Pharmacologic Management of Severe Bronchopulmonary Dysplasia

William E. Truog, MD,* Tamorah R. Lewis, MD, PhD,† Nicolas A. Bamat, MD, MSCE‡

*Division of Neonatology, Children's Mercy-Kansas City and the Department of Pediatrics, University of Missouri-Kansas City School of Medicine, Kansas City, MO

†Divisions of Neonatology and Clinical Pharmacology, Toxicology and Therapeutic Innovation, Children's Mercy-Kansas City and the Department of Pediatrics, University of Missouri-Kansas City School of Medicine, Kansas City, MO

‡Division of Neonatology, Children's Hospital of Philadelphia, Department of Pediatrics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Practice Gap

Severe bronchopulmonary dysplasia (sBPD) contributes to late infant mortality and long-term morbidity including the need for prolonged hospitalization. Few if any medications have been shown to lead to meaningful outcomes. This "drug gap" arises because of variability in developmental pharmacokinetics, pharmacodynamics and pharmacogenetics, and heterogeneity in the underlying pathophysiology of sBPD, leading to variability in responses to drug treatment. We seek to describe current drug use in sBPD, some examples of the promise of precision therapeutics, and the need for new classes of medications to be tested for potential benefit.

Abstract

Few medications are available and well tested to treat infants who already have developed or inevitably will develop severe bronchopulmonary dysplasia (sBPD). Infants who develop sBPD clearly have not benefited from decades of research efforts to identify clinically meaningful preventive therapies for very preterm infants in the first days and weeks of their postnatal lives. This review addresses challenges to individualized approaches to medication use for sBPD. Specific challenges include understanding the combination of an individual infant's postmenstrual and postnatal age and the developmental status of drug-metabolizing enzymes and receptor expression. This review will also explore the reasons for the variable responsiveness of infants to specific therapies, based on current understanding of developmental pharmacology and pharmacogenetics. Data demonstrating the remarkable variability in the use of commonly prescribed drugs for sBPD are presented, and a discussion about the current use of some of these medications is provided. Finally, the potential use of antifibrotic medications in late-stage sBPD, which is characterized by a profibrotic state, is addressed.

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ABBREVIATIONS

ADRB2	β_2-adrenergic receptor
BPD	bronchopulmonary dysplasia
CAMP	Childhood Asthma Management Program
CRHR	corticotropin-releasing hormone receptor
DART	dexamethasone for a respiratory trial
F_{IO_2}	fraction of inspired oxygen
htSNP	haplotype-tag single nucleotide polymorphism
NICHD	Eunice Kennedy Shriver National Institute of Child Health and Human Development
PMA	postmenstrual age
SABA	short-acting β-agonist
sBPD	severe bronchopulmonary dysplasia
SNP	single nucleotide polymorphism
SPATS2L	spermatogenesis-associated serine rich 2–like
UGT	uridine diphosphate-glucuronosyltransferase

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

1. Improve their understanding of developmental pharmacology relevant to drugs potentially useful in severe bronchopulmonary dysplasia (sBPD).
2. Explain the rationale for the use of diuretic and anti-inflammatory drugs in sBPD.
3. Recognize the need for improved targeting with new classes of drugs for individualized approaches to the mitigation of sBPD.

INTRODUCTION

Identifying, studying, and widely using medications that mitigate evolving or already established severe bronchopulmonary dysplasia (sBPD) remain daunting challenges for pediatric medical science.

Among the reasons for the current paucity of effective medications is a lack of agreement about who suffers from sBPD (Table 1). (1)(2)(3) Further, the variability in airway reactivity with the respiratory cycle among patients with similar histories and chest radiography findings (4) is only now being slowly addressed. Less lumping and more directed splitting of the subtypes of sBPD, coupled with biomarker availability, would improve individualization of drug use. (5) These changes will help investigators to assess targeted therapies and minimize both overuse and underuse of promising medications that are available currently or expected to become available soon. A targeted strategy opens the door to shorter but impactful clinical trials of medications in meaningfully stratified sBPD subtypes.

TABLE 1. Definition of Severe BPD: Status at 36 Weeks' PMA

NICHD (Jobe and Bancalari) (1)	F_{IO_2} >0.3; or any PPV
Higgins et al 2019 workshop (2)	Invasive PPV with F_{IO_2} ≥0.21; or NIPPV or CPAP or NC >3L/min
Jensen et al (grade 3 BPD) (3)	Invasive PPV; any F_{IO_2}

BPD=bronchopulmonary dysplasia; CPAP=continuous positive airway pressure; F_{IO_2}=fraction of inspired oxygen; NICHD=Eunice Kennedy Shriver National Institute of Child Health and Human Development; NC=nasal cannula; NIPPV= noninvasive positive pressure ventilation; PMA=postmenstrual age; PPV=positive pressure ventilation.

This review summarizes some of the reasons for the shortage of available medications in 2020 for sBPD and what the future may hold for targeted drug development. This review does not include medications targeting pulmonary hypertension in sBPD. Rather, our focus is on the few potentially effective treatments for already established large and small airway disease and lung parenchymal disease, including hyperinflation and hypoinflation.

A major task in the study of sBPD is to establish a definition. Current working definitions have several limitations. One frequently cited limitation is that the definition of sBPD is defined by its therapy. Most contemporary definitions rely on both oxygen and positive pressure usage (Table 1). The use of 36 weeks' postmenstrual age (PMA) as the agreed-upon time for defining sBPD (or other categories) in infants born before 32 weeks' gestation allows interinstitutional comparisons as cross-sectional studies and intrainstitutional comparisons as longitudinal studies. However, this definition means that some infants with sBPD, for instance, those born at 30 to 32 weeks' gestation, will have reached the defining PMA in only a few postnatal weeks. These infants will have started postnatal life with anatomically different lungs than infants born at 22 to 24 weeks' gestation, that is, those who will have much longer timelines before reaching 36 weeks' PMA. This variability in lung development stages can occur in a central to peripheral and/or a cephalad to caudad pattern. In short, variations of sBPD can look similar by degree of respiratory support at 36 weeks' PMA, but that support is often imposed on quite different lung architecture and physiology. This potential heterogeneity in interindividual lung development at the time of medication use contributes to variable clinical responses.

In addition to variable intrinsic lung physiology at the time of drug therapy, developmental pharmacology can help explain drug response or lack thereof. Drug clearance pathways and pharmacokinetics, target organ and drug receptors, and pharmacogenomics all likely contribute to variability in drug response across the spectrum of gestation/PMA.

Incomplete lung development at birth and a vulnerability to superimposed insults create the potential for long-term lung maldevelopment. This maldevelopment may reduce lung function in young adults with uncertain longer-term consequences. (6)(7) Given our capacity to support the most extremely preterm infants successfully and the lack of any breakthrough in preventing extremely preterm birth, much is riding on physicians' ability to mitigate the worst effects of sBPD.

A list of some of the factors challenging drug makers and drug testers is provided in Table 2.

PRINCIPLES OF PHARMACOLOGY

Similar to other neonatal diseases, sBPD is subject to variable and unpredictable efficacy and toxicity of drug therapy. Precision therapeutics is an approach to drug therapy that assumes each infant is unique and aims to account for unique sources in variability when drugs are prescribed. Although physicians tend to focus on dose and clinical response, a key mediator in pharmacology is systemic and local drug exposure. In the NICU, drug exposure can be highly variable even with the same weight-based dose. A number of clinical pharmacology studies aim to identify these sources of variability and introduce novel dosing paradigms that can standardize drug exposure and decrease the variability in drug response.

TABLE 2. **Some Factors Challenging the Development of Medications for sBPD**

Heterogeneous disease under 1 umbrella diagnosis in clinical trials
No available biomarkers to correlate with meaningful clinical outcomes
Complex disorder involving multiple cell types in the lung
Variable impairment to gas exchange with impairment in O_2 and/or CO_2 exchange predominant, likely depending on degree of shunt and high V/Q areas and dead space
Variable development of cystic changes by lobe or region
No readily measurable inflammatory markers for airways and/or parenchyma
Developmental pharmacology and pharmacogenetics
Uncertainty regarding long-term benefits of medications
Must survive to 36 weeks' PMA to establish a diagnosis of sBPD by current criteria

PMA=postmenstrual age; sBPD=severe bronchopulmonary dysplasia; V/Q=ventilation/perfusion.

Ontogeny (development) of drug-metabolizing enzymes and drug target proteins is an important source of interindividual variability. For example, an infant who is born at 23 weeks' gestation and treated with a drug at 4 weeks of age likely metabolizes that drug differently than an infant of similar birth gestational age who is started on the same drug at 8 weeks of age. Although dosing based on weight in part corrects for developmental changes, weight-based dosing often does not capture other development processes. As displayed in Table 3, the levels of protein expression of key hepatic drug-metabolizing enzymes are generally lower at birth (with the exception of CYP3A7) and increase with advancing age. (8) Each enzyme and enzyme class has slightly different trajectories of development. For the uridine diphosphate-glucuronosyltransferase (UGT) enzymes, extensive proteomic profiling has revealed that each UGT has a distinct ontogenic profile, but the expression is generally low at birth and increases within the first few months of age (Figure). (9)

In addition to ontogeny, another major source of interindividual variability in drug exposure and drug response is pharmacogenetics. Genetic variability in drug metabolism and response genes has been studied extensively in other patient populations, but pharmacogenetic studies to improve drug therapy in preterm infants with sBPD are just beginning. The following section will summarize some examples of known pharmacogenetic influences of drug response for drugs commonly used to treat sBPD.

β-Agonists

β-agonist bronchodilator agents have assumed a large role in the treatment of sBPD, with variable benefit. Lessons learned about underlying associations of variability in responses among older patient populations may have relevance to infants with sBPD. Pharmacogenetic studies of β-agonists in adult and pediatric populations have focused on the gene encoding the β_2-adrenergic receptor (*ADRB2*), but other important genes for airway smooth muscle regulation lie within the associated G-protein receptor pathway, the nitric oxide biosynthetic pathway, and other novel loci identified in recent genome-wide studies. The *ADRB2* gene has 9 functionally significant identified variants, including single nucleotide polymorphisms (SNPs), which change the amino acid code, including $Gly^{16}Arg$, $Gln^{27}Glu$, and $Thr^{164}Ile$. (10) Studies of the β-receptor gene showed that patients with asthma who are homozygous for Arg^{16} experienced a greater acute bronchodilator response to a 1-time dose of albuterol compared with those who are homozygous for Gly^{16}. This result was also observed in other asthma populations. (11)

TABLE 3. **Cytochrome P450 (CYP) Protein Expression as Observed in a Data Set of 20 Liver Samples**

CYP	PERINATAL-INFANT GROUP	>1 YEAR
Western blot (pmol/mg)	2 fetuses, 2 newborns, 6 infants, mean (SD)	6 children, 4 adults 2–72 years, mean (SD)
Total CYP	390.3 (189.88)	644.59 (316.37)
Class 1		
CYP3A7	538.7 (200.75)	*96.9 (204.4)*
Class 2		
CYP2B6	*2.65 (5.94)*	*19.36 (23.9)*
CYP3A4/5	173.31 (129.06)	239.40 (162.86)
Class 3		
CYP1A2	*3.27 (6.35)*	24.93 (24.70)
CYP2C9	79.78 (35.98)	74.39 (24.99)
CYP2D6	43.66 (40.15)	53.46 (25.38)
CYP2E1	94.32 (48.18)	136.91 (50.90)

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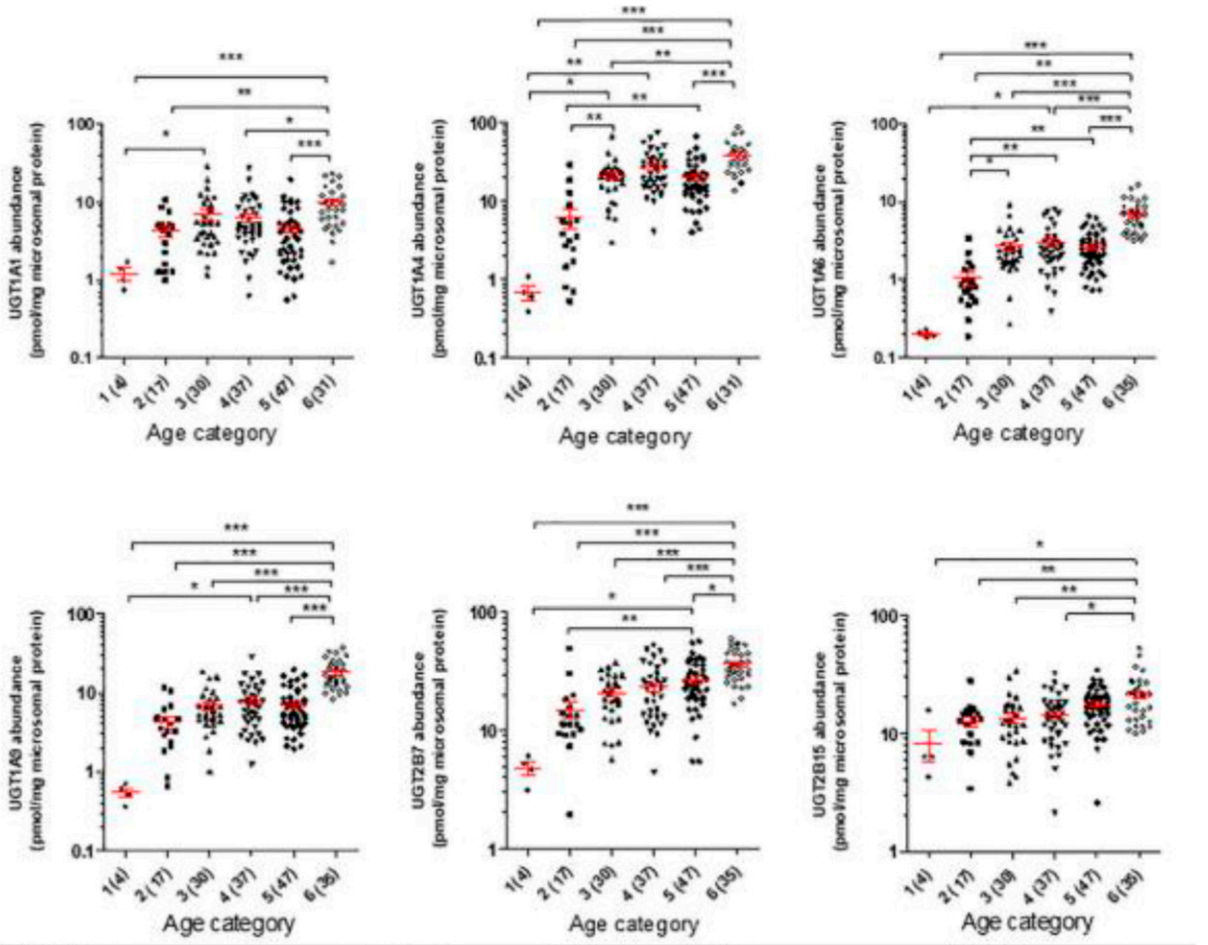
In addition to the β-receptor, other genes have been implicated in drug response. β-agonists bind to ADRBP2 to activate a G-protein–coupled receptor pathway via adenylyl cyclase. The Childhood Asthma Management Program (CAMP) found that variation in the corticotropin-releasing hormone receptor (*CFHR*) gene led to an increased response to inhaled steroids in patients with asthma. (12)(13) Five SNPs of *CFHR* have been associated with the acute bronchodilator response to short-acting β-agonists (SABAs) in children in CAMP and those with asthma in 2 clinical trials. (14)(15)

Nitric oxide signaling is also important for the modulation of a β-agonist response. The CAMP and 3 asthma trial cohorts reported that patients with asthma with an SNP in the arginase 1 *(ARG1)* gene, rs2781659, had an improved bronchodilator response to albuterol. (16) Haplotypes of *ARG1* were able to regulate gene expression in vitro and this was associated with the bronchodilator response to SABAs. (14) Inhibition of arginase leads to an increase of nitric oxide production in animal models of arterial function (17); thus, genetic variation in arginase potentially could alter airway smooth muscle relaxation during β-agonist treatment.

A genome-wide association study by Himes and colleagues (18) identified an SNP within the promoter region of the spermatogenesis-associated, serine-rich 2–like gene (rs295137 in the spermatogenesis-associated serine-rich 2–like gene or *SPATS2L*). (15) This SNP was found to be associated with the acute SABA bronchodilation in 1,644 non-Hispanic white patients with asthma from 6 clinical trial cohorts; the Severe Asthma Research Program had similar findings in 501 subjects. (15) The importance of *SPATS2L* in the ADRBP2 pathway was confirmed with siRNA knockdown of this gene; this led to increased ADRBP2 expression in human airway smooth muscle cells. (18)

A genome-wide association study in Latino children with asthma (Genes, Environment and Admixture in Latino Asthmatics Cohort) identified rare genetic variants associated with the SABA response within solute carrier genes on chromosome 14 (Arg585Gln in *SLC24A4*) and chromosome 1 (*SLC22A15*). (19) This same study identified on immunohistochemistry and quantitative polymerase chain reaction that SLC22A15 was expressed in bronchial epithelial cells, confirming the potential importance of solute carrier genes on β-agonist response. (19)

In summary, this rich pharmacogenomic scientific background offers opportunities to improve targeting of multiple medications, including SABAs, in sBPD. Increased research on the mechanisms of variability in β-agonist response could lead to improved efficacy of this class of drugs. Given the pharmacogenetic data, it is possible that augmentation or modulation of complementary and interesting smooth muscle relaxation signaling pathways could alter drug response and lead to improved outcomes.



Age category	Age range	Total	Gender			Ethnicity						
			M	F	U	C	AA	His	PI	NA	A	U
Neonatal (Category 1)	0 to 27 d	4	3	1	-	2	2	-	-	-	-	-
Infancy (Category 2)	28 to 364 d	17	15	2	-	8	8	1	-	-	-	-
Early childhood (Category 3)	1 to < 6 yr	30	17	12	1	12	6	2	-	1	-	9
Middle Childhood (Category 4)	6 to < 12 yr	37	20	16	1	17	5	-	1	-	-	14
Adolescence (Category 5)	12 to 18 yr	47	30	17	-	27	6	1	-	-	-	13
Adulthood (Category 6)	>18 yr	39	15	24	-	37	1	-	-	-	1	

Figure. Developmental trajectories of six major uridine diphosphate-glucuronosyltransferases from human liver samples. From Bhatt DK, Mehrotra A, Gaedigk A, et al. Age- and genotype-dependent variability in the protein abundance and activity of six major uridine diphosphate-glucuronosyltransferases in human liver. *Clin Pharmacol Ther.* 2019;105(1):131–141.

Inhaled and Systemic Corticosteroids

Evidence from studies in pediatric asthma show that genetic variation can contribute to meaningful differences in the clinical effect of steroids (increases in forced expiratory volume [FEV_1]). Single-nucleotide variants in multiple genes in steroid response or steroid modification pathways are associated with small but statistically significant effects. (20) Genetic variability in corticotrophin-releasing hormone receptor 1 (*CRHR1)* is associated with inhaled corticosteroid response in multiple study populations, including 470 adults with asthma (fluniso-lide, primary outcome percentage change in FEV_1 in 8 weeks, 88% white), 311 children with asthma (budesonide, primary outcome percentage change in FEV_1 in 8 weeks, 100% white), and 336 adults (triamcinolone, primary outcome percentage change in FEV_1 in 6 weeks). Haplotype-tag SNPs (htSNPs) in *CRHR1* are able to separate the entire population into 4 distinct haplotypes with frequencies of 0.46, 0.27, 0.21, and 0.05. The htSNPs significantly associated with phenotypic response are rs1876828, rs242939 (first 2 populations), and rs1876828 (all 3 populations). (21) These htSNPs are not thought to affect protein function but are marker SNPs in linkage disequilibrium with either protein-altering variants, alternate splice sites, promoter region variants, or regulatory region changes that affect the steroid pathway.

Compared with wild-type carriers, individuals homozygous for variant haplotypes in *CRHR1* have double to quadruple the phenotypic response in lung function when treated with inhaled steroids. (22) *CRHR1* is the primary receptor responsible for regulating the release of adrenocorticotropic hormone, which regulates endogenous cortisol levels, and thus plays a pivotal role in steroid biology. If *CRHR1* basal activity (genetically regulated) determines pretreatment endogenous steroid levels, then it may predispose individuals to varying responses from exogenously administered steroids.

Genetic variation in *CRHR1* is associated with the degree of respiratory response to systemic hydrocortisone and dexamethasone in BPD. (23) Preterm infants who carry the risk allele in *CRHR1* display less of a decrease in the respiratory severity score on day 7 of treatment compared with those who do not carry the risk allele. In this retrospective cohort, all of the infants who continued to get worse (increasing respiratory severity score) despite systemic steroids were risk-allele homozygotes. This finding has biologic plausibility. *CRHR1* modulates corticosterone production through control of adrenocorticotropic hormone–regulated hypothalamic pituitary adrenal axis function. (24) Although not yet proven, SNPs in *CRHR1* may affect baseline endogenous corticosteroid levels and baseline airway inflammation, leading to variation in response to exogenous administration of systemic corticosteroids. Variability in patient response to corticosteroids was attributed to the genetic variation in *CRHR1* in multiple diseases, including chronic obstructive pulmonary disease, (25) asthma, (22) and persistent pulmonary hypertension of the newborn. (26) The neonatal respiratory response to exposure to maternal corticosteroid therapy prenatally was found to be associated with genetic variation in the ligand for *CRHR1*, corticotropin-releasing hormone. (27) Preterm neonates with the risk allele at rs7225082 were more likely to need continuous positive airway pressure/ventilator support because of a decreased response to maternal corticosteroids and had a poorer response to postnatal corticosteroids. (27) Because of the significance of this gene in other patient populations, the biologic plausibility, and the same directionality of effect in 2 patient populations, it is possible that genetic variation in *CRHR1* plays an important role in the corticosteroid response of patients with sBPD.

CURRENT STATUS OF MEDICATION USAGE IN INTENSIVE CARE UNITS

Medication use needs further rigorous study and thoughtful clinical application throughout pediatrics. The topic is particularly relevant to the quality of care in infants with sBPD, because this subpopulation is frequently exposed to many medications. Contributing factors include prolonged postnatal hospitalizations, high disease severity, and the common presence of various comorbidities of preterm birth in infants with sBPD. A recently published study quantified the extent of these medication exposures. (28) Using the Pediatric Health Information System database, the authors identified 3,252 infants with a birth gestational age of less than 32 weeks who developed sBPD while admitted to US children's hospitals. All medication exposures between 36 weeks' PMA and either hospital discharge or 1 year of age were recorded. Infants with sBPD were exposed to a median (interquartile range) of 30 (17–45) distinct medications. By comparison, infants discharged from NICUs managed by the Pediatrix Medical Group had a median of 4 medication courses, suggesting 7-fold higher medication exposure in preterm infants developing sBPD. (29) A report of children admitted to US children's hospital pediatric intensive care units identified 50% fewer medication exposures, with an average of 20 during hospitalization. (30) These comparisons highlight the magnitude of medication exposures in infants with sBPD.

Although medication exposures in patients with sBPD are frequent, the extent varies between centers. This is true for the overall number of medication exposures and the use of specific therapeutic classes. In the previously cited report, Bamat and colleagues noted marked variation between centers in the number of cumulative medication exposures despite statistical adjustment for differences in case-mix, with a greater than 2-fold difference in estimated medication exposures between the lowest and highest utilizing centers. (28) In studies of infants with evolving or established BPD, Slaughter and colleagues used the Pediatric Health Information System database to demonstrate marked between-center variation in 2 commonly used therapeutic classes: inhaled bronchodilators and diuretics. (31)(32) The percentage of infants exposed to inhaled bronchodilators ranged from 0% to 81% between centers, whereas diuretic exposures of more than 5 days' duration ranged from 4% to 86%. (31)(32). These findings are consistent with a more recent report of the single-day point prevalence of select therapeutic classes among 8 centers participating in the BPD Collaborative Group, a national multicenter effort focused on the treatment of infants with sBPD. A wide utilization range was noted not only for inhaled bronchodilators (0%–67%) and diuretics (28%–87%), but also for inhaled corticosteroids (0%–87%), systemic corticosteroids (0%–27%), and antireflux medications (6%–50%). (33) The lack of research evidence to guide

professional consensus is known to increase unwarranted practice variation. (34) The uncertain value of nearly all medications in sBPD likely contributes to the variation noted in these studies.

The most frequent therapeutic classes and individual medications used in infants with sBPD are listed in Tables 4 and 5. (28) Both tables exclude medications associated with nutritional support, such as vitamins and electrolyte supplements, as well as medications delivered as part of routine health care maintenance, such as vaccinations. Each table displays the percentage of patient days in which a therapeutic class or medication was used, in rank order. Diuretics, the most frequently used class of medications, were administered in 57% of patient-days. Within the diuretic group, furosemide was the most common agent (33% of patient-days). Other diuretics (chlorothiazide, spironolactone, or combinations such as hydrochlorothiazide with either amiloride, spironolactone, or triamterene) were found to be among the top 20 most frequently used medications. Other commonly used agents included systemic corticosteroids (16% of days), hydrocortisone (8% of days), prednisolone (4% of days), and dexamethasone (3% of days). Frequent bronchodilator use (15% of days) was largely explained by the use of albuterol (11% of days), whereas frequent inhaled corticosteroid use (13% of days) was largely explained by the use of budesonide (12% of days). The presence of therapeutic classes not directly targeting improvements in lung function points to the high disease severity and frequent comorbidities present in sBPD. The frequent use of anesthetics, analgesics, and sedatives likely reflects the common need for procedural and surgical interventions, apprehension that movement and agitation while receiving mechanical ventilation can pose threats to the stability of pulmonary gas exchange, and concern that endotracheal intubation leads to patient discomfort. The frequent use of anti-infective agents likely reflects concerns for comorbid infections, whereas the frequent use of antireflux and promotility agents highlights common concerns that comorbid gastrointestinal dysmotility and gastroesophageal reflux can exacerbate lung injury. Although medication use in sBPD typically has a sound rationale and plausible benefit, it is important to note that evidence of pharmacologic efficacy and safety in this subpopulation is broadly lacking. As such, clinical decisions about medication use should be made judiciously.

WIDELY USED MEDICATIONS AND RATIONALE FOR THEIR USE

Diuretics

Diuretics are a group of structurally heterogeneous medications with the shared pharmacologic characteristic of increasing the production of urine. The most-used diuretics in sBPD increase urine production by inhibiting or decreasing the expression of ion channels responsible for the reabsorption of electrolytes and water from the renal tubules. Furosemide inhibits the Na-K-Cl cotransporter in the thick ascending loop of Henle, chlorothiazide inhibits the sodium-chloride transporter in the distal convoluted tubule, and spironolactone antagonizes aldosterone at the mineralocorticoid receptor, thereby reducing the expression of the epithelial sodium channel in the distal tubule and collecting duct.

The rationale for using diuretics in sBPD has physiologic plausibility. BPD is caused by injury to the developing lung, disrupting airway, parenchymal, vascular, and lymphatic development. Excess pulmonary blood flow, capillary leak, and inadequate lymphatic fluid reabsorption all contribute to pulmonary edema and impaired pulmonary function. (35)(36) Pharmacotherapies reducing this edema through diuresis could plausibly improve pulmonary mechanics, gas exchange, and ultimately, pulmonary outcomes of clinical importance.

However, there is a paucity of clinical research on diuretics that can be confidently extrapolated to infants with established sBPD. The clinical phenotype of BPD has changed over time, with a transition from the "old" to "new" BPD now widely accepted. (37)(38) The old BPD was characterized by lung inflammation and fibrosis. Although these remain features in some infants with sBPD, the new BPD is often characterized by greater degrees of pulmonary maturational arrest. Drivers of this phenotypic evolution include the increased survival of infants with lower gestational ages and the adoption of antenatal corticosteroids, postnatal surfactant, and strategies to minimize ventilator-induced lung injury, practices that became widespread in the 1990s. (37) Definitions of severe BPD have also changed. sBPD was defined in 2001 and is determined at 36 weeks' PMA (Table 1). Most studies of diuretic use in BPD date from the 1980s and early 1990s and enrolled preterm infants before 36 weeks' PMA—developmentally less mature infants with "old," evolving BPD. The preceding section on pharmacology mentions the limitations of extrapolating data from younger preterm infants to developmentally distinct older infants with established sBPD. In the case of diuretics, the ontogeny of transporters involved in furosemide renal clearance, driving both elimination and pharmacodynamic effect in the renal tubule, provides a concrete example. Renal clearance first increases gradually after birth as glomerular filtration rises with postnatal age, but then increases exponentially when tubular secretion matures and plays a prominent role in furosemide urinary excretion

TABLE 4. **Top 10 Most Frequently Used Therapeutic Classes in Infants with sBPD Admitted to US Children's Hospitals**

RANK	MEDICATION	PERCENTAGE OF DAYS USED
1	Diuretics	57
2	Anesthetics/analgesics/sedatives	37
3	Antireflux and promotility agents	33
4	Anti-infective agents	27
5	Anticoagulants	20
6	Systemic corticosteroids	16
7	Bronchodilators	15
8	Inhaled corticosteroids	13
9	Stimulants	12
10	Gastrointestinal agents	11

sBPD=severe bronchopulmonary dysplasia.
Adapted from Bamat NA, Kirpalani H, Feudtner C, et al. Medication use in infants with severe bronchopulmonary dysplasia admitted to United States children's hospitals. J Perinatol. *2019;39(9):1291–1299.*

around 32 weeks' PMA. (39) Because of this, inferences from therapeutic strategies studied in younger preterm infants may not apply to older infants with established BPD. These historical and pharmacologic considerations underscore the limitations of extrapolation and the importance of conducting pharmacologic research in contemporary cohorts of infants with established sBPD.

With these limitations acknowledged, the most relevant clinical research on diuretic therapy in sBPD does not provide evidence of clinical efficacy. For furosemide, 4 studies published between 1983 and 1990 prospectively enrolled a total of 47 subjects in small cohorts that included some subjects who would now be classified as having sBPD. (40)(41)(42)(43) Together, these studies suggest that furosemide may improve pulmonary mechanics, but has an uncertain impact on pulmonary gas exchange. No clinically important outcomes have been reported. Further, the existing data are at least 30 years old and come exclusively from spontaneously breathing infants without ventilatory support, limiting their relevance to infants with "new" sBPD. Clinical research on chlorothiazide and spironolactone in sBPD has focused on the combined use of these medications. Four such studies enrolling subjects consistent with a classification of sBPD were published between 1984 and 1994. (41)(44)(45)(46) In a masked crossover trial, Kao et al (44) identified improved airway resistance and pulmonary compliance after a week of combination therapy in 10 subjects. (44) In contrast, Engelhardt and colleagues did not detect improvements in pulmonary mechanics or oxygenation among 21 subjects randomized to hydrochlorothiazide and spironolactone versus placebo for 6 to 8 days. (42) Lastly, in the most substantial study of diuretics in sBPD, Kao and colleagues enrolled 43 subjects who underwent extubation from mechanical ventilation but required supplemental oxygen in a parallel group trial, with randomization to diuretics or placebo until oxygen use was discontinued (~ 4–5 months) and subsequent follow-up at 1 year PMA. Four weeks after enrollment, infants receiving diuretics had improved pulmonary mechanics and required lower fraction of inspired oxygen (F_{IO_2}) to meet target oxygen saturations. However, no difference was observed in the total duration of supplemental oxygen, and the gains in pulmonary mechanics dissipated after therapy was discontinued. At 1-year follow-up, weight, height, and number of rehospitalizations were similar between groups. (46) Therefore, most of the existing data suggest that diuretic combinations acting on the distal tubules improve pulmonary mechanics, with added uncertainty regarding improved gas exchange and no data supporting long-term clinically meaningful benefits. As with existing furosemide studies, all study subjects were off ventilatory support, limiting extrapolation.

It is worth emphasizing that diuretics, the most frequently used therapeutic class in sBPD, broadly lack research evidence of clinically important efficacy. Meanwhile, safety remains uncertain. The ion channels targeted

TABLE 5. **Top 10 Most Frequently Used Therapeutic Classes in Infants with Severe BPD Admitted to United States Children's Hospitals**

RANK	MEDICATION	PERCENTAGE OF DAYS USED
1	Furosemide	33
2	Chlorothiazide	19
3	Heparin	18
4	Lorazepam	13
5	Morphine	12
6	Budesonide	12
7	Caffeine	12
8	Albuterol	11
9	Ranitidine	11
10	Lansoprazole	11
11	Ursodiol	10
12	Spironolactone	9
13	Levothyroxine	8
14	Sildenafil	8
15	Hydrocortisone	8
16	Midazolam	7
17	Phenobarbital	7
18	Acetaminophen	6
19	Vancomycin	6
20	Diuretic combinations	6

Adapted from Bamat NA, Kirpalani H, Feudtner C, et al. Medication use in infants with severe bronchopulmonary dysplasia admitted to United States children's hospitals. J Perinatol. *2019;39(9):1291–1299.*

by diuretics are expressed in various tissues, and possible harm includes renally mediated concerns such as electrolyte derangements, renal dysfunction, and metabolic bone disease, but also extends to extrarenal concerns such as maintenance of the patent ductus arteriosus and ototoxicity with potentially irreversible hearing loss. (47)(48) Further research to determine both efficacy and safety is urgently needed.

Systemic and Inhaled Corticosteroids

Few medications have evoked as much scrutiny as systemic postnatal corticosteroids, especially given that cost is not a primary driving factor. From 1983, when the first controlled trial of dexamethasone for amelioration of BPD was published, until the present, postnatal steroid use has been based on the assumption that inflammation and fluid retention in the lungs are important to the pathophysiology of evolving BPD or sBPD. (49) Dose, duration of treatment, objective benefit, and sustained benefit, if any, have all been difficult to determine. As BPD has evolved into a very different disorder than that found in 1983, postnatal steroid use continues to be controversial but common. In a recent randomized trial of extremely preterm infants at high risk of developing sBPD, postnatal systemic corticosteroids were used in 74.9% of enrollees. (50) The uncertainty surrounding corticosteroid use for BPD was shown in the 2015 review by Stoll et al. (51) In the longitudinal data set of the Neonatal Research Network, BPD is the only complication of extreme prematurity that continues to increase in association with greater survival and more profoundly preterm gestational ages. Postnatal corticosteroid use, though common, has not returned to 1990s levels.

Implicit in the case for systemic or inhaled corticosteroid use in sBPD is that an important part of the pathophysiology can be targeted and, by so doing, create sufficient improvement to obtain sustained reduction in other aspects of support, such as reduced F_{IO_2} and its associated local reactive oxygen species production. Improving lung parenchymal inflammation and edema, reducing resistance to airflow in small airways indirectly, reducing the risks of barotrauma, or suppressing inflammation that persists or recurs periodically in older infants with sBPD may all occur with corticosteroid use. These potential changes should improve airflow and ventilation-perfusion matching.

More recently, in line with the goal of individualized therapeutics in neonatology, efforts have been under way to identify, before treatment, which infants might show clinically meaningful and sustained benefits from corticosteroid administration. (52) Using some combination of pharmacometabolomics and pharmacogenomics, these efforts aim to target the undoubted benefits of corticosteroids much more precisely and direct their earlier use (52) more narrowly than at present. One trend for postnatal systemic use has been a smaller overall dose. Two variations of the commonly used dexamethasone for a respiratory trial (DART) produced no differences in meaningful clinical outcomes between cumulative doses of 0.72 mg/kg and 0.89 mg/kg. (53) In a second retrospective study, earlier use (defined as 2–4 weeks after delivery) appeared to result in objective benefits not found in infants of similar gestation who were treated with a DART course after 40 days of age. (54) These results, if confirmed and combined with tools for endotyping individual patients, could provide meaningful amelioration of disease by targeting a particularly critical

time in the pathophysiology of evolving BPD. Still, questions remain about usage in 22- to 25-week gestational age infants, who may be started at typically 3 or 4 weeks of age—still a time of profound structural immaturity of the lungs. (55) For these infants, the BPD predictor (56) takes into account gestational age at birth and therefore may be useful as a tool for guiding systemic steroid use in such infants with profound pulmonary immaturity.

Inhaled corticosteroids have a seductive rationale: the target organ can be reached via the airways, with the goal to maximize efficacy and minimize systemic adverse effects. Thus, inhaled corticosteroids have been started and used commonly in all phases of the evolution of sBPD. Some infants with sBPD may benefit from sustained use of inhaled steroids, assuming the targeted part of the airways can be reached without concomitant disruption to other support, such as loss of lung end-expiratory volume if the patient needs to be disconnected from the support system delivering positive pressure ventilation. Some additional issues with inhaled steroids include variable delivery and variable but more than trivial systemic uptake, especially with prolonged treatment, thereby offsetting the beneficial effects of localized delivery. For the individual patient, it can be very difficult to assess the overall benefit, if any, of starting or continuing this class of medication by this route. This uncertainly is well reflected in a recent large systematic review of both bronchodilator and corticosteroid therapies in infants with BPD. The authors conclude that it remains unclear if either class of inhaled therapies improves long-term pulmonary outcomes. (57)

Other Anti-inflammatory Medications

Two nonsteroidal anti-inflammatory classes of medications that have been evaluated in sBPD are leukotriene receptor antagonists and mast cell membrane–stabilizing agents. Cysteinyl leukotriene blockers have been used effectively in asthma. Two small studies have been reported in different stages of BPD. Rupprecht et al (58) reported that montelukast was effective as rescue treatment in 8 of 9 infants with life-threatening late-stage sBPD. Initial enthusiasm for this agent was dampened by a later report of a clinical trial involving 66 infants in early-stage BPD (59) who failed to show drug-related reduction in progression to moderate or severe BPD. Nonetheless, although not useful as an emergency medication, montelukast or another member of this class of drugs may be useful in selected infants to reduce bronchoconstriction, mucus production, and lung microvascular permeability. For a detailed review of other specific inflammatory modulators that may be helpful in ameliorating BPD in the future, please see the review by Savani. (60)

Bronchodilators

Bronchodilators target dilation of the bronchi and bronchioles, thereby improving airway resistance, work of breathing, and pulmonary gas exchange. This is typically achieved through the relaxation of airway smooth muscle. Albuterol is the most commonly used bronchodilator in sBPD. (28) Albuterol (also known as salbutamol) is a selective β_2-adrenergic agonist of airway smooth muscle. Although intravenous formulations of albuterol are available and have been studied in sBPD, (61) administration typically occurs via inhalation, either through nebulization or pressurized aerosolization. (62) The use of bronchodilators in sBPD hinges on the assumption that most infants with sBPD have obstructive airflow patterns. (4)(63)

Less well evaluated is the potential role for inhaled ipratropium, a cholinergic receptor antagonist, in patients with sBPD. In 1998, De Boeck et al (64) demonstrated in a small group of 1-year-old post-BPD patients that this agent failed to improve airway resistance or other measurements of lung mechanics. The authors speculated that late-stage BPD is characterized more by fibrosis than by airway reactivity or bronchoconstriction and that inhaled medications, which may be helpful in earlier stages of the disorder, may not be helpful later. However, 1998 was a generation ago in terms of the evolution of sBPD. No systematic study, to the authors' knowledge, has been conducted evaluating this drug in a contemporary population of sBPD infants.

Limited clinical research data inform the use of bronchodilators in infants with sBPD. The updated Cochrane review did not identify any randomized clinical trials comparing bronchodilators to control or placebo treatment in infants with established BPD of any severity. (58) Although Kirpalani et al (61) used a single-arm before-and-after trial of intravenous albuterol in 6 ventilator-dependent infants with sBPD, they reported no consistent improvement in gas exchange lasting greater than 1 hour. (57) More recently, Shepherd and colleagues included an evaluation of bronchodilator response to aerosolized albuterol in a prospective cohort study classifying sBPD phenotypes on the basis of infant pulmonary function testing. (4) Bronchodilator responsiveness was defined as a more than 10% increase in FEV_1 at 0.5 seconds and was noted in 61 (66%) of the 93 subjects tested. (4) Moreover, the authors noted an association between phenotype classification and the likelihood of responding to albuterol, with a response noted in 74% of infants classified as having primarily obstructive disease, but only 25% of infants classified as having primarily restrictive disease. This finding is important because it provides concrete data to support the idea that infants with sBPD represent a group of infants with heterogeneous

(albeit sometimes overlapping) underlying disease pathophysiology. Isolating infants with specific phenotypes is of critical importance to testing and identifying effective pharmacotherapies. Research evaluating the efficacy of albuterol on clinically important outcomes in select phenotypes of sBPD infants is still needed.

Medications for Gastroesophageal Reflux Disease

One goal of treatment for sBPD is to mitigate ongoing insults to the lungs and airways. Reflux of milk or stomach contents has the potential to irritate and inflame large and smaller airways, and aspiration of these contents can incite or exacerbate parenchymal inflammatory response. Although these possibilities form a seemingly compelling rationale for therapy, little evidence is available to suggest that antireflux medications are helpful, especially when used over very long periods. Transpyloric feedings may mitigate the risk to the lungs but this manipulation of continuous feedings via tubes passed through the pyloric valve carries its own risks. Thoughtful individualization of either medication use and/or transpyloric feedings is required. Establishing an objective sign of improvement for each infant under consideration for this approach is essential.

FUTURE DEVELOPMENTS: ROLE OF ANTIFIBROSIS MEDICATIONS IN sBPD

Severe BPD manifests elements of many different pulmonary disorders arising later in life, though it is identical to none. Pertinent similar disorders include pediatric asthma, pulmonary hypertension, chronic obstructive pulmonary disease, and progressive interstitial pulmonary fibrosis. It is intriguing to consider selective carefully regulated use of medications that affect the progression of pulmonary fibrosis and remodeling. If given during maximum fibrotic development, a time point that likely differs among patients, these medications may diminish pulmonary fibrosis. Antifibrotic medications include members of a class of pyridines, which act to suppress fibrosis by inhibiting, at least in vivo, transforming growth factor β promotors. One medication in this class, pirfenidone, is used widely in adults with interstitial pulmonary fibrosis and biosimilar disorders. (65)

CONCLUSIONS

Two themes link all the medication summaries in this review. One theme is that, without deep phenotyping and endotyping of individual patients, informed by meaningful biomarkers of evolving stages of progression of sBPD, the best-designed and executed clinical trials will be fraught with risks of committing both type 1 and type 2 errors. Physician investigators must become more rigorous in the study of drugs to treat sBPD. Clear-cut criteria, as assessed using precise objective measures such as improvement in pulmonary gas exchange, or decrease in the work of breathing, or improvement in ventilatory index, are often lacking, both at the beginning of therapy and at predetermined post-therapy points. Physicians and researchers must then rely on subjective assessments of improvement, which can vary widely over time in the same patient and be assessed differently by different observers.

In many nurseries, this situation has led to continuing seemingly safe medications in many infants who may no longer or never did benefit from their use. Our recommendation is that physicians initiating the medications discussed in this article use the most clear-cut possible baseline status assessment and expect to have a clinically relevant benefit from the medication. In other words, start with the therapeutic endpoint already established. In some cases, this would include baseline gas exchange values or even estimates of clinical work of breathing. In other cases, more objective but difficult to quantify assessment of airway mechanics should be identified at baseline. These are tentative but important steps toward an individualized approach to therapeutics.

The second theme is that sBPD can become a less common disorder because of the tools now available to treat infants born at or after 30 weeks' gestation. However, for extremely preterm infants, our goal must continue to be mitigation of this disorder. Far greater challenges have been overcome in other domains of modern medicine. It is past time to do so for sBPD.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the management of bronchopulmonary dysplasia/chronic lung disease.

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1. A 10-week old infant who was born at 28 weeks' gestational age is considered to have severe bronchopulmonary dysplasia (sBPD), as she is continuing on mechanical ventilation and has had a clinical history consistent with that diagnosis. She is receiving albuterol as adjunctive therapy. Which of the following statements concerning β-agonist treatments and sBPD is correct?
    A. All preterm infants with sBPD have a very consistent, positive response to albuterol, but the effects tend to be relatively mild.
    B. The main pathway for improving sBPD is through cholinergic receptors in pulmonary β cells.
    C. β-agonists bind to the β_2-adrenergic receptor to activate a G-protein–coupled receptor pathway via adenylyl cyclase.
    D. Inhaled nitric oxide in combination with albuterol will result in strong smooth muscle contraction in the airway.
    E. Although variations in β_2-adrenergic receptor gene expression have been observed, there has been no correlation with any clinical findings.
2. A 27-week gestational age infant is now 10 weeks old and continues to require respiratory support in the form of positive pressure ventilation and oxygen. He has received several courses of hydrocortisone in an attempt to improve respiratory function. If the infant carries the risk allele in *CRHR1*, which of the following is most likely to be present compared with an infant who does not carry the risk allele?
    A. Less decrease in respiratory severity score on day 7 of treatment with systemic hydrocortisone.
    B. More chance of discontinuing continuous positive airway pressure earlier.
    C. Less risk of developing asthma in childhood.
    D. Increased risk of late-onset intraventricular hemorrhage.
    E. The orientation of the larynx is more anterior and superior.
3. A preterm infant born at 25 weeks' gestational age is now at a corrected age of 36 weeks. The infant continues to receive nasal cannula oxygen at 0.5 L/min at a fraction of inspired oxygen of 100%. She is receiving furosemide daily. Which of the following statements concerning diuretics and BPD is correct?
    A. Diuretics, and particularly furosemide, are rarely used in the NICU in patients with BPD.
    B. The primary action of furosemide is inhibiting the Na-K-Cl cotransporter in the thick ascending loop of Henle.
    C. While there is fairly strong evidence for the sustained effectiveness of furosemide and reducing oxygen requirement in BPD, the evidence is strongest for those considered older patients with "new BPD" of the current era.
    D. Although effectiveness in the various subgroup populations of preterm infants has not been fully established, one positive aspect of furosemide is the lack of any adverse effects in very preterm infants at each stage of development.
    E. The largest benefit for BPD, with the use of furosemide and diuretics in general, has been an observed decrease in oxygen duration and earlier discharge from the hospital in several large multicenter randomized clinical trials.

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4. A 10-week-old infant born at 27 weeks' gestational age has had fluctuating need for respiratory support. She has recently received a course of hydrocortisone. What is the primary rationale for the use of corticosteroids in BPD?
    A. Increasing smooth muscle relaxation by activating endothelial receptors.
    B. Reducing systemic vascular resistance to increase oxygen delivery to vital organs.
    C. Increasing the viscosity of mucus to reduce mucus plugging.
    D. Improving lung parenchymal inflammation and edema, reducing resistance to airflow in small airways indirectly, reducing the risks of barotrauma, or suppressing inflammation.
    E. Increasing fluid clearance by activating receptors in the distal renal vasculature.
5. An infant born at 24 weeks' gestational age is now 40 weeks' corrected age and continues to have an oxygen requirement. Several strategies have been attempted to improve respiratory function. Which of the following statements about various adjunctive strategies for respiratory care is described most appropriately?
    A. Montelukast has been shown to be an effective preventive medication for BPD when used during the first week after birth for extremely preterm infants.
    B. Inhaled ipratropium is a β-agonist that has been found to be most effective in late-stage BPD.
    C. Several randomized trials have shown that transpyloric feedings improve both feeding tolerance and respiratory symptoms, but only if consistently performed from the first week after birth.
    D. Pirfenidone, a drug used for adults with interstitial pulmonary fibrosis, is in a class of pyridines, and could act to suppress fibrosis by inhibiting transforming growth factor β.
    E. High-dose albuterol given daily as a preventive therapy during the first 2 weeks after birth has been effective in reducing the incidence of BPD, but only for infants born at 22 to 24 weeks' gestational age.

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