Respiratory Failure in Term Neonates [≥ 37 Weeks GA]

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11 November 2009

Background

• Parents of a preterm infant realize that the risk of death is present inversely proportional to gestational age

• Table next slide represents guidelines for counseling parents in the perinatal period concerning expected preterm outcomes
**Expectation of parents of a term newborn**

- All parents of term infants expect a normal birth, delivery and perinatal outcome
- **Expected survival is 100% in their minds**
- When pathophysiologic conditions are present and when these conditions alter normal physiologic transition from fetal to neonatal circulation, extensive counseling is required to explain why this happened and the prognosis for long-term survival

**NICU Admissions Among Term & Near Term Infants**

Clark R et al 2005

**Not All Respiratory Distress in Term Infants is Benign**

Clark R et al 2005

**The goal then is to transition from**

Fetal Circulation

Clark R et al 2005
to normal neonatal circulation

Normal Physiologic Changes in PVR @ Delivery “Transition”

Pulmonary Hypertension Happens

Various Factors That Modify Pulmonary Vascular Resistance

Endogenous Mediators and Mechanisms
- Hypoxia
- Endogenous prostaglandins
- Endothelin
- Angiotensin II
- Prostaglandins E2, D2
- Sodium
- Calcium
- Nitric oxide
- Adenosine
- Arginine
- Thromboxane A2
- Thrombin
- Platelet-activating factor
- Acetylcholine
- Prostaglandins E2

Mechanical Factors
- Coronary, subepithelial alteration of lung
- Excess vessel proliferation, muscular remodeling
- Pulmonary hypertension
- Abnormal pulmonary arterioles
- Pulmonary shunting
- Hyperventilation
- Ventricular dysfunction, systemic hypertension

Endogenous Mediators and Mechanisms
- Decrease PVR
- Increase PVR
Disorders Associated with ↑ Risk of Persistent Pulmonary Hypertension

- Intrauterine:
  - UPI-SGA [chronic hypoxia]
  - Diaphragmatic Hernia
  - Potter’s Syndrome [Renal agenesis]
  - Oligohydramnios syndromes [adverse effect on fetal anatomic lung growth]
  - Maternal Drugs [ASA, indomethacin]
  - LGA infants; especially IDM
  - Persistent Fetal Circulation

- Intrapartum:
  - Asphyxia
  - PAS [AF ± meconium]
  - Postmaturity (>42 weeks; UGI]
  - Elective cesarean section, no antecedent labor

- Postpartum:
  - 1st lung disease [RDS]
  - Metabolic
    - Hypoglycemia, especially associated with IDMs
    - hypocalcemia
  - Infection – especially early onset GBS
  - Rheologic – PC/HV syndrome
  - Intubation, suctioning
  - Hypothermia
  - Sepsis

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  - Oligohydramnios syndromes [adverse effect on fetal anatomic lung growth]
  - Maternal Drugs [ASA, indomethacin]
  - LGA infants; especially IDM
  - Persistent Fetal Circulation

Pathophysiologic Conditions Associated with ↑ PVR

- Hypoxia
- Hypercapnia
- Acidosis
- Hypothermia
- PC/HV
- Hypovolemia
- Hypotension
- Air Leak Syndromes
Respiratory Distress

- Respiratory distress is characterized by the following signs:
  - Cyanosis
  - Tachypnea
  - Retractions
  - Expiratory grunting
  - Nasal flaring

Differential Causes of Respiratory distress

- Sepsis
  - GBS, E.coli, H.flu B, Listeria all associated with early-onset disease
- Polycythemia
  - Associated with hyperviscosity when central hct > 65% not uncommonly complicated by PPHN
- Cardiac
  - Cyanotic and non-cyanotic congenital types

Causes of Respiratory distress

- Shock
  - Hypovolemic
  - Cardiogenic
  - Septic
- Metabolic
  - Acidosis
  - Hypoglycemia
  - Hyperammonemia [and other forms of IEM]

Respiratory causes (continued)

- Airway obstruction
- Poor respiratory muscle effort
- Parenchymal
- Space-occupying lesions
Respiratory Causes

- Airway obstruction
  - Choanal atresia
  - Glossoptosis [Pierre-Robin anomaly]
  - Vocal cord paralysis
- Subglottic lesions
  - Subglottic stenosis
  - Tracheomalacia
- Paratracheal lesions
  - Gater
  - Superior mediastinal masses
  - Cystic hygroma
  - Vascular ring

Respiratory causes [continued]

- Poor respiratory muscle effort $^2 \rightarrow$
  - Phrenic nerve injury
  - Phrenic nerve compression from tumors including neuroblastoma
  - Iatrogenic injury during CT insertions
- Myopathies including
  - Muscular dystrophies
  - Myasthenia gravis
  - Progressive spinal muscular atrophy
  [Werdnig-Hoffman Disease]

Respiratory causes [continued]

- Parenchymal
  - Transient tachypnea of the newborn [TTN]
  - Respiratory Distress Syndrome [RDS] $^2$ surfactant deficiency
  - Meconium Aspiration Syndrome [MAS] $^2$ deep aspiration of MSAF prior to and/or during delivery.
    - Associated PPHN may require alternate-use surfactant replacement, HFV, alkalization, iNO Rx and ECMO in refractory cases not responsive to HFV/iNO Rx
- Pneumonia – most often as EOGBS disease
  - Associated with PPHN frequently
  - Other bacterial infections include E.coli; H.flu B; Listeria and pneumococcus.
  - Ampicillin/gentamicin first line therapy
  - With E.coli, addition of ceftriaxone for gram negative coverage essential

Respiratory causes [continued]

- Space-occupying lesions
  - Diaphragmatic hernia [CDH]
    - Almost always associated with PPHN $^2$ ipsilateral pulmonary hypoplasia. Commonly require ECMO stabilization prior to surgical correction
  - Pneumothorax/pneumomediastinum
    - Spontaneous PTx noted ~ 1-2%
    - Look for SUA and associated renal malformations
    - When spontaneous, try 100% O$_2$ to “wash out” nitrogen
    - If tension PTx noted, needle thoracentesis ± CT placement may be required
Respiratory causes (continued)

- Chylothorax, pleural effusion
  - As with fetal hydrops [immune or non-immune causes]
- Others such as →
  - Tumors
  - Enteric or bronchial cysts
  - Cystic adenomatoid malformation of the lungs [CAM]
  - Congenital lobar emphysema

Focus in on

Common

Pathophysiologic Conditions

Idiopathic persistent pulmonary hypertension of the newborn*

Figure 15: Diagram of idiopathic persistent pulmonary hypertension of the newborn (PPHN).

Figure 16: Radiograph of the chest of an infant who has idiopathic persistent pulmonary hypertension (PPHN). Note the equal inflation of the lungs with no pulmonary disease. When hypertensive is out of proportion to the severity of pulmonary disease, other diagnoses include extracardiac right-to-left shunting, associated with PPHN or cyanotic heart disease.
Chorioamnionitis

• Listing of common organisms associated with early-onset & late-onset neonatal sepsis

| Table 11.1 COMMON MICROORGANISMS ISOLATED FROM EARLY-ONSET NEONATAL INFECTIONS |
| Group B streptococci | Escherichia coli | Staphylococcus aureus | Group A streptococci | Enterococcus spp. |

| Table 12.2 COMMON MICROORGANISMS ISOLATED FROM LATE-ONSET NEONATAL INFECTIONS |
| Group B streptococci | Escherichia coli | Staphylococcus aureus | Group A streptococci | Methicillin-resistant Staphylococcus aureus |

Intrapartum Antibiotic Prophylaxis Increases the Incidence of Gram-Negative Neonatal Sepsis


A significant increase in use IAP ampicillin noted between 1st & 4th quarters of 1997 coincident with newly published guidelines for perinatal mgmt for GBS sepsis.

The incidence of neonatal GBS ↓ from 1-7/1000 (18-10/2000 lbs but there was a concurrent ↑ in the incidence of gram-sepsis from 0.3/1000 to 1.3/1000

These data provide compelling evidence that the policy of providing ampicillin chemoprophylaxis in selected patients needs to be reconsidered.

A better choice may be IV penicillin G with a much narrower coverage against GBS.

Congenital Diaphragmatic Hernia (CDH)

- Clinical Points:
  - complex disease with high mortality
  - Pathophysiology:
    - lung immaturity
    - hypoxia
    - may include left ventricular underdevelopment
  - Treatment:
    - no consensus
Air Leak Syndromes (ALS)

- ALSs originate in alveolar rupture in the neonatal period. When it accumulates in the lungs and without extension, pulmonary interstitial emphysema results.
- When it dissect to the hilum and into the pleural, pericardial, or anterior mediastinal spaces, clinical signs appear, depending upon the location of extraneous air accumulation.

Air Leak Syndromes

- Spontaneous pneumomediastinum occurs during the initial breaths following delivery, usually in term infants or it may occur among infants with RDS or TTN
- Effective management of pneumothorax (PTX) if associated with mediastinal shift involves initial needle thoracentesis followed usually by placement of a chest tube connected to pleurevac suction (especially when the infant is on positive pressure ventilation)
- Pneumopericardium may be associated with ~ 50% mortality and generally is accompanied by clinical features of cardiac tamponade, including abrupt cyanosis, hypotension and inaudible cardiac sounds on auscultation; CXR shows radiolucent ring around the heart; Air at the diaphragmatic cardiac surface is diagnostic; An indwelling catheter for continuous closed drainage may be required following pericardiocentesis

Meconium Aspiration Syndrome (MAS)

- Clinical points:
  - Hx of meconium stained amniotic fluid in 00-10% of deliveries
  - Of those, ~ 5% develop MAS
- Pathophysiology:
  - Air trapping
  - Pulmonary Vasculature pathology
- Treatment:
  - Avoid ventilator strategies that promote gas trapping
MECONIUM ASPIRATION SYNDROME

ADDITIONAL PHYSIOLOGIC OBSERVATIONS

- Hon (1963) suggested that cord compression → results in vagal stimulation and passage of meconium
- Saling (1967) stated that fetal hypoxia causes fetal gut vasoconstriction → hyperperistalsis and sphincter relaxation → passage of meconium
- Motilin, a hormone responsible for GI motility has been demonstrated to be present in higher concentrations among term & post-term neonates than in premature neonates.

PATHOPHYSIOLOGY OF MECONIUM ASPIRATION IN FETAL LUNGS

- MAS noted to develop in 2-33% of infants born through MSAF
- Of these, ≥ 30% may require mechanical ventilation (conventional or HFV)
- 33% have associated PPHN and mortality varies between 4-20% in different reports

APPEARANCE OF MECONIUM vs. G.A.

Matthew and Whelan (1979) reviewed records of > 1000 infants delivered at Salt-Bow River Hospital between 4/12-4/71 and noted the following results:

<table>
<thead>
<tr>
<th>Gestational Age (wks)</th>
<th># births (n=1034)</th>
<th># meconium-stained amniotic fluid (n=126)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 33 weeks</td>
<td>732 (70.6%)</td>
<td>34 (26.6%)</td>
</tr>
<tr>
<td>24-&lt;33 weeks</td>
<td>207 (20.4%)</td>
<td>6 (1.5%)</td>
</tr>
<tr>
<td>&lt; 24 weeks</td>
<td>67 (6.5%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>
Algorithm for MAS

- Aspiration of meconium can cause either partial or complete obstruction of the airways.
- Partial obstruction results in a "ball-valve effect", with areas of atelectasis and air trapping, increasing risk of ALS
- Complete airway obstruction → alveolar collapse and V/Q mismatch

Algorithm for MAS (continued)

- Animal studies have demonstrated mechanical dysfunction in the lungs is most severe during the early phase of MAS with decreased lung compliance due to
  - random obstruction of the airways
  - surfactant inactivation from the inflammatory response to meconium
- In vitro studies have demonstrated that neutrophils and plasma proteins stimulated in the course of the inflammatory response are potential inhibitors of surfactant

Algorithm for MAS (continued)

- ~ 33% of infants with MAS develop PPHN
- Factors associated with PPHN include:
  - acidosis
  - hypoxia
  - hypercapnia
  - hypovolemia
- Neonatal pulmonary vessels possess a unique ability to undergo rapid changes in architecture, particularly thickening, distal extension of smooth muscle and muscularization of alveolar septal arterioles.

Normal & Pathologic Changes in Pulmonary Arteriolar Musculature

- Diagrammatic representation of acinus
  - TB=terminal bronchiole; RB=respiratory bronchiole; AD=alveolar duct; A=alveolus
  - Depiction of pulmonary arteriolar muscular extension down the arteriole among infants with clinical persistent pulmonary hypertension

11/12/2009
Ventilator Strategies, Adjunctive Measures and alternate use Surfactant to treat MAS

- ↑ pH > 7.5-7.6 to promote pulmonary vascular dilation
- High Frequency Jet Ventilation: **indications for use**
  - Restrictive lung disease:
    - hypoplasia or intrinsic/extrinsic compression of lung tissue including PIE, CDH, pulmonary hypoplasia
  - Obstructive lung disease:
    - ↑ Rlu ≥ 1- particulate matter partially obstructing airway including: meconium aspiration syndrome
  - Atelectatic Lung Disease:
    - deficiency or ineffective surfactant → alveolar collapse including: RDS, ARDS

Ventilator Strategies, Adjunctive Measures and alternate use Surfactant to treat MAS (continued)

- Minimal stimulation/sedation/+ muscle relaxation to capture ventilation
- pressor support (dopamine, dobutamine, epinephrine)
- volume support (PRBCs, 5% ALB, FFP) to maintain adequate Uo, CVP (pre-load)
- Inhaled nitric oxide (INO): variable response
  - Kinsella (1997) trial: 40% required ECMO and/or died
- PAGE (perflurocarbon assisted gas exchange) – used experimentally > 10 years ago, but now on hold by FDA

Ventilator Strategies, Adjunctive Measures and alternate use Surfactant to treat MAS (continued)

- Alternate use surfactant therapy
  - Auten (1991) reported experience with alternate-use surfactant Rx for infants with PAS and congenital pneumonia.
  - The premise of their study is surfactant inactivation noted to occur in models of injury associated with meconium aspiration and pneumonia.
  - This is routinely used among infants with MAS who required assisted ventilation for respiratory failure; a trial with Surfaxin [an artificial surfactant] lavage failed to demonstrate a statistically significant advantage over ET curosurf installations in comparative studies

Ventilator Strategies, Adjunctive Measures and alternate use Surfactant to treat MAS (continued)

- ECMO (extracorporeal membrane oxygenation)
  - **ECMO Entry Criteria**
    - weight > 2 kg
    - ≤ 7 days of assisted ventilation (including HFV)
    - reversible lung disease
    - failure to respond to maximal conventional medical management
Extracorporeal Membrane Oxygenation

Inhaled Nitric Oxide Therapy

**Background**

**NO: Mechanism**

Conversion of guanosine triphosphate to cyclic guanosine monophosphate

\[
\text{GTP} \xrightarrow{\text{Soluble Guanylate Cyclase + NO}} \text{cGMP}
\]

- Causes vascular smooth muscle relaxation by decreasing concentration of free calcium in smooth muscle cells
**iNO: Clinical Indications**

- Hypoxic respiratory failure in neonates born at or near term caused by:
  - Primary persistent pulmonary hypertension
  - Respiratory distress syndrome
  - Aspiration syndromes
  - Pneumonia or sepsis
  - Congenital diaphragmatic hernia

**iNO: Guidelines for Use**

- Limit use to ventilated [CV or HFV] infants with PaO₂ less than 80 mm Hg receiving 100% oxygen with proven or suspected pulmonary hypertension and an OI ≥ 15
- PAH confirmed with prior echocardiogram analysis
- Essential to insure adequate lung inflation
  - Loss of FRC will cause both hypoxemia and pulmonary hypertension and will not respond to exogenous NO
iNO: Guidelines for Use

- Oxygenation Index (OI)
  \[ OI = \frac{\text{FiO}_2 \times \text{MAP} \times 100}{\text{PaO}_2} \]
- \( OI > 40 \) = ECMO
- \( OI > 15 \) = iNO

When to Transfer:

- Severe acidosis with probable sepsis
  - VUMC data in 21 infants with \( pH < 7.3 \) will need ECMO even if initial iNO response [York, et al.]
- No response to iNO within 1 hour
  - Changes of dose not indicated
  - Longer trial dangerous!
- Failure to continue to improve
  - Persistent requirement of high vent support/100% \( O_2 \) requirements and
  - Persistently high OI and rising

Hypoxic respiratory failure: etiology and outcomes at one referral center 2000 – 2005

- Looked at a referral population of term and near-term infants with hypoxic respiratory failure (HRF) noting survival, need for iNO ± ECMO
- All infants \( \geq 36 \) weeks GA admitted \( \leq 72^\circ \) age between years 2000 – 2005

Hypoxic respiratory failure: etiology and outcomes at one referral center 2000 – 2005

- 630 infants were reviewed and 315 infants were identified with \( 1^\circ \) diagnosis of HRF
  - 117 had worst OI \( \leq 14 \)
  - 71 had worst OI 15-25
  - 67 had worst OI > 25
- 32 infants required ECMO, including
  - 2 who died with pulmonary malformations
  - 2 who died with septic shock
Hypoxic respiratory failure: etiology and outcomes at one referral center 2000 – 2005

315 had other primary diagnoses but were treated with > 24 hrs assisted ventilation

In their retrospective study over 5 years between 2000-2005, term or near-term infants with isolated HRF are likely to survive, given the low incidence of pulmonary disorders not supportable by iNO or ECMO

Outcomes of Term Neonates with Respiratory Failure between 7/1/01 – 7/1/08

<table>
<thead>
<tr>
<th>Condition</th>
<th>#</th>
<th>CV</th>
<th>RPO/pH</th>
<th>Surfact</th>
<th>iNO</th>
<th>Transl</th>
<th>Surv</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMD</td>
<td>20</td>
<td>35</td>
<td>14</td>
<td>22</td>
<td>0</td>
<td>22</td>
<td>0</td>
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<tr>
<td>Apnea</td>
<td>31</td>
<td>19</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>19</td>
<td>0</td>
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<tr>
<td>#NOA</td>
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<td>10</td>
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<td>10</td>
<td>0</td>
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<td>0</td>
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<tr>
<td>#Naralyzed</td>
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<td>1</td>
</tr>
<tr>
<td>C/Po2</td>
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<td>10</td>
<td>0</td>
<td>10</td>
<td>0</td>
<td>10</td>
<td>0</td>
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<tr>
<td>Airway Obstruction</td>
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<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
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<tr>
<td>Congenital</td>
<td>6</td>
<td>6</td>
<td>0</td>
<td>6</td>
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<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Dorsum</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>1</td>
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<tr>
<td>S. epiglottis</td>
<td>3</td>
<td>1</td>
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<td>Pneumonitis</td>
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<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Totals</td>
<td>124</td>
<td>124</td>
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<td>124</td>
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</tr>
</tbody>
</table>

*2/1 arrested ECMO: Final diagnosis trachea/bronchus

*diad

Description of Patients with Airway Obstructive Respiratory Failure

<table>
<thead>
<tr>
<th>Condition</th>
<th>#</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stridor Idiopathic</td>
<td>1</td>
</tr>
<tr>
<td>vocal cord paralysis</td>
<td>1</td>
</tr>
<tr>
<td>choanal atresia</td>
<td>1</td>
</tr>
<tr>
<td>Pierre Robin Anomalad</td>
<td>1</td>
</tr>
<tr>
<td>septal deviation/encephalocoele</td>
<td>1</td>
</tr>
<tr>
<td>cleft palate/Ebert's syndrome</td>
<td>1</td>
</tr>
<tr>
<td>arthrogryposis/Freeman-Sheldon</td>
<td>1</td>
</tr>
<tr>
<td>*diad</td>
<td></td>
</tr>
</tbody>
</table>
Description of Patients with CHD associated with respiratory failure

<table>
<thead>
<tr>
<th>Condition</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transposition great vessels</td>
<td>3</td>
</tr>
<tr>
<td>Pulmonary atresia</td>
<td>2</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>2</td>
</tr>
<tr>
<td>Double outlet RV/PS</td>
<td>2</td>
</tr>
<tr>
<td>Hypoplastic LV syndrome</td>
<td>2</td>
</tr>
<tr>
<td>Coarctation</td>
<td>1</td>
</tr>
<tr>
<td>Total anomalous pulmonary return</td>
<td>1</td>
</tr>
</tbody>
</table>

Conclusions

- 14 "categories" of underlying pathophysiology are represented in this retrospective data
- Perinatal aspirations accounted for ~39% of 163 infants reviewed
- Overall survival approached 95%
- Poorest survival (~74%) noted among infants with perinatal asphyxia
- ARDS presenting as term "RDS" accounted for 7% of the population
- Use of alternate-use surfactant & iNO were used as protocols for each were introduced as a treatment modality during the retrospective study period
- Survival was comparable with other published studies

Wisdom of Buzz

Never trust a neonate!

Most Home Runs in a World Series

<table>
<thead>
<tr>
<th>Rank</th>
<th>Player</th>
<th>Team</th>
<th>Year</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Chase Utley</td>
<td>PHI</td>
<td>2009</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>Reggie Jackson</td>
<td>NYY</td>
<td>1977</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Barry Bonds</td>
<td>SF</td>
<td>2002</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>Lenny Dykstra</td>
<td>PHI</td>
<td>1993</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>Willie Aikens</td>
<td>KC</td>
<td>1980</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Gene Tenace</td>
<td>OAK</td>
<td>1972</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>Hank Bauer</td>
<td>NYY</td>
<td>1955</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Duke Snider</td>
<td>BRO</td>
<td>1955</td>
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<tr>
<td></td>
<td>Duke Snider</td>
<td>BRO</td>
<td>1962</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Lou Gehrig</td>
<td>NYY</td>
<td>1928</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Babe Ruth</td>
<td>NYY</td>
<td>1928</td>
<td>4</td>
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References