at TNF α had recruited 4197 patients and showed a cumulative reduction in 28-day mortality rates (OR: 0.87 [95% CI: 0.76–0.98]).¹³³ This modest benefit has led to consideration of polyclonal TNF α antibodies.¹³⁴ Other trials have evaluated the efficacy of IL-1 receptor antagonist and platelet-activating factor receptor antagonist with similar cumulative ORs.¹³⁵ Such modest reductions in mortality have not yet passed into clinical practice because of continued uncertainty.

These limited benefits to date may reflect the redundancy of the inflammatory system, which has led to attempts

to broaden the inflammatory target. Because of its pivotal role in microthrombi formation in sepsis, protein C has been the focus of much attention. However, despite initial excitement (PROWESS [Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis]),¹³⁶ the promise of recombinant activated protein C has not been borne out in adults. The meta-analysis of 4911 participants with severe sepsis revealed no reduction in 28-day mortality rates (RR: 0.92 [95% CI: 0.72–1.18]).¹³⁷ There have been no trials limited to newborns, and this group may be at increased risk for bleeding complications.^{138,139} Similar to neonatologists who lack useful treatments for BPD, adult intensivists are revisiting the use of low-dose corticosteroids for the treatment of sepsis.¹⁴⁰

The Anti-inflammatory Component of Stem Cell Therapy for Preventing BPD

Research using stem cells to prevent or treat developing BPD has burgeoned over the past decade.^{141–144} There are several different stem cells (embryonic stem cells, bone marrow–derived stem cells, and tissue progenitor cells), but most work in neonatal lung injury has focused on bone marrow–derived mesenchymal stem cells (MSCs). Controversy remains as to whether these cells can actually engraft in the lung and differentiate into lung epithelial cells.¹⁴⁵ If they do, these cells may protect and repair the damaged lung by several mechanisms: physical repair by adopting a native cell phenotype or repair of existing cells by exerting immunomodulatory, anti-inflammatory, and antiapoptotic effects. Some of the protective effect of MSC administration are conferred by paracrine mediators, termed the “MSC secretome.”¹⁴³ Results of preclinical studies indicate a role of MSCs in the treatment of acute lung injury in adults¹⁴⁶; however, their role in the treatment of BPD remains to be defined.

TABLE 3 Efficacy of Continuous Positive Airway Pressure for Prevention of BPD or Death

Study or Subgroup	CPAP		Intubation		Weight, %	RR M-H, Fixed (95% CI)	RR M-H, Fixed, 95% CI
	Events	Total	Events	Total			
Morley et al ¹⁵⁴ (2008)	104	307	118	303	22.1	0.87 (0.70–1.07)	
Finer et al ¹⁵⁵ (2010)	323	663	353	653	66.2	0.90 (0.81–1.00)	
Dunn et al ¹⁵⁶ (2010)	68	223	62	216	11.7	1.06 (0.80–1.42)	
Total (95% CI)	—	1193	—	1172	100.0	0.91 (0.83–1.00)	
Total events	495		533				

The primary outcome of the studies depicted was pooled and analyzed by using RevMan 5 software (Cochrane Collection). M-H indicates Mantel-Haenszel odds ratio. Heterogeneity: $\chi^2 = 1.32$, $df = 2$ ($P = .52$); $I^2 = 0\%$. Test for overall effect: $z = 1.97$ ($P = .05$).

In newborn rodents, systemic administration of stem cells obtained from either bone marrow or cord blood attenuates hyperoxia-induced lung inflammation.^{147–150} However, administration of conditioned medium from mesenchymal cells can provide similar levels of protection.¹⁴⁹ Furthermore, newborn rats treated with cord blood MSCs display attenuated pulmonary myeloperoxidase, IL-6, TNF α , and transforming growth factor β expression.¹⁴⁷ More data are needed to determine if anti-inflammatory effects help explain the protection seen with stem cell administration.

Gentle Ventilation: Limiting the Damage We Cause

Inflammation is a major component of ventilator-induced lung injury in adults¹⁵¹ and newborn infants.^{152,153} Three ventilatory strategies impact inflammatory changes in the lung: non-invasive approaches; low-tidal-volume ventilation; and the use of positive end-expiratory pressure (PEEP).

The “gentle-ventilation” approach is increasingly taken with the preterm infant to avoid intubation with noninvasive ventilator support. It is true that individual trials of aggressive early continuous positive airway pressure (CPAP) therapy versus intubated ventilation in the delivery room have not resulted in a reduced rate of BPD.^{154–156} Nonetheless, pooling data on combined mortality and BPD at 36 weeks’

corrected age has suggested a benefit (Table 3). Other strategies of gentle ventilation include intubation to deliver surfactant and early extubation.^{157,158} Nasal intermittent mandatory ventilation (NIMV) holds promise,¹⁵⁹ but larger trial results are pending.¹⁶⁰

An extension of gentle ventilation is a low-tidal-volume strategy. An adult RCT that demonstrated that low-tidal-volume ventilation improved mortality rates in adults with acute respiratory distress syndrome¹⁶¹ sparked much work in newborns. Mechanistically, only sparse RCT data have shown effects of differing modes of ventilation on inflammatory mediators. Lista et al¹⁶² randomly assigned preterm infants to either high-frequency oscillatory ventilation or low-tidal-volume guarantee and found reduced inflammatory markers in tracheal aspirates in those who were assigned to low-tidal-volume guarantee. A Cochrane analysis confirmed a statistically significant reduction of death and/or BPD (number needed to treat: 8) (RR: 0.73 [95% CI: 0.57–0.93]) with targeted low-tidal-volume ventilation.¹⁶³ Together with animal studies, these data suggest that using gentle ventilation may result in decreased pulmonary inflammation in preterm neonates who need respiratory support.

For adult disease, Gattinoni et al¹⁶⁴ urged PEEP to recruit lung volume.

Muscedere et al¹⁶⁵ showed that in an in vitro model, setting PEEP above the lower inflection point preserved the lung’s mechanical properties and attenuated proinflammatory cytokine expression.¹⁶⁶ Using appropriate lung-opening pressure with an adequate lower inflection point in newborn piglets exposed to mechanical ventilation reduces the influx of activated leukocytes into the lungs.¹⁶⁷ However, finding the appropriate opening pressures in adult humans is tricky¹⁶⁸ and is impractical in neonates because it requires paralysis. This may explain why use of an “appropriate PEEP” was never implemented clinically or tested in trials despite observed benefits in infants.¹⁶⁹ Studies that define empirical levels of PEEP that should be set in newborns have been sparse.^{170,171} However, several adult trials of high-PEEP versus low-PEEP strategies have been completed.¹⁷² In general, an empirical oxygen grid against varying PEEP levels was used to set PEEP, rather than pulmonary function tests. An individual patient meta-analysis revealed an overall reduction of the end point of days in hospital and days on respiratory support,¹⁷³ which suggests that simply identifying and using ideal PEEP may reduce inflammatory changes in the preterm lung.

Azithromycin

Macrolides have both antimicrobial and anti-inflammatory properties.¹⁷⁴

TABLE 4 Efficacy of Selected Treatments for the Prevention of BPD

Treatments to Prevent BPD	Control		BPD		RR (95% CI)
	n/N	%	n/N	%	
Caffeine ²⁴⁷	447/954	46.9	350/963	36.3	0.63 (0.52–0.76)
Vitamin A ²⁴⁸	193/347	55.6	163/346	47.1	0.89 (0.80–0.99)
Early corticosteroids, <8 d of age ²¹⁵	535/1638	32.7	423/1648	25.7	0.79 (0.71–0.88)
Late corticosteroids, >7 d of age ²¹⁷	146/230	63.5	108/241	44.8	0.72 (0.61–0.85)
Superoxide dismutase ¹⁹⁶	36/154	23.4	37/148	25.0	1.02 (0.89–1.16) ^a
Azithromycin ¹⁷⁶	10/16	83.3	9/19	64.3	0.71 (0.33–1.53) ^a
Continuous positive airway pressure (unpublished data)	533/1172	45.4	495/1193	41.5	0.91 (0.83–1.00) ^a

^a Calculated by authors using published data.

Azithromycin decreased IL-6 expression and improved lung morphology and mortality rates in neonatal rats exposed to hyperoxia.¹⁷⁵ Furthermore, azithromycin inhibited inflammatory stress-induced NF- κ B activation in tracheal aspirate cells taken from premature infants.⁴³ A pilot study that evaluated the safety and effectiveness of azithromycin in extremely low birth weight infants showed that the treatment group received fewer days of mechanical ventilation, but the study was underpowered to find a difference in the rate of BPD.¹⁷⁶ A phase 2 study is currently underway to determine the effectiveness of this therapy in decreasing the incidence of BPD.¹⁷⁷

NO and Its Role as an Anti-inflammatory Agent

Data from several large RCTs performed to determine if NO can prevent BPD in preterm infants are still being combined into a meta-analysis from individual patient data.¹⁷⁸ However, the National Institutes of Health Consensus for Inhaled Nitric Oxide Therapy for Premature Infants mandates new trials before it can be considered a standard of care.¹⁷⁹ Here we briefly discuss the anti-inflammatory properties of NO.^{180,181} Many of its anti-inflammatory properties are mediated through the inhibition of canonical, inflammatory stress-induced, and atypical, oxidant stress-induced NF- κ B activation.^{44,182–193} This is seen in healthy adult human

subjects who have a higher endogenous NO production and associated NF- κ B inhibition when compared with asthmatic subjects and those with pulmonary hypertension.¹⁹⁴ To date, no data exist to answer whether NO affects NF- κ B signaling in the preterm lung.

Antioxidants

The role of antioxidants in preventing BPD was reviewed recently.¹⁹⁵ The largest RCT evaluated intratracheal copper zinc superoxide dismutase to prevent BPD in infants who weighed <1200 g.¹⁹⁶ This treatment did not alter the incidence of BPD, but treated infants had significantly better pulmonary outcomes at 1 year of age. Some have voiced a concern about the potential untoward effect of scavenging reactive oxygen species given their role in intracellular signaling in the developing lung, brain, and retina.¹⁹⁷ The role of antioxidants for the prevention of BPD remains unclear.

PERCEPTION: THE LACK OF USEFUL THERAPIES FORCES US TO REVISIT AN OLD NEMESIS—CORTICOSTEROIDS

Neonatologists and corticosteroids have had a long and unstable relationship.^{198–201} Systemic glucocorticoids decrease inflammation and increase both surfactant synthesis and lung epithelial differentiation in the developing lung.^{202,203} Irrespective of the precise mechanism, corticosteroids seem

to have some benefit in treating ventilator-dependent infants at high risk for BPD. Efficacy of postnatal dexamethasone for treating ventilator dependency in BPD was first shown in 1983.²⁰⁴ As postnatal corticosteroid use became routine, infants were treated prophylactically with longer courses and higher doses. This treatment practice dominated the 1990s. When Yeh et al²⁰⁵ showed an increased risk of cerebral palsy in infants exposed to corticosteroids early, practices abruptly changed. A meta-analysis of controlled trials revealed a relationship between early dexamethasone exposure and cerebral palsy.²⁰⁶ A major outcry ensued against steroids that limited their use, even for late disease.^{207,208} Unfortunately, no distinction was made between the early, indiscriminate use of steroids and late, targeted use of this therapy. The influential statements of the American Academy of Pediatrics made it virtually impermissible to use steroids,²⁰⁹ although there were occasional voices urging caution over the interpretation of the data.^{210,211} This climate sabotaged an RCT that was designed to address the impact of postnatal corticosteroids on the primary outcome of neurodevelopmental outcome, which was stopped early because of a lack of equipoise.²¹² Consequently, clinicians are left with broad confidence estimates for all efficacy or harm outcomes (Table 4).

The limited number of useful therapies available to prevent BPD, along with a decrease in steroid use, seemed to result in a rising incidence of BPD.^{212–214} The recent meta-regression that demonstrated that corticosteroids will decrease the risk of poor neurodevelopmental outcome if an infant's baseline risk of developing BPD is >55%, along with recent updates of the Cochrane reviews, have affected our thinking.^{215–217}

They argue that the widespread use of steroids to prevent BPD is contraindicated but that therapy for ventilator dependency or early BPD is warranted.²¹⁸ Thus, determining an infant's risk of developing BPD becomes even more clinically important. Simple lung mechanics are unlikely to be helpful.²¹⁹ Although exhaled NO has been proposed as a marker of inflammation, whether it is a better predictor of BPD over simple clinical predictors (eg, birth weight) remains unclear.²²⁰ However, end-tidal carbon monoxide on day-of-life 14 does predict BPD well (OR: 15.17 [95% CI: 2.02–113.8]).²²¹ Confirmation of this and other new predictive tools are needed.

REFERENCES

1. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet*. 2008;371(9606):75–84
2. Stoll BJ, Hansen NI, Bell EF, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. *Pediatrics*. 2010;126(3):443–456
3. Greenough A. Long-term pulmonary outcome in the preterm infant. *Neonatology*. 2008;93(4):324–327
4. Anderson PJ, Doyle LW. Neurodevelopmental outcome of bronchopulmonary dysplasia. *Semin Perinatol*. 2006;30(4):227–232
5. Schmidt B, Roberts R, Millar D, Kirpalani H. Evidence-based neonatal drug therapy for prevention of bronchopulmonary dysplasia in very-low-birth-weight infants. *Neonatology*. 2008;93(4):284–287
6. Wright J, Christman J. The role of nuclear factor κ B in the pathogenesis of pulmonary diseases: implications for therapy. *Am J Respir Med*. 2003;2(3):211–219
7. Fok TF. Adjunctive pharmacotherapy in neonates with respiratory failure. *Semin Fetal Neonatal Med*. 2009;14(1):49–55
8. Philip AG. Oxygen plus pressure plus time: the etiology of bronchopulmonary dysplasia. *Pediatrics*. 1975;55(1):44–50
9. Speer CP. New insights into the pathogenesis of pulmonary inflammation in preterm infants. *Biol Neonate*. 2001;79(3–4):205–209
10. Speer CP. Pulmonary inflammation and bronchopulmonary dysplasia. *J Perinatol*. 2006;26(suppl 1):S57–S62; discussion S63–S64
11. Speer CP. Inflammation and bronchopulmonary dysplasia: a continuing story. *Semin Fetal Neonatal Med*. 2006;11(5):354–362
12. Bhandari V, Gruen JR. The genetics of bronchopulmonary dysplasia. *Semin Perinatol*. 2006;30(4):185–191
13. Ryan RM, Ahmed Q, Lakshminrusimha S. Inflammatory mediators in the immunobiology of bronchopulmonary dysplasia. *Clin Rev Allergy Immunol*. 2008;34(2):174–190
14. Speer CP. Chorioamnionitis, postnatal factors and proinflammatory response in the pathogenetic sequence of bronchopulmonary dysplasia. *Neonatology*. 2009;95(4):353–361
15. Hayes D Jr, Feola DJ, Murphy BS, Shook LA, Ballard HO. Pathogenesis of bronchopulmonary dysplasia. *Respiration*. 2010;79(5):425–436
16. Jobe AJ. The new BPD: an arrest of lung development. *Pediatr Res*. 1999;46(6):641–643
17. Bose CL, Dammann CE, Laughon MM. Bronchopulmonary dysplasia and inflammatory biomarkers in the premature neonate. *Arch Dis Child Fetal Neonatal Ed*. 2008;93(6):F455–F461
18. Bhandari A, Bhandari V. Pitfalls, problems, and progress in bronchopulmonary dysplasia. *Pediatrics*. 2009;123(6):1562–1573
19. Paananen R, Husa AK, Vuolteenaho R, Herva R, Kaukola T, Hallman M. Blood cytokines during the perinatal period in very preterm infants: relationship of inflammatory response and bronchopulmonary dysplasia. *J Pediatr*. 2009;154(1):39–43.e33
20. Ambalavanan N, Carlo WA, D'Angio CT, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Cytokines associated with bronchopulmonary dysplasia or death in extremely low birth weight infants. *Pediatrics*. 2009;123(4):1132–1141
21. Bose C, Laughon M, Allred EN, et al; Elgan Study Investigators. Blood protein concentrations in the first two postnatal weeks that predict bronchopulmonary dysplasia among infants born before the 28th week of gestation. *Pediatr Res*. 2011;69(4):347–353
22. Perkins ND. Integrating cell-signalling pathways with NF- κ B and IKK function. *Nat Rev Mol Cell Biol*. 2007;8(1):49–62
23. Saugstad OD. Update on oxygen radical disease in neonatology. *Curr Opin Obstet Gynecol*. 2001;13(2):147–153
24. Saugstad OD. Oxidative stress in the newborn: a 30-year perspective. *Biol Neonate*. 2005;88(3):228–236
25. Saugstad OD. Hypoxanthine as an indicator of hypoxia: its role in health and disease through free radical production. *Pediatr Res*. 1988;23(2):143–150
26. Hayden MS, Ghosh S. Shared principles in NF- κ B signaling. *Cell*. 2008;132(3):344–362

CONCLUSIONS: WHERE ARE WE HEADED?

The role of inflammation in the pathogenesis of BPD is firmly established. Unfortunately, clinicians have few therapeutic interventions for limiting inflammation and preventing BPD. Because the etiology of BPD is multifactorial, anti-inflammatory therapies may represent only part of the solution. Only by combining bench translational studies and rigorous trials will practice at the bedside result in limiting lung injury in the preterm infant.

27. Hoffmann A, Natoli G, Ghosh G. Transcriptional regulation via the NF- κ B signaling module. *Oncogene*. 2006;25(51):6706–6716
28. Chen LF, Greene WC. Shaping the nuclear action of NF- κ B. *Nat Rev Mol Cell Biol*. 2004;5(5):392–401
29. Renner F, Schmitz ML. Autoregulatory feedback loops terminating the NF- κ B response. *Trends Biochem Sci*. 2009;34(3):128–135
30. Hoffmann A, Levchenko A, Scott ML, Baltimore D. The I κ B-NF- κ B signaling module: temporal control and selective gene activation. *Science*. 2002;298(5596):1241–1245
31. Kilpinen S, Henttinen T, Lahdenpohja N, Hukkunen J, Hurme M. Signals leading to the activation of NF- κ B transcription factor are stronger in neonatal than adult T lymphocytes. *Scand J Immunol*. 1996;44(1):85–88
32. Vancurova I, Bellani P, Davidson D. Activation of nuclear factor- κ B and its suppression by dexamethasone in polymorphonuclear leukocytes: newborn versus adult. *Pediatr Res*. 2001;49(2):257–262
33. Wright CJ, Zhuang T, La P, Yang G, Dennery PA. Hyperoxia-induced NF- κ B activation occurs via a maturationally sensitive atypical pathway. *Am J Physiol Lung Cell Mol Physiol*. 2009;296(3):L296–L306
34. Yang G, Abate A, George AG, Weng YH, Dennery PA. Maturational differences in lung NF- κ B activation and their role in tolerance to hyperoxia. *J Clin Invest*. 2004;114(5):669–678
35. Dieperink HI, Blackwell TS, Prince LS. Hyperoxia and apoptosis in developing mouse lung mesenchyme. *Pediatr Res*. 2006;59(2):185–190
36. Benjamin JT, Carver BJ, Plosa EJ, et al. NF- κ B activation limits airway branching through inhibition of Sp1-mediated fibroblast growth factor-10 expression. *J Immunol*. 2010;185(8):4896–4903
37. Karin M, Lin A. NF- κ B at the crossroads of life and death. *Nat Immunol*. 2002;3(3):221–227
38. Bourbia A, Cruz MA, Rozycki HJ. NF- κ B in tracheal lavage fluid from intubated premature infants: association with inflammation, oxygen, and outcome. *Arch Dis Child Fetal Neonatal Ed*. 2006;91(1):F36–F39
39. Cao L, Liu C, Cai B, et al. Nuclear factor- κ B expression in alveolar macrophages of mechanically ventilated neonates with respiratory distress syndrome. *Biol Neonate*. 2004;86(2):116–123
40. Cheah FC, Winterbourn CC, Darlow BA, Moccatta TJ, Vissers MC. Nuclear factor κ B activation in pulmonary leukocytes from infants with hyaline membrane disease: associations with chorioamnionitis and *Ureaplasma urealyticum* colonization. *Pediatr Res*. 2005;57(5 pt 1):616–623
41. Haddad JJ, Land SC, Tarnow-Mordi WO, Zembala M, Kowalczyk D, Lauterbach R. Immunopharmacological potential of selective phosphodiesterase inhibition. II. Evidence for the involvement of an inhibitory- κ B/nuclear factor- κ B-sensitive pathway in alveolar epithelial cells. *J Pharmacol Exp Ther*. 2002;300(2):567–576
42. Aghai Z, Kumar S, Farhath S, et al. Dexamethasone suppresses expression of nuclear factor- κ B in the cells of tracheobronchial lavage fluid in premature neonates with respiratory distress. *Pediatr Res*. 2006;59(6):811–815
43. Aghai ZH, Kode A, Saslow JG, et al. Azithromycin suppresses activation of nuclear factor- κ B and synthesis of proinflammatory cytokines in tracheal aspirate cells from premature infants. *Pediatr Res*. 2007;62(4):483–488
44. Wright CJ, Agboke F, Chen F, La P, Yang G, Dennery PA. Nitric oxide inhibits hyperoxia-induced NF- κ B activation in neonatal pulmonary microvascular endothelial cells. *Pediatr Res*. 2010;68(6):484–489
45. Bokodi G, Treszl A, Kovacs L, Tulassay T, Vasarhelyi B. Dysplasia: a review. *Pediatr Pulmonol*. 2007;42(10):952–961
46. Lavoie PM, Dube MP. Genetics of bronchopulmonary dysplasia in the age of genomics. *Curr Opin Pediatr*. 2010;22(2):134–138
47. Parton LA, Strassberg SS, Qian D, Galvin-Parton PA, Cristea IA. The genetic basis for bronchopulmonary dysplasia. *Front Biosci*. 2006;11:1854–1860
48. Parker RA, Lindstrom DP, Cotton RB. Evidence from twin study implies possible genetic susceptibility to bronchopulmonary dysplasia. *Semin Perinatol*. 1996;20(3):206–209
49. Bhandari V, Bizzarro MJ, Shetty A, et al; Neonatal Genetics Study Group. Familial and genetic susceptibility to major neonatal morbidities in preterm twins. *Pediatrics*. 2006;117(6):1901–1906
50. Lavoie PM, Pham C, Jang KL. Heritability of bronchopulmonary dysplasia, defined according to the consensus statement of the national institutes of health. *Pediatrics*. 2008;122(3):479–485
51. Attia J, Ioannidis JP, Thakkinstian A, et al. How to use an article about genetic association. A. Background concepts. *JAMA*. 2009;301(1):74–81
52. Attia J, Ioannidis JP, Thakkinstian A, et al. How to use an article about genetic association: B. Are the results of the study valid? *JAMA*. 2009;301(2):191–197
53. Attia J, Ioannidis JP, Thakkinstian A, et al. How to use an article about genetic association: C. What are the results and will they help me in caring for my patients? *JAMA*. 2009;301(3):304–308
54. Derzbach L, Bokodi G, Treszl A, Vasarhelyi B, Nobilis A, Rigo J Jr. Selectin polymorphisms and perinatal morbidity in low-birthweight infants. *Acta Paediatr*. 2006;95(10):1213–1217
55. Härtel C, König I, Köster S, et al. Genetic polymorphisms of hemostasis genes and primary outcome of very low birth weight infants. *Pediatrics*. 2006;118(2):683–689
56. Pavlovic J, Papağaroufalis C, Xanthou M, et al. Genetic variants of surfactant proteins A, B, C, and D in bronchopulmonary dysplasia. *Dis Markers*. 2006;22(5–6):277–291
57. Bokodi G, Derzbach L, Banyasz I, Tulassay T, Vasarhelyi B. Association of interferon gamma T+874A and interleukin 12 p40 promoter CTCTAA/GC polymorphism with the need for respiratory support and perinatal complications in low birthweight neonates. *Arch Dis Child Fetal Neonatal Ed*. 2007;92(1):F25–F29
58. Capoluongo E, Vento G, Rocchetti S, et al. Mannose-binding lectin polymorphisms and pulmonary outcome in premature neonates: a pilot study. *Intensive Care Med*. 2007;33(10):1787–1794
59. Concolino P, Capoluongo E, Santonocito C, et al. Genetic analysis of the dystroglycan gene in bronchopulmonary dysplasia affected premature newborns. *Clin Chim Acta*. 2007;378(1–2):164–167
60. Hilgendorff A, Heidinger K, Pfeiffer A, et al. Association of polymorphisms in the mannose-binding lectin gene and pulmonary morbidity in preterm infants. *Genes Immun*. 2007;8(8):671–677
61. Strassberg SS, Cristea IA, Qian D, Parton LA. Single nucleotide polymorphisms of tumor necrosis factor-alpha and the susceptibility to bronchopulmonary dysplasia. *Pediatr Pulmonol*. 2007;42(1):29–36
62. Bertalan R, Patocs A, Vasarhelyi B, et al. Association between birth weight in preterm neonates and the *Bcl* polymorphism of the glucocorticoid receptor gene. *J Steroid Biochem Mol Biol*. 2008;111(1–2):91–94
63. Hadchouel A, Decobert F, Franco-Montoya ML, et al. Matrix metalloproteinase gene

- polymorphisms and bronchopulmonary dysplasia: identification of MMP16 as a new player in lung development. *PLoS One*. 2008;3(9):e3188
64. Karjalainen MK, Haataja R, Hallman M. Haplotype analysis of ABCA3: association with respiratory distress in very premature infants. *Ann Med*. 2008;40(1):56–65
 65. Kwinta P, Bik-Multanowski M, Mitkowska Z, Tomasik T, Legutko M, Pietrzyk JJ. Genetic risk factors of bronchopulmonary dysplasia. *Pediatr Res*. 2008;64(6):682–688
 66. Chauhan M, Bombell S, McGuire W. Tumour necrosis factor (–308A) polymorphism in very preterm infants with bronchopulmonary dysplasia: a meta-analysis. *Arch Dis Child Fetal Neonatal Ed*. 2009;94(4):F257–F259
 67. Hilgendorff A, Heidinger K, Bohnert A, et al. Association of polymorphisms in the human surfactant protein-D (SFTPD) gene and postnatal pulmonary adaptation in the preterm infant. *Acta Paediatr*. 2009; 98(1):112–117
 68. Ataç FB, Ince DA, Verdi H, et al. Lack of association between FXIII-Val34Leu, FVII-323 del/ins, and transforming growth factor beta1 (915G/T) gene polymorphisms and bronchopulmonary dysplasia: a single-center study. *DNA Cell Biol*. 2010;29(1): 13–18
 69. Ince DA, Ataç FB, Ozkır S, et al. The role of plasminogen activator inhibitor-1 and angiotensin-converting enzyme gene polymorphisms in bronchopulmonary dysplasia. *Genet Test Mol Biomarkers*. 2010; 14(5):643–647
 70. Koroglu OA, Onay H, Erdemir G, et al. Mannose-binding lectin gene polymorphism and early neonatal outcome in preterm infants. *Neonatology*. 2010;98(4): 305–312
 71. Mailaparambil B, Krueger M, Heizmann U, Schlegel K, Heinze J, Heinzmann A. Genetic and epidemiological risk factors in the development of bronchopulmonary dysplasia. *Dis Markers*. 2010;29(1):1–9
 72. Spiegler J, Gilhaus A, König IR, et al. Polymorphisms in the renin-angiotensin system and outcome of very-low-birthweight infants. *Neonatology*. 2010;97(1):10–14
 73. Viscardi RM. Ureaplasma species: role in diseases of prematurity. *Clin Perinatol*. 2010;37(2):393–409
 74. Yoder BA, Coalson JJ, Winter VT, Siler-Khodr T, Duffy LB, Cassell GH. Effects of antenatal colonization with *Ureaplasma urealyticum* on pulmonary disease in the immature baboon. *Pediatr Res*. 2003; 54(6):797–807
 75. Viscardi RM, Atamas SP, Luzina IG, et al. Antenatal *Ureaplasma urealyticum* respiratory tract infection stimulates proinflammatory, profibrotic responses in the preterm baboon lung. *Pediatr Res*. 2006; 60(2):141–146
 76. Polglase GR, Hillman NH, Pillow JJ, et al. Ventilation-mediated injury after preterm delivery of *Ureaplasma parvum* colonized fetal lambs. *Pediatr Res*. 2010;67(6): 630–635
 77. Polglase GR, Dalton RG, Nitsos I, et al. Pulmonary vascular and alveolar development in preterm lambs chronically colonized with *Ureaplasma parvum*. *Am J Physiol Lung Cell Mol Physiol*. 2010;299(2): L232–L241
 78. Novy MJ, Duffy L, Axthelm MK, et al. *Ureaplasma parvum* or *Mycoplasma hominis* as sole pathogens cause chorioamnionitis, preterm delivery, and fetal pneumonia in rhesus macaques. *Reprod Sci*. 2009; 16(1):56–70
 79. Schelonka RL, Katz B, Waites KB, Benjamin DK Jr. Critical appraisal of the role of *Ureaplasma* in the development of bronchopulmonary dysplasia with metaanalytic techniques. *Pediatr Infect Dis J*. 2005;24(12): 1033–1039
 80. Payne MS, Goss KC, Connett GJ, et al. Molecular microbiological characterization of preterm neonates at risk of bronchopulmonary dysplasia. *Pediatr Res*. 2010;67(4): 412–418
 81. Colaizzi TT, Morris CD, Lapidus J, Sklar RS, Pillers DA. Detection of ureaplasma DNA in endotracheal samples is associated with bronchopulmonary dysplasia after adjustment for multiple risk factors. *Pediatr Res*. 2007;61(5 pt 1):578–583
 82. Aaltonen R, Vahlberg T, Lehtonen L, Alanen A. *Ureaplasma urealyticum*: no independent role in the pathogenesis of bronchopulmonary dysplasia. *Acta Obstet Gynecol Scand*. 2006;85(11):1354–1359
 83. Goldenberg RL, Andrews WW, Goepfert AR, et al. The Alabama Preterm Birth Study: umbilical cord blood *Ureaplasma urealyticum* and *Mycoplasma hominis* cultures in very preterm newborn infants. *Am J Obstet Gynecol*. 2008;198(1):41–e45
 84. Newton ER. Preterm labor, preterm premature rupture of membranes, and chorioamnionitis. *Clin Perinatol*. 2005;32(3): 571–600
 85. Salafia CM, Vogel CA, Vintzileos AM, Bantam KF, Pezzullo J, Silberman L. Placental pathologic findings in preterm birth. *Am J Obstet Gynecol*. 1991;165(4 pt 1):934–938
 86. Watterberg KL, Demers LM, Scott SM, Murphy S. Chorioamnionitis and early lung inflammation in infants in whom bronchopulmonary dysplasia develops. *Pediatrics*. 1996;97(2):210–215
 87. Elimian A, Verma U, Beneck D, Cipriano R, Visintainer P, Tejani N. Histologic chorioamnionitis, antenatal steroids, and perinatal outcomes. *Obstet Gynecol*. 2000; 96(3):333–336
 88. Redline RW, Wilson-Costello D, Hack M. Placental and other perinatal risk factors for chronic lung disease in very low birth weight infants. *Pediatr Res*. 2002;52(5): 713–719
 89. Kent A, Dahlstrom JE. Chorioamnionitis/funisitis and the development of bronchopulmonary dysplasia. *J Paediatr Child Health*. 2004;40(7):356–359
 90. Dempsey E, Chen MF, Kokottis T, Vallerand D, Usher R. Outcome of neonates less than 30 weeks gestation with histologic chorioamnionitis. *Am J Perinatol*. 2005;22(3): 155–159
 91. Andrews WW, Goldenberg RL, Faye-Petersen O, Cliver S, Goepfert AR, Hauth JC. The Alabama Preterm Birth study: polymorphonuclear and mononuclear cell placental infiltrations, other markers of inflammation, and outcomes in 23- to 32-week preterm newborn infants. *Am J Obstet Gynecol*. 2006;195(3):803–808
 92. Goldenberg RL, Andrews WW, Faye-Petersen OM, Cliver SP, Goepfert AR, Hauth JC. The Alabama preterm birth study: corticosteroids and neonatal outcomes in 23- to 32-week newborns with various markers of intrauterine infection. *Am J Obstet Gynecol*. 2006;195(4):1020–1024
 93. Richardson BS, Wakim E, daSilva O, Walton J. Preterm histologic chorioamnionitis: impact on cord gas and pH values and neonatal outcome. *Am J Obstet Gynecol*. 2006; 195(5):1357–1365
 94. Kewitz G, Wudel S, Hopp H, Hopfenmuller W, Vogel M, Roots I. Below median birth weight in appropriate-for-gestational-age preterm infants as a risk factor for bronchopulmonary dysplasia. *J Perinat Med*. 2008;36(4):359–364
 95. Been JV, Zimmermann LJ. Histological chorioamnionitis and respiratory outcome in preterm infants. *Arch Dis Child Fetal Neonatal Ed*. 2009;94(3):F218–F225
 96. Been JV, Rours IG, Kornelisse RF, et al. Histologic chorioamnionitis, fetal involvement, and antenatal steroids: effects on neonatal outcome in preterm infants. *Am J Obstet Gynecol*. 2009;201(6):587.e1–587.e8
 97. Kaukola T, Tuimala J, Herva R, Kingsmore S, Hallman M. Cord immunoproteins as

- predictors of respiratory outcome in preterm infants. *Am J Obstet Gynecol*. 2009;200(1):100.e1–100.e8
98. Laughon M, Allred EN, Bose C, et al; ELGAN Study Investigators. Patterns of respiratory disease during the first 2 postnatal weeks in extremely premature infants. *Pediatrics*. 2009;123(4):1124–1131
 99. Prendergast M, May C, Broughton S, et al. Chorioamnionitis, lung function and bronchopulmonary dysplasia in prematurely born infants. *Arch Dis Child Fetal Neonatal Ed*. 2010; In press
 100. Lee HJ, Kim EK, Kim HS, Choi CW, Kim BI, Choi JH. Chorioamnionitis, respiratory distress syndrome and bronchopulmonary dysplasia in extremely low birth weight infants. *J Perinatol*. 2011;31(3):166–170
 101. Lahra MM, Beeby PJ, Jeffery HE. Intrauterine inflammation, neonatal sepsis, and chronic lung disease: a 13-year hospital cohort study. *Pediatrics*. 2009;123(5):1314–1319
 102. Cheah FC, Pillow JJ, Kramer BW, et al. Airway inflammatory cell responses to intra-amniotic lipopolysaccharide in a sheep model of chorioamnionitis. *Am J Physiol Lung Cell Mol Physiol*. 2009;296(3):L384–L393
 103. Prince LS, Okoh VO, Moninger TO, Matalon S. Lipopolysaccharide increases alveolar type II cell number in fetal mouse lungs through Toll-like receptor 4 and NF- κ B. *Am J Physiol Lung Cell Mol Physiol*. 2004;287(5):L999–L1006
 104. Jung HS, Yoon BH, Jun JK, Kim M, Kim YA, Kim CJ. Differential activation of mitogen activated protein kinases and nuclear factor- κ B in lipopolysaccharide-treated term and preterm amnion cells. *Virchows Arch*. 2005;447(1):45–52
 105. Kramer BW, Kaemmerer U, Kapp M, et al. Decreased expression of angiogenic factors in placentas with chorioamnionitis after preterm birth. *Pediatr Res*. 2005;58(3):607–612
 106. Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med*. 2005;6(1):2–8
 107. Hofer N, Muller W, Resch B. Systemic inflammatory response syndrome (SIRS) definition and correlation with early-onset bacterial infection of the newborn. *Arch Dis Child Fetal Neonatal Ed*. 2010;95(2):F151
 108. Stoll BJ, Hansen N, Fanaroff AA, et al. Changes in pathogens causing early-onset sepsis in very-low-birth-weight infants. *N Engl J Med*. 2002;347(4):240–247
 109. Klinger G, Levy I, Sirota L, Boyko V, Lerner-Geva L, Reichman B; Israel Neonatal Network. Outcome of early-onset sepsis in a national cohort of very low birth weight infants. *Pediatrics*. 2010;125(4). Available at: www.pediatrics.org/cgi/content/full/125/4/e736
 110. Fanaroff AA, Korones SB, Wright LL, et al. Incidence, presenting features, risk factors and significance of late onset septicemia in very low birth weight infants. The National Institute of Child Health and Human Development Neonatal Research Network. *Pediatr Infect Dis J*. 1998;17(7):593–598
 111. Stoll BJ, Hansen N, Fanaroff AA, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. *Pediatrics*. 2002;110(2 pt 1):285–291
 112. Bhandari V. Hyperoxia-derived lung damage in preterm infants. *Semin Fetal Neonatal Med*. 2010;15(4):223–229
 113. Didrik Saugstad O. Oxygen and oxidative stress in bronchopulmonary dysplasia. *J Perinat Med*. 2010;38(6):571–577
 114. Vento M, Moro M, Escrig R, et al. Preterm resuscitation with low oxygen causes less oxidative stress, inflammation, and chronic lung disease. *Pediatrics*. 2009;124(3). Available at: www.pediatrics.org/cgi/content/full/124/3/e439
 115. Saugstad OD, Aune D. In search of the optimal oxygen saturation for extremely low birth weight infants: a systematic review and meta-analysis. *Neonatology*. 2010;100(1):1–8
 116. Carlo WA, Finer NN, Walsh MC, et al. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med*. 2010;362(21):1959–1969
 117. BOOSTII: Benefits of Oxygen Saturation Targeting. Available at: www.ctc.usyd.edu.au/BoostII/main_body/Home.htm. Accessed February 22, 2011
 118. ClinicalTrials.gov. Canadian Oxygen Trial (COT). Available at: <http://clinicaltrials.gov/ct2/show/NCT00637169>. Accessed February 22, 2011
 119. Tschumperlin DJ, Boudreau F, Liu F. Recent advances and new opportunities in lung mechanobiology. *J Biomech*. 2010;43(1):99–107
 120. Sanchez-Esteban J, Wang Y, Grupp PA, Rubin LP. Mechanical stretch induces fetal type II cell differentiation via an epidermal growth factor receptor-extracellular-regulated protein kinase signaling pathway. *Am J Respir Cell Mol Biol*. 2004;30(1):76–83
 121. Kumar A, Lnu S, Malya R, et al. Mechanical stretch activates nuclear factor- κ B, activator protein-1, and mitogen-activated protein kinases in lung parenchyma: implications in asthma. *FASEB J*. 2003;17(13):1800–1811
 122. Wang Y, Maciejewski BS, Lee N, et al. Strain-induced fetal type II epithelial cell differentiation is mediated via cAMP-PKA-dependent signaling pathway. *Am J Physiol Lung Cell Mol Physiol*. 2006;291(4):L820–L827
 123. Copland IB, Reynaud D, Pace-Asciak C, Post M. Mechanotransduction of stretch-induced prostanoid release by fetal lung epithelial cells. *Am J Physiol Lung Cell Mol Physiol*. 2006;291(3):L487–L495
 124. Copland IB, Post M. Stretch-activated signaling pathways responsible for early response gene expression in fetal lung epithelial cells. *J Cell Physiol*. 2007;210(1):133–143
 125. Wang Y, Maciejewski BS, Drouillard D, et al. A role for caveolin-1 in mechanotransduction of fetal type II epithelial cells. *Am J Physiol Lung Cell Mol Physiol*. 2010;298(6):L775–L783
 126. Hillman NH, Moss TJ, Kallapur SG, et al. Brief, large tidal volume ventilation initiates lung injury and a systemic response in fetal sheep. *Am J Respir Crit Care Med*. 2007;176(6):575–581
 127. Kornecki A, Tsuchida S, Ondiveeran HK, et al. Lung development and susceptibility to ventilator-induced lung injury. *Am J Respir Crit Care Med*. 2005;171(7):743–752
 128. Copland IB, Martinez F, Kavanagh BP, et al. High tidal volume ventilation causes different inflammatory responses in newborn versus adult lung. *Am J Respir Crit Care Med*. 2004;169(6):739–748
 129. Liu YY, Liao SK, Huang CC, Tsai YH, Quinn DA, Li LF. Role for nuclear factor- κ B in augmented lung injury because of interaction between hyperoxia and high stretch ventilation. *Transl Res*. 2009;154(5):228–240
 130. Held HD, Boettcher S, Hamann L, Uhlig S. Ventilation-induced chemokine and cytokine release is associated with activation of nuclear factor- κ B and is blocked by steroids. *Am J Respir Crit Care Med*. 2001;163(3 pt 1):711–716
 131. Wallace MJ, Probyn ME, Zahra VA, et al. Early biomarkers and potential mediators of ventilation-induced lung injury in very preterm lambs. *Respir Res*. 2009;10:19
 132. Reyburn B, Li M, Metcalfe DB, et al. Nasal ventilation alters mesenchymal cell turn-

- over and improves alveolarization in pre-term lambs. *Am J Respir Crit Care Med*. 2008;178(4):407–418
133. Marshall JC. Clinical trials of mediator-directed therapy in sepsis: what have we learned? *Intensive Care Med*. 2000; 26(suppl 1):S75–S83
 134. Rice TW, Wheeler AP, Morris PE, et al. Safety and efficacy of affinity-purified, anti-tumor necrosis factor- α , ovine Fab for injection (CytoFab) in severe sepsis. *Crit Care Med*. 2006;34(9):2271–2281
 135. Eichacker PQ, Parent C, Kalil A, et al. Risk and the efficacy of antiinflammatory agents: retrospective and confirmatory studies of sepsis. *Am J Respir Crit Care Med*. 2002;166(9):1197–1205
 136. Bernard GR, Vincent JL, Laterre PF, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med*. 2001;344(10):699–709
 137. Marti-Carvajal A, Salanti G, Cardona AF. Human recombinant activated protein C for severe sepsis. *Cochrane Database Syst Rev*. 2008;(1):CD004388
 138. Kylat RI, Ohlsson A. Recombinant human activated protein C for severe sepsis in neonates. *Cochrane Database Syst Rev*. 2006;(2):CD005385
 139. Nadel S, Goldstein B, Williams MD, et al. Drotrecogin alfa (activated) in children with severe sepsis: a multicentre phase III randomised controlled trial. *Lancet*. 2007; 369(9564):836–843
 140. Minneci PC, Deans KJ, Eichacker PQ, Natanson C. The effects of steroids during sepsis depend on dose and severity of illness: an updated meta-analysis. *Clin Microbiol Infect*. 2009;15(4):308–318
 141. Lee JW, Gupta N, Serikov V, Matthay MA. Potential application of mesenchymal stem cells in acute lung injury. *Expert Opin Biol Ther*. 2009;9(10):1259–1270
 142. van Haaften T, Thebaud B. Adult bone marrow-derived stem cells for the lung: implications for pediatric lung diseases. *Pediatr Res*. 2006;59(4 pt 2):94R–99R
 143. Abman SH, Matthay MA. Mesenchymal stem cells for the prevention of bronchopulmonary dysplasia: delivering the secretome. *Am J Respir Crit Care Med*. 2009; 180(11):1039–1041
 144. Pierro M, Thebaud B. Mesenchymal stem cells in chronic lung disease: culprit or savior? *Am J Physiol Lung Cell Mol Physiol*. 2010;298(6):L732–L734
 145. Kassmer SH, Krause DS. Detection of bone marrow-derived lung epithelial cells. *Exp Hematol*. 2010;38(7):564–573
 146. Matthay MA, Thompson BT, Read EJ, et al. Therapeutic potential of mesenchymal stem cells for severe acute lung injury. *Chest*. 2010;138(4):965–972
 147. Chang YS, Oh W, Choi SJ, et al. Human umbilical cord blood-derived mesenchymal stem cells attenuate hyperoxia-induced lung injury in neonatal rats. *Cell Transplant*. 2009;18(8):869–886
 148. van Haaften T, Byrne R, Bonnet S, et al. Airway delivery of mesenchymal stem cells prevents arrested alveolar growth in neonatal lung injury in rats. *Am J Respir Crit Care Med*. 2009;180(11):1131–1142
 149. Aslam M, Baveja R, Liang OD, et al. Bone marrow stromal cells attenuate lung injury in a murine model of neonatal chronic lung disease. *Am J Respir Crit Care Med*. 2009;180(11):1122–1130
 150. Balasubramaniam V, Ryan SL, Seedorf GJ, et al. Bone marrow-derived angiogenic cells restore lung alveolar and vascular structure after neonatal hyperoxia in infant mice. *Am J Physiol Lung Cell Mol Physiol*. 2010;298(3):L315–L323
 151. Tremblay LN, Slutsky AS. Ventilator-induced lung injury: from the bench to the bedside. *Intensive Care Med*. 2006;32(1): 24–33
 152. Attar MA, Donn SM. Mechanisms of ventilator-induced lung injury in premature infants. *Semin Neonatol*. 2002;7(5): 353–360
 153. Sweet DG, Carnielli V, Greisen G, et al. European consensus guidelines on the management of neonatal respiratory distress syndrome in preterm infants: 2010 update. *Neonatology*. 2010;97(4):402–417
 154. Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet JM, Carlin JB. Nasal CPAP or intubation at birth for very preterm infants. *N Engl J Med*. 2008;358(7):700–708
 155. Finer NN, Carlo WA, Walsh MC, et al. Early CPAP versus surfactant in extremely preterm infants. *N Engl J Med*. 2010;362(21): 1970–1979
 156. Dunn M, Kaempf J, de Klerk A, et al. Delivery room management of preterm infants at risk for respiratory distress syndrome (RDS). EPAS2010;1670.2
 157. Stevens TP, Harrington EW, Blennow M, Soll RF. Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome. *Cochrane Database Syst Rev*. 2007;(4):CD003063
 158. Rojas MA, Lozano JM, Rojas MX, et al; Colombian Neonatal Research Network. Very early surfactant without mandatory ventilation in premature infants treated with early continuous positive airway pressure: a randomized, controlled trial. *Pediatrics*. 2009;123(1):137–142
 159. Lemyre B, Davis PG, de Paoli AG. Nasal intermittent positive pressure ventilation (NIPPV) versus nasal continuous positive airway pressure (NCPAP) for apnea of prematurity. *Cochrane Database Syst Rev*. 2002;(1):CD002272
 160. ClinicalTrials.gov. Nasal Intermittent Positive Pressure Ventilation in Premature Infants (NIPPV). Available at: <http://clinicaltrials.gov/ct2/show/NCT00433212?term=Kirpalani&rank=1>. Accessed March 2, 2011
 161. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med*. 2000;342(18):1301–1308
 162. Lista G, Castoldi F, Bianchi S, Battaglioli M, Caviglioli F, Bosoni MA. Volume guarantee versus high-frequency ventilation: lung inflammation in preterm infants. *Arch Dis Child Fetal Neonatal Ed*. 2008;93(4): F252–F256
 163. Wheeler K, Klingenberg C, McCallion N, Morley CJ, Davis PG. Volume-targeted versus pressure-limited ventilation in the neonate. *Cochrane Database Syst Rev*. 2010; (11):CD003666
 164. Gattinoni L, Pelosi P, Crotti S, Valenza F. Effects of positive end-expiratory pressure on regional distribution of tidal volume and recruitment in adult respiratory distress syndrome. *Am J Respir Crit Care Med*. 1995;151(6):1807–1814
 165. Muscedere JG, Mullen JB, Gan K, Slutsky AS. Tidal ventilation at low airway pressures can augment lung injury. *Am J Respir Crit Care Med*. 1994;149(5):1327–1334
 166. Tremblay L, Valenza F, Ribeiro SP, Li J, Slutsky AS. Injurious ventilatory strategies increase cytokines and c-fos m-RNA expression in an isolated rat lung model. *J Clin Invest*. 1997;99(5):944–952
 167. Monkman SL, Andersen CC, Nahmias C, et al. Positive end-expiratory pressure above lower inflection point minimizes influx of activated neutrophils into lung. *Crit Care Med*. 2004;32(12):2471–2475
 168. Mehta S, Stewart TE, MacDonald R, et al. Temporal change, reproducibility, and interobserver variability in pressure-volume curves in adults with acute lung injury and acute respiratory distress syndrome. *Crit Care Med*. 2003;31(8):2118–2125
 169. Mathe JC, Clement A, Chevalier JY, Gaultier C, Costil J. Use of total inspiratory pressure-volume curves for determina-

- tion of appropriate positive end-expiratory pressure in newborns with hyaline membrane disease. *Intensive Care Med.* 1987; 13(5):332–336
170. Castoldi F, Daniele I, Fontana P, Caviglioli F, Lupo E, Lista G. Lung recruitment maneuver during volume guarantee ventilation of preterm infants with acute respiratory distress syndrome. *Am J Perinatol.* 2011; In press
 171. De Jaegere A, van Veenendaal MB, Michiels A, van Kaam AH. Lung recruitment using oxygenation during open lung high-frequency ventilation in preterm infants. *Am J Respir Crit Care Med.* 2006;174(6): 639–645
 172. Gattinoni L, Caironi P, Cressoni M, et al. Lung recruitment in patients with the acute respiratory distress syndrome. *N Engl J Med.* 2006;354(17):1775–1786
 173. Briel M, Meade M, Mercat A, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. *JAMA.* 2010; 303(9):865–873
 174. Tamaoki J, Kadota J, Takizawa H. Clinical implications of the immunomodulatory effects of macrolides. *Am J Med.* 2004; 117(suppl 9A):S5–11S
 175. Ballard HO, Bernard P, Qualls J, Everson W, Shook LA. Azithromycin protects against hyperoxic lung injury in neonatal rats. *J Invest Med.* 2007;55(6):299–305
 176. Ballard HO, Anstead MI, Shook LA. Azithromycin in the extremely low birth weight infant for the prevention of bronchopulmonary dysplasia: a pilot study. *Respir Res.* 2007;8:41
 177. ClinicalTrials.gov. Trial II of Lung Protection With Azithromycin in the Preterm Infant. Available at: <http://clinicaltrials.gov/ct2/show/NCT00319956?term=azithromycin+AND+bronchopulmonary+dysplasia&rank=1>. Accessed May 19, 2011
 178. Askie LM, Ballard RA, Cutter G, et al. Inhaled Nitric Oxide in preterm infants: a systematic review and individual patient data meta-analysis. *BMC Pediatr.* 2010;10:15
 179. Cole FS, Alleyne C, Barks JD, et al. NIH Consensus Development Conference Statement: inhaled nitric-oxide therapy for premature infants. *Pediatrics.* 2011; 127(2):363–369
 180. Arul N, Konduri GG. Inhaled nitric oxide for preterm neonates. *Clin Perinatol.* 2009; 36(1):43–61
 181. Cirino G, Distrutti E, Wallace JL. Nitric oxide and inflammation. *Inflamm Allergy Drug Targets.* 2006;5(2):115–119
 182. Reynaert N, Ckless K, Korn S, et al. Nitric oxide represses inhibitory κ B kinase through S-nitrosylation. *Proc Natl Acad Sci U S A.* 2004;101(24):8945–8950
 183. Matthews J, Botting C, Panico M, Morris H, Hay R. Inhibition of NF- κ B DNA binding by nitric oxide. *Nucleic Acids Res.* 1996; 24(12):2236–2242
 184. Kelleher ZT, Matsumoto A, Stamler JS, Marshall HE. NOS₂ regulation of NF- κ B by S-nitrosylation of p65. *J Biol Chem.* 2007; 282(42):30667–30672
 185. Marshall H, Stamler J. Inhibition of NF- κ B by S-nitrosylation. *Biochemistry.* 2001; 40(6):1688–1693
 186. Ckless K, van der Vliet A, Janssen-Heininger Y. Oxidative-nitrosative stress and post-translational protein modifications: implications to lung structure-function relations—arginase modulates NF- κ B activity via a nitric oxide-dependent mechanism. *Am J Respir Cell Mol Biol.* 2007;36(6):645–653
 187. Janssen-Heininger Y, Poynter M, Baeuerle P. Recent advances towards understanding redox mechanisms in the activation of nuclear factor κ B. *Free Radic Biol Med.* 2000;28(9):1317–1327
 188. Spiecker M, Peng H, Liao J. Inhibition of endothelial vascular cell adhesion molecule-1 expression by nitric oxide involves the induction and nuclear translocation of I κ B α . *J Biol Chem.* 1997; 272(49):30969–30974
 189. Levrand S, Pesse B, Feihl F, et al. Peroxynitrite is a potent inhibitor of NF- κ B activation triggered by inflammatory stimuli in cardiac and endothelial cell lines. *J Biol Chem.* 2005;280(41):34878–34887
 190. Yakovlev V, Barani I, Rabender C, et al. Tyrosine nitration of I κ B α : a novel mechanism for NF- κ B activation. *Biochemistry.* 2007;46(42):11671–11683
 191. Peng HB, Libby P, Liao JK. Induction and stabilization of I κ B α by nitric oxide mediates inhibition of NF- κ B. *J Biol Chem.* 1995;270(23):14214–14219
 192. Franek W, Chowdary Y, Lin X, et al. Suppression of nuclear factor- κ B activity by nitric oxide and hyperoxia in oxygen-resistant cells. *J Biol Chem.* 2002;277(45): 42694–42700
 193. Howlett CE, Hutchison JS, Veinot JP, Chiu A, Merchant P, Fliss H. Inhaled nitric oxide protects against hyperoxia-induced apoptosis in rat lungs. *Am J Physiol.* 1999; 277(3 pt 1):L596–L605
 194. Raychaudhuri B, Dweik R, Connors MJ, et al. Nitric oxide blocks nuclear factor- κ B activation in alveolar macrophages. *Am J Respir Cell Mol Biol.* 1999;21(3):311–316
 195. Davis JM, Auten RL. Maturation of the antioxidant system and the effects on preterm birth. *Semin Fetal Neonatal Med.* 2010; 15(4):191–195
 196. Davis JM, Parad RB, Michele T, Allred E, Price A, Rosenfeld W; North American Recombinant Human CuZnSOD Study Group. Pulmonary outcome at 1 year corrected age in premature infants treated at birth with recombinant human CuZn superoxide dismutase. *Pediatrics.* 2003;111(3): 469–476
 197. Jankov RP, Negus A, Tanswell AK. Antioxidants as therapy in the newborn: some words of caution. *Pediatr Res.* 2001;50(6): 681–687
 198. Jobe AH. Postnatal corticosteroids for bronchopulmonary dysplasia. *Clin Perinatol.* 2009;36(1):177–188
 199. Doyle LW, Ehrenkranz RA, Halliday HL. Dexamethasone treatment after the first week of life for bronchopulmonary dysplasia in preterm infants: a systematic review. *Neonatology.* 2010;98(4):289–296
 200. Doyle LW, Ehrenkranz RA, Halliday HL. Dexamethasone treatment in the first week of life for preventing bronchopulmonary dysplasia in preterm infants: a systematic review. *Neonatology.* 2010;98(3):217–224
 201. Doyle LW, Ehrenkranz RA, Halliday HL. Postnatal hydrocortisone for preventing or treating bronchopulmonary dysplasia in preterm infants: a systematic review. *Neonatology.* 2010;98(2):111–117
 202. Bancalari E. Corticosteroids and neonatal chronic lung disease. *Eur J Pediatr.* 1998; 157(suppl 1):S31–S37
 203. Laughon MM, Smith PB, Bose C. Prevention of bronchopulmonary dysplasia. *Semin Fetal Neonatal Med.* 2009;14(6):374–382
 204. Mammel MC, Green TP, Johnson DE, Thompson TR. Controlled trial of dexamethasone therapy in infants with bronchopulmonary dysplasia. *Lancet.* 1983; 1(8338):1356–1358
 205. Yeh TF, Lin YJ, Huang CC, et al. Early dexamethasone therapy in preterm infants: a follow-up study. *Pediatrics.* 1998;101(5). Available at: www.pediatrics.org/cgi/content/full/101/5/e7
 206. Barrington KJ. The adverse neurodevelopmental effects of postnatal steroids in the preterm infant: a systematic review of RCTs. *BMC Pediatr.* 2001;1:1
 207. Barrington KJ. Postnatal steroids and neurodevelopmental outcomes: a problem in the making. *Pediatrics.* 2001;107(6): 1425–1426

208. Jobe AH. Glucocorticoids in perinatal medicine: misguided rockets? *J Pediatr*. 2000;137(1):1–3
209. Postnatal corticosteroids to treat or prevent chronic lung disease in preterm infants. *Pediatrics*. 2002;109(2):330–338
210. Taylor C, Shah PS, Dunn MS. Meta-analysis of postnatal steroid use challenged. *Pediatrics*. 2002;109(4):716–717; author reply 716–717
211. Jacobs HC, Chapman RL, Gross I. Premature conclusions on postnatal steroid effects. *Pediatrics*. 2002;110(1 pt 1):200–201; author reply 200–201
212. Shinwell ES, Lerner-Geva L, Lusky A, Reichman B. Less postnatal steroids, more bronchopulmonary dysplasia: a population-based study in very low birth-weight infants. *Arch Dis Child Fetal Neonatal Ed*. 2007;92(1):F30–F33
213. Yoder BA, Harrison M, Clark RH. Time-related changes in steroid use and bronchopulmonary dysplasia in preterm infants. *Pediatrics*. 2009;124(2):673–679
214. Kobaly K, Schluchter M, Minich N, et al. Outcomes of extremely low birth weight (<1 kg) and extremely low gestational age (<28 weeks) infants with bronchopulmonary dysplasia: effects of practice changes in 2000 to 2003. *Pediatrics*. 2008;121(1):73–81
215. Halliday HL, Ehrenkranz RA, Doyle LW. Early (< 8 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants. *Cochrane Database Syst Rev*. 2010;(1):CD001146
216. Doyle LW, Halliday HL, Ehrenkranz RA, Davis PG, Sinclair JC. Impact of postnatal systemic corticosteroids on mortality and cerebral palsy in preterm infants: effect modification by risk for chronic lung disease. *Pediatrics*. 2005;115(3):655–661
217. Halliday HL, Ehrenkranz RA, Doyle LW. Late (>7 days) postnatal corticosteroids for chronic lung disease in preterm infants. *Cochrane Database Syst Rev*. 2009;(1):CD001145
218. Halliday HL. Postnatal steroids: the way forward. *Arch Dis Child Fetal Neonatal Ed*. 2011;96(3):F158–F159
219. Kirpalani H, Schmidt B, Gaston S, Santos R, Wilkie R. Birthweight, early passive respiratory system mechanics, and ventilator requirements as predictors of outcome in premature infants with respiratory failure. *Pediatr Pulmonol*. 1991;10(3):195–198
220. May C, Williams O, Milner AD, et al. Relation of exhaled nitric oxide levels to development of bronchopulmonary dysplasia. *Arch Dis Child Fetal Neonatal Ed*. 2009;94(3):F205–F209
221. May C, Patel S, Kennedy C, et al. Prediction of bronchopulmonary dysplasia. *Arch Dis Child Fetal Neonatal Ed*. 2011; In press
222. Watterberg KL; American Academy of Pediatrics, Committee on Fetus and Newborn. Postnatal corticosteroids to prevent or treat bronchopulmonary dysplasia. *Pediatrics*. 2010;126(4):800–808
223. Rademaker KJ, de Vries LS, Uiterwaal CS, Groenendaal F, Grobbee DE, van Bel F. Postnatal hydrocortisone treatment for chronic lung disease in the preterm newborn and long-term neurodevelopmental follow-up. *Arch Dis Child Fetal Neonatal Ed*. 2008;93(1):F58–F63
224. Yates HL, Newell SJ. Minidex: very low dose dexamethasone (0.05 mg/kg per day) in chronic lung disease. *Arch Dis Child Fetal Neonatal Ed*. 2011;96(3):F190–F194
225. Schmidt B, Asztalos EV, Roberts RS, Robertson CM, Sauve RS, Whitfield MF. Impact of bronchopulmonary dysplasia, brain injury, and severe retinopathy on the outcome of extremely low-birth-weight infants at 18 months: results from the trial of indomethacin prophylaxis in preterms. *JAMA*. 2003;289(9):1124–1129
226. Walsh MC, Morris BH, Wraga LA, et al. Extremely low birthweight neonates with protracted ventilation: mortality and 18-month neurodevelopmental outcomes. *J Pediatr*. 2005;146(6):798–804
227. Eichenwald EC, Stark AR. Are postnatal steroids ever justified to treat severe bronchopulmonary dysplasia? *Arch Dis Child Fetal Neonatal Ed*. 2007;92(5):F334–F337
228. Kunsch C, Rosen CA. NF- κ B subunit-specific regulation of the interleukin-8 promoter. *Mol Cell Biol*. 1993;13(10):6137–6146
229. Auten RL Jr, Mason SN, Tanaka DT, Welty-Wolf K, Whorton MH. Anti-neutrophil chemokine preserves alveolar development in hyperoxia-exposed newborn rats. *Am J Physiol Lung Cell Mol Physiol*. 2001;281(2):L336–L344
230. De Dooy J, Ieven M, Stevens W, De Clerck L, Mahieu L. High levels of CXCL8 in tracheal aspirate samples taken at birth are associated with adverse respiratory outcome only in preterm infants younger than 28 weeks gestation. *Pediatr Pulmonol*. 2007;42(3):193–203
231. Baier RJ, Loggins J, Kruger TE. Monocyte chemoattractant protein-1 and interleukin-8 are increased in bronchopulmonary dysplasia: relation to isolation of *Ureaplasma urealyticum*. *J Investig Med*. 2001;49(4):362–369
232. Hiscott J, Marois J, Garoufalos J, et al. Characterization of a functional NF- κ B site in the human interleukin 1 beta promoter: evidence for a positive autoregulatory loop. *Mol Cell Biol*. 1993;13(10):6231–6240
233. Johnson BH, Yi M, Masood A, et al. A critical role for the IL-1 receptor in lung injury induced in neonatal rats by 60% O₂. *Pediatr Res*. 2009;66(3):260–265
234. Libermann TA, Baltimore D. Activation of interleukin-6 gene expression through the NF- κ B transcription factor. *Mol Cell Biol*. 1990;10(5):2327–2334
235. Choo-Wing R, Nedrelo JH, Homer RJ, Elias JA, Bhandari V. Developmental differences in the responses of IL-6 and IL-13 transgenic mice exposed to hyperoxia. *Am J Physiol Lung Cell Mol Physiol*. 2007;293(1):L142–L150
236. Choi CW, Kim BI, Kim HS, Park JD, Choi JH, Son DW. Increase of interleukin-6 in tracheal aspirate at birth: a predictor of subsequent bronchopulmonary dysplasia in preterm infants. *Acta Paediatr*. 2006;95(1):38–43
237. von Bismarck P, Claass A, Schickor C, Krause MF, Rose-John S. Altered pulmonary interleukin-6 signaling in preterm infants developing bronchopulmonary dysplasia. *Exp Lung Res*. 2008;34(10):694–706
238. Chetty A, Cao GJ, Severgnini M, Simon A, Warburton R, Nielsen HC. Role of matrix metalloproteinase-9 in hyperoxic injury in developing lung. *Am J Physiol Lung Cell Mol Physiol*. 2008;295(4):L584–L592
239. Ekekeze II, Thibeault DW, Simon SD, Norberg M, Merrill JD, Ballard RA, et al. Low levels of tissue inhibitors of metalloproteinases with a high matrix metalloproteinase-9/tissue inhibitor of metalloproteinase-1 ratio are present in tracheal aspirate fluids of infants who develop chronic lung disease. *Pediatrics*. 2004;113(6):1709–1714
240. Teferedegne B, Green MR, Guo Z, Boss JM. Mechanism of action of a distal NF- κ B-dependent enhancer. *Mol Cell Biol*. 2006;26(15):5759–5770
241. Vozzelli MA, Mason SN, Whorton MH, Auten RL Jr. Antimacrophage chemokine treatment prevents neutrophil and macrophage influx in hyperoxia-exposed newborn rat lung. *Am J Physiol Lung Cell Mol Physiol*. 2004;286(3):L488–L493
242. Baier RJ, Majid A, Parupia H, Loggins J, Kruger TE. CC chemokine concentrations increase in respiratory distress syndrome and correlate with development of bron-

- chopulmonary dysplasia. *Pediatr Pulmonol*. 2004;37(2):137–148
243. Johnston CJ, Mango GW, Finkelstein JN, Stripp BR. Altered pulmonary response to hyperoxia in Clara cell secretory protein deficient mice. *Am J Respir Cell Mol Biol*. 1997;17(2):147–155
 244. Ramsay PL, DeMayo FJ, Hegemier SE, Wearden ME, Smith CV, Welty SE. Clara cell secretory protein oxidation and expression in premature infants who develop bronchopulmonary dysplasia. *Am J Respir Crit Care Med*. 2001;164(1):155–161
 245. Levine CR, Gewolb IH, Allen K, et al. The safety, pharmacokinetics, and anti-inflammatory effects of intratracheal recombinant human Clara cell protein in premature infants with respiratory distress syndrome. *Pediatr Res*. 2005;58(1):15–21
 246. Kevill KA, Bhandari V, Kettunen M, et al. A role for macrophage migration inhibitory factor in the neonatal respiratory distress syndrome. *J Immunol*. 2008;180(1):601–608
 247. Schmidt B, Roberts RS, Davis P, et al. Caffeine therapy for apnea of prematurity. *N Engl J Med*. 2006;354(20):2112–2121
 248. Tyson JE, Wright LL, Oh W, et al. Vitamin A supplementation for extremely low-birth-weight infants. National Institute of Child Health and Human Development Neonatal Research Network. *N Engl J Med*. 1999;340(25):1962–1968

PREDICTING THE FUTURE: *Both science fiction novelists and ethicists have long debated whether knowing exactly how long you were going to live is something that people should or want to know. Would you ask for a blood test that predicts how long you might live? Evidently, there are plenty of people willing to spend several hundred dollars for a blood test that some say quantifies your risk of death in the near future or the development of cancer. As reported in The New York Times (Business: May 18, 2011), several companies are now offering blood tests that measure the length of telomeres. Telomeres are repetitive DNA sequences on the ends of chromosomes that prevent chromosomal degradation during replication. Telomeres are consumed or shortened after each replicative cycle eventually becoming so short that chromosomal replication can no longer occur. A few studies in humans have shown that people with the shortest telomeres were more likely to die in the near future or develop chronic diseases such as cancer or Alzheimer's. Companies have seized upon this and marketed a variety of tests to measure telomere length. While nobody disputes the importance of telomeres in maintaining chromosomal integrity during replication, the implications of individual telomere length are not nearly as evident. Telomere length is remarkably variable so length in one person may not necessarily predict risk in another individual. Some of the blood tests measure average telomere length while others report not only the average but the shortest telomere length, which in some studies are the ones associated with health problems. What to do with the information remains a bit problematic. Some advocates of testing suggest that the test be used as a biologic marker of an individual's overall health. Still, as one cannot lengthen the telomere, the advice, whether you have short telomeres or long is that one should eat a healthy diet, exercise regularly, and avoid smoking. That advice is free.*

Noted by WVR, MD