SEVERE BRONCHOPULMONARY DYSPLASIA EVALUATION AND MANAGEMENT

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PURPOSE: To standardize care of severe bronchopulmonary dysplasia at postmenstrual age ≥ 36 weeks gestation.

LEVEL: Interdependent (*requires a physician order)

SUPPORTIVE DATA: Bronchopulmonary dysplasia (BPD) is commonly defined as the need for supplemental oxygen for at least 28 days in infants born prior to 32 weeks gestation, and is divided into 3 severity grades (mild, moderate, or severe) based on respiratory support needs at 36 weeks postmenstrual age (see table below). Severe BPD occurs in about 16% of infants born prior to 32 weeks and carries a 5% risk for death after discharge. Centers that have standardized care of severe BPD have shown improved morbidity and mortality outcomes with over 75-80% survival to discharge.

Table I. BPD definition with severity

BPD severity	Definition (Modified from Jobe and Bancalari[4])	Relative incidence (Data from Ehrenkranz et al[5])	Postdischarge mortality (Data from Ehrenkranzet al[5])
None	O_2 treatment <28 d and breathing room air at 36 wk PMA or discharge home, whichever comes first	23.1%	1.8%
Mild	O_2 treatment at least 28 d and breathing room air at 36 wk PMA or discharge home, whichever comes first	30.3%	1.5%
Moderate	O_2 treatment at least 28 d and receiving <30% O_2 at 36 wk PMA or discharge home, whichever comes first	30.2%	2.0%
Severe (type 1)	O_2 treatment at least 28 d and receiving ≥30% O_2 or nasal CPAP/HFNC at ≥36 wk PMA	16.4%	4.8%
Severe (type 2)	O_2 treatment at least 28 d and receiving mechanical ventilation at ≥36 wk PMA.		

HFNC, high flow nasal cannula; *O_2*, oxygen.

For infants with severe BPD who are 37-40 weeks postmenstrual age, goals of care should to be directed away from a lung protective strategy to a strategy that optimizes respiratory management and reduces work of breathing in favor of lung growth and healing. In addition, increased clinical stability improves tolerance of developmental therapies, which are likely to improve long-term neurodevelopmental outcomes.

RISK FACTORS FOR SEVERE BRONCHOPULMONARY DYSPLASIA

- Extreme prematurity, male sex, white race
- Intrauterine growth restriction
- Oligohydramnios
- Prolonged time on ventilator
- Hypoxia, hyperoxia
- Inflammation, perinatal or postnatal infections

BPD SCREENING

1. If <32 weeks gestation at birth and requires supplemental oxygen for at least 28 days, add BPD to problem list.
2. At 36 weeks corrected gestation, all preterm infants on respiratory support (oxygen or flow), will undergo BPD stratification testing. Update problem list to include BPD severity.
    a. Please see oxygen reduction challenge testing guideline at your institution.

3. Any infant found to have moderate to severe BPD will undergo echocardiogram to screen for pulmonary hypertension (PH). In addition, consider screening infants with mild BPD and recurrent, severe cyanotic episodes.
    a. Echocardiogram parameters to note:
        i. Tricuspid regurgitant jet velocity (TRJV)
        ii. Shunt direction
        iii. Right ventricular (RV) function
        iv. Ventricular septal position
        v. RV dilation and hypertrophy
        vi. Shunt gradient
        vii. Tricuspid annular place systolic excursion (TAPSE)
        viii. Pulmonary regurgitant velocity
        ix. Pulmonary artery acceleration time (PAAT)
        x. Left ventricular (LV) size and hypertrophy, LV systolic and diastolic function
        xi. Pericardial effusion
        xii. Structural abnormalities, shunts, and pulmonary artery or vein stenosis
        xiii. Concurrent systolic blood pressure

Table III. Echocardiogram findings of pulmonary hypertension and its severity

None: RVSP <1/3 systemic pressure by TR gradient; septal position rounded and committed to LV; no RVH; normal RV size and function; If present, large VSD or PDA gradients suggesting <1/3 systemic RV pressures (Ao pressure – gradient = PA pressure)
Mild: RVSP 1/3-1/2 systemic pressure; septal flattening in systole, mild RVH and RV dilatation, RV function may be normal.*
Moderate: RVSP ½-2/3 systemic pressure; septum flat or with late systolic posterior bowing, moderate RVH or dilatation, RV may have reduced function*.
Severe: RVSP >2/3 systemic pressure; If present, shunt with predominant R-L gradient, pansystolic posterior septal bowing, Severe RVH, RV dysfunction, RV dilatation, "low-velocity" shunting across PDA or VSD.*

Dilated right atrium, right to left atrial shunt, posterior bowing of the atrial septum, dilated inferior vena cava and dilated coronary sinus are also evidence of RA hypertension and RV diastolic dysfunction.
*RV size, hypertrophy, and function will depend on the duration of PH and should not be used as measures of RV pressures, but as supportive evidence.

    b. If no PH evident, continue to rescreen every month until respiratory status significantly improved.
    c. If PH is present, see management recommendations below.
4. For infants with severe BPD, consider referral to SBPD Team for evaluation and possible transfer to BCHO.

BPD MANAGEMENT

1. Ventilation management after 36-40 weeks postmenstrual age (PMA).
    a. For noninvasively ventilated infants, preferred ventilation modes are HFNC, CPAP, or NIV/NAVA
    b. For invasively ventilated infants, attempt extubation. If unable to wean to minimal settings, consider facilitating extubation with hydrocortisone or dexamethasone burst. If infant responded well to hydrocortisone previously or has not been exposed to steroids, choose hydrocortisone. If infant did not respond to hydrocortisone previously, choose dexamethasone.
        i. Comparable hydrocortisone protocol: 33.75 mg/kg over 10 days
            1. Day 1-3: 1.25 mg/kg q6h for 3 days
            2. Day 4-6: 1.25 mg/kg q8h for 3 days
            3. Day 7-8: 1.25 mg/kg q12h for 2 days
            4. Day 9-10: 1.25 mg/kg q24h for 2 days

ii. DART protocol: dexamethasone 0.89 mg/kg IV over 10 days
    1. Day 1-3: 0.15 mg/kg/day IV q12h
    2. Day 4-6: 0.1 mg/kg/day IV q12h
    3. Day 7-8: 0.05 mg/kg/day IV q12h
    4. Day 9-10: 0.02 mg/kg/day IV q24h

c. If unable to extubate, convert to chronic ventilation settings using PRVC + PS or PSVG. Goal settings:
    i. PEEP 7-10
    ii. Tidal volume 8-12 ml/kg
    iii. PIP 25-40
    iv. Rate 12-25
    v. i-time 0.5-0.7
    vi. Saturation parameters: 92-95%
    vii. If infant is unable to tolerate chronic ventilation strategy, evaluate for conditions such as restrictive lung disease, severe tracheobronchomalacia, and/or other causes of ventilation-perfusion mismatch.
d. For invasively ventilated infants, optimize mucus clearance
    i. Routine bag suctioning with normal saline
    ii. Consider DNAse
e. Limit blood gases once respiratory management is stabilized as pCO_2 is an unreliable indicator in this setting.
    i. Titrate ventilator settings based on respiratory stability, work of breathing, oxygen requirement, tolerance of care and handling, and need for sedation.
    ii. Slowly wean tidal volume if oxygen requirement decreases.
    iii. May be able to successfully extubate if infant is stable in $<$ 40% FiO2 with low work of breathing even if tidal volume remains high

2. If lung disease is steroid responsive, consider low-dose, chronic steroid therapy.
    a. Inhaled steroid
        i. Budesonide (Pulmicort) 1 neb q12-24h
        ii. Fluticasone (Flovent) 2 puffs q12h
        iii. Beclomethasone (Qvar) 2 puffs q12h
    b. Hydrocortisone 0.5 mg/kg PO QOD
    c. Prednisone
3. Infants with SBPD are predisposed to airway smooth muscle hyperreactivity. 40-66% of infants will show decreased airway resistance and improved gas exchange after administration of bronchodilator. However, bronchodilators have not been shown to prevent or ameliorate BPD. In addition, bronchodilators may be harmful as they can worsen airway malacia and obstruction; therefore, use with some caution.
    a. Trial albuterol or levalbuterol for bronchospasm
        i. Albuterol 2.5 mg neb or 2 puffs q4-12h
        ii. Levalbuterol 0.31-1.25 mg or 2 puffs q4-12h
        iii. Trial for 24h. Positive response is characterized by decreased bronchospasm with diminished aeration and wheezing with improved respiratory stability
    b. Trial ipratropium for excessive secretion production and bronchospasm
        i. Ipratropium 0.5 mg neb q6-12h
        ii. Trial for 24h. Positive response is characterized by decreased secretions, obstructive events, and bronchospasm.

4. Trial diuretics
    a. Start with 3-day trial of diuretics, then discontinue therapy. If infant improves with treatment and deteriorates when treatment is discontinued, start chronic therapy.
        i. Chlorothiazide (20-40 mg/kg/day PO q12h)
        ii. Spironolactone (2-4 mg/kg/day PO q12-24h) – *consider avoiding due to handling restrictions*
        iii. Furosemide (1-4 mg/kg/day PO q12-48h or 0.5-2 mg/kg/day IV q12-48h)
    b. If infant does not show improvement or does not deteriorate within 3-5 days, do not start chronic therapy in an effort to avoid side effects such as poor growth and metabolic/electrolyte derangements.
    c. If decision made to continue long-term, check electrolytes routinely and supplement with arginine chloride, potassium chloride, or sodium chloride as needed to maintain:
        i. Na $\geq$ 130
        ii. K $\geq$ 3.0
        iii. Cl $\geq$ 90
    d. Avoid aggressive fluid restriction as it has not been shown to improve outcomes for severe BPD. However, poor growth and nutrition are highly associated with worse outcomes.
5. Avoid further pulmonary damage from chronic aspiration. If infant has evidence of gastroesophageal reflux, consider NJ feeds and/or antacids.
6. Optimize nutrition
    a. Follow growth parameters closely, including z-scores.
        i. Weight is an unreliable measure of lean mass growth as it may be affected by fluid status.
        ii. Linear growth is the best measurement of lean body mass accretion and organ growth and development; thus, always use length board if feasible.
    b. May have high caloric needs of $>$ 130 kcal/kg/day, especially during early unstable period. Needs may decrease significantly over time as work of breathing and stability improve. Avoid excessive weight to length ratio.
    c. May have higher protein needs, particularly during unstable, highly metabolic periods. Start with protein goal at upper end of normal for age (2 g/kg/day for term infant), then titrate based on growth.
    d. For total fluids, initially provide 130-150 ml/kg/day. May need less as infant grows older.
    e. Consider gastric tube placement, Nissen fundoplication
7. When respiratory status is stable, prioritize developmental therapies
    a. Develop individualized comprehensive developmental plan
    b. Engage families in therapies, including daily holding and interaction
    c. Identify primary care nursing team
8. Use sedation judiciously and monitor sedation scores. If infant requires significant sedation and/or is unstable when agitated, consult Complex Pain and Palliative Care Program (PACT Team).
9. Obtain brain MRI prior to discharge to facilitate obtaining outpatient developmental services.
10. If any family members use tobacco, encourage smoking cessation. Maternal smoking results in decreased forced expiratory flows, decreased passive respiratory compliance, increased hospitalization for respiratory infections, and an increased prevalence of childhood wheeze and asthma in exposed infants. If the family is interested, refer to 1-800-NO-BUTTS and/or primary care doctor for nicotine replacement therapy.

FURTHER EVALUATION AND CONSIDERATIONS

1. Request flexible bronchoscopy to evaluate airway for vocal cord dysfunction, subglottic stenosis, laryngomalacia, tracheomalacia, bronchomalacia, and other anomalies.
2. If infant has atypical presentation or NICU course, consider further evaluation for other causes of chronic respiratory failure such as:
    a. Gastroesophageal reflux disease (GERD)
    b. Surfactant protein deficiencies
    c. Cystic fibrosis
    d. Immune deficiency
    e. Pulmonary infections including CMV pneumonitis, mycoplasma, or ureaplasma
    f. H-type tracheoesophageal fistula
    g. Primary ciliary dyskinesia
    h. Alveolar capillary dysplasia
    i. Pulmonary lymphangiectasia
    j. Pulmonary interstitial glycogenosis
    k. Other developmental lung diseases
3. Tracheostomy placement is a complex and difficult decision that must involve extensive discussions among care providers and family members. Overall goal of tracheostomy placement is to provide respiratory stability to enhance survival and neurodevelopmental and growth outcomes.
4. If infant is expected to have poor chance of survival or prolonged hospitalization, consult Palliative Care Program and/or Pastoral Services.

CONSULTATIONS

1. SBPD Team
    a. Provide continuity of care
        i. Keep comprehensive records of each patient and provide monthly progress reports as applicable
        ii. Coordinate communication and care between Medical, Nursing, Respiratory, Therapy, and Nutrition teams
        iii. Improve communication with families and their satisfaction with care
    b. Optimize outcomes
        i. Develop best practice guidelines, monitor adherence to guidelines, and act as a resource for primary Neonatology team
        ii. Streamline discharge planning
        iii. Improve mortality and neurodevelopmental outcomes
2. Nutrition
3. Physical Therapy, Occupational/Speech Therapy
4. Pulmonology
5. Gastroenterology
6. Complex Pain and Palliative Care Program (PACT Team)
7. Pulmonary Hypertension Program

SPECIAL CONSIDERATIONS FOR BPD WITH PH MANAGEMENT

1. Optimize respiratory management, avoid severe acidosis or hypercarbia (goal pH $\geq$ 7.25, $pCO_2 \leq 65$).
2. Goal saturations 92-95%. Avoid intermittent or sustained hypoxia.
3. Follow serial echocardiograms +/- blood brain natriuretic peptide (BNP) levels every 1-4 weeks.
4. Therapeutic agents and cardiac catheterization

a. If respiratory management is optimized and infant continues to have severe or symptomatic PH, start therapeutic agents and consult Pulmonary Hypertension Program at UCSF Mission Bay.
    i. Begin with iNO 20 ppm and monitor response.
    ii. Transition to sildenafil as feasible.
        1. Oral: start with 0.5 mg/kg q8h, titrate over 1-2 weeks up to 0.75 mg/kg q6h (max 3 mg/kg/day or 10 mg q8h).
        2. IV: start with 0.25 mg/kg q8h, titrate slowly up to 0.5 mg/kg q6-8h. Administer over 60 minutes.
        3. Monitor for systemic hypotension, bronchospasm, gastroesophageal reflux, irritability, nasal stuffiness, and fever.
    iii. If infant has gastroesophageal reflux or is otherwise unable to transition to sildenafil, consider bosentan.
        1. Start with 0.5 mg/kg PO q12h, titrate over 2-4 weeks up to max of 2 mg/kg PO q12h.
        2. Monitor for liver dysfunction, ventilation-perfusion mismatch, hypotension, and anemia. Draw liver function tests monthly (and during viral infections), CBC quarterly.
b. If therapy is optimized but PH is not responsive or poorly responsive to treatment, consider cardiac catheterization. Goals of evaluation are to better define PH and assess for potential contributing factors such as LV diastolic dysfunction, anatomic shunts (ASD or PDA), pulmonary vein stenosis, and systemic collaterals.

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