

Prematurity:

Complications and Clinical Strategies

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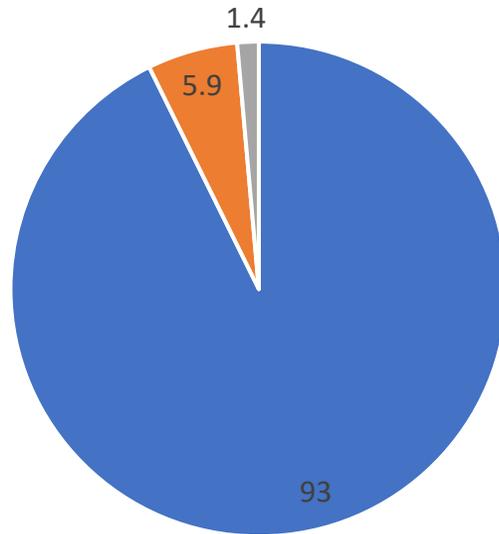


Prematurity

- Definition:
 - Liveborn infant delivered before 37 weeks gestation (259 days) from the first day of the last menstrual period
- Classification (by gestational age)
 - Preterm (premature): Infants born at less than 37 completed weeks gestation
 - Late preterm: Infants born at 34 weeks 0 days to 36 weeks 6 days completed weeks gestation
- Birth weight classification
 - Low birth weight (LBW): birthweight less than 2500 grams (5.5 lbs.)
 - Very low birth weight (VLBW): birthweight less than 1500 grams (3.3 lbs.)
 - Extremely low birth weight (ELBW): birthweight less than 1000 grams (2.2 lbs.)

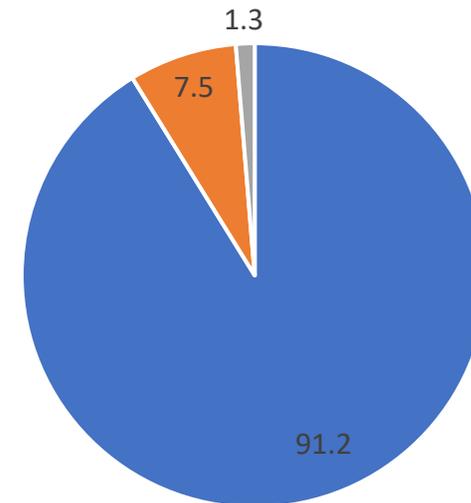
Percent of Live Births in the Birthweight and Gestational Age Categories: California 2018

Distribution of birthweight categories:
California, 2018



- Not low birthweight (> 2500 grams)
- Moderately low birthweight (1500-2499 grams)
- Very low birthweight (< 1500 grams)

Distribution of gestational age categories:
California, 2018



- Not preterm (greater than or equal to 37 weeks gestation)
- Moderately preterm (32-36 completed weeks gestation)
- Very preterm (less than 32 weeks gestation)

Source:

National Center for Health Statistics, final natality date

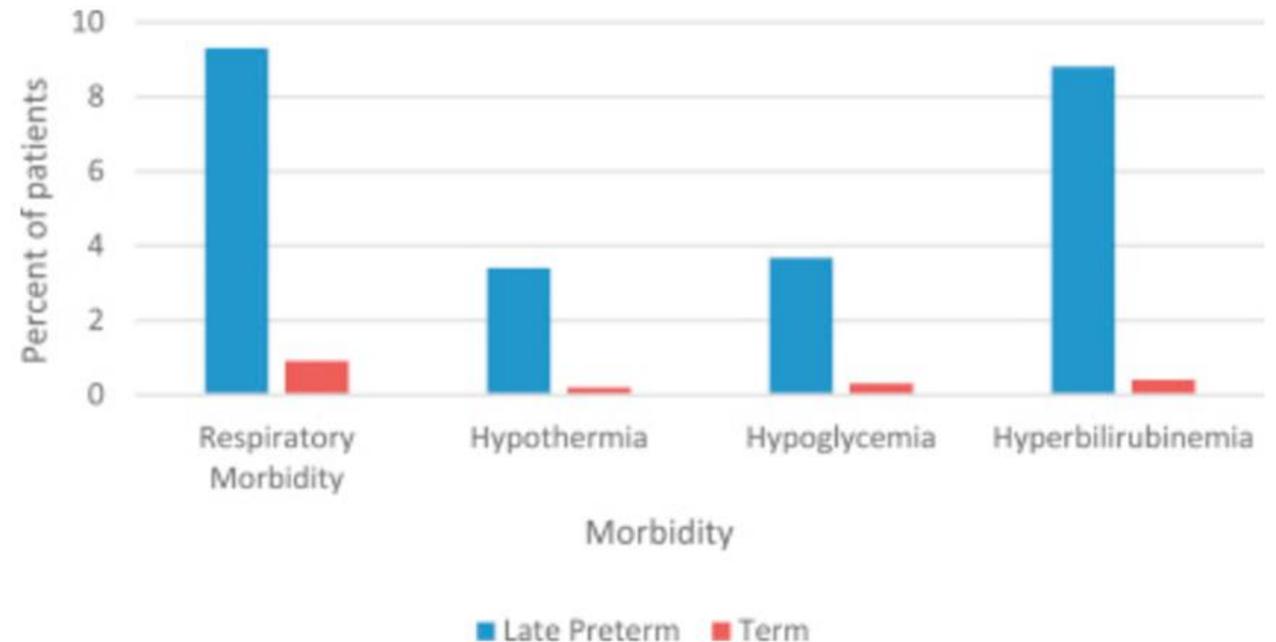
Retrieved September 16, 2020 from www.marchofdimes.org/peristats

Problems of Prematurity

- Problems of prematurity are related to difficulty in extrauterine adaptation due to immaturity of organ systems
 - Associated with ~ 1/3 of all infant deaths in the US
 - Accounts for
 - ~ 45% of children with cerebral palsy
 - ~35% of children with vision impairment
 - ~25% of children with cognitive or hearing impairment
- The risks of complications increases with increasing immaturity
 - Those infants born at or before 25 weeks gestation have the highest mortality rate and the greatest risk of severe impairment.

Problems of prematurity: Late preterm infants

- Although the risk of complications decreases with increasing gestational age, even moderately preterm infants are at risk for significant morbidity:
 - Respiratory distress
 - Hypothermia
 - Hypoglycemia
 - Hyperbilirubinemia
 - Feeding difficulties



Clinical morbidities noted during birth hospitalization from pooled data for late preterm and term patients. Source: [Late Preterm Infants: Morbidities, Mortality, and Management Recommendations](#). Huff K, Rose RS, Engle WA. *Pediatr Clin North Am.* 2019 Apr;66(2):387-402

Problems of Prematurity

- Prevention
 - Obstetric management; maternal illness, infection
 - Inhibition of preterm labor
 - Steroids to facilitate lung maturation
- Problems and Management
 - Initial, acute
 - Long term

Spectrum of Problems in Premature and Low Birthweight Infants

RESPIRATORY

- Respiratory Distress Syndrome
- Air leak syndromes: pneumothorax, pneumomediastinum, interstitial emphysema
- Pneumonia
- Apnea
- Neonatal chronic lung disease

CARDIOVASCULAR

- Patent ductus arteriosus
- Hypotension
- Bradycardia (with apnea)

HEMATOLOGIC

- Early or late onset

GASTROINTESTINAL

- Necrotizing enterocolitis
- Hyperbilirubinemia (direct and indirect)
- Spontaneous intestinal perforation

METABOLIC-ENDOCRINE

- Hypoglycemia
- Hyperglycemia
- Hypocalcemia
- Late metabolic acidosis

CENTRAL NERVOUS SYSTEM

- Intraventricular hemorrhage
- Periventricular leukomalacia
- Seizures
- Retinopathy of prematurity

RENAL

- Hyponatremia
- Hypernatremia
- Hyperkalemia
- Renal glycosuria

INFECTION

- Early-onset
- Late-onset
- Nosocomial
- Viral

Hypothermia

- Hypothermia
 - Rapid heat loss occurs because of relatively large surface area and inability to generate enough heat
 - Associated with increased mortality
 - Associated with intraventricular hemorrhage, respiratory insufficiency and metabolic disorders (hypoglycemia, metabolic acidosis) in survivors
 - Prevention:
 - Maintain delivery room temperature at minimum 26°C
 - Dry thoroughly/remove wet blankets
 - Use prewarmed radiant warmers
 - Use barriers to heat loss (polyethylene/polyurethane body wrap, stockinette caps) and external heat sources (warming mattress)
 - Care in incubator or radiant warmer to avoid hypothermia

Respiratory abnormalities



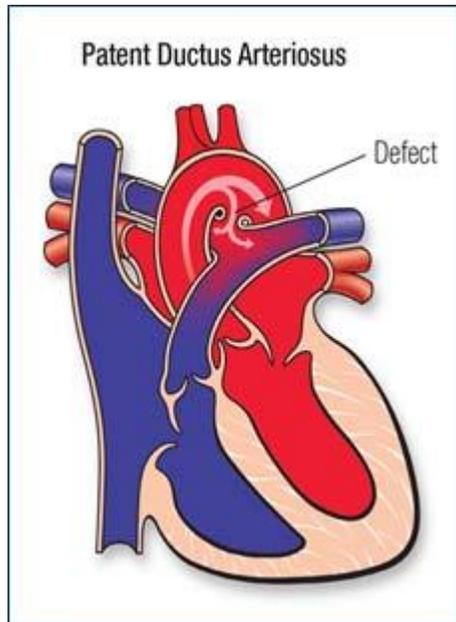
- Respiratory abnormalities:
 - Respiratory Distress Syndrome
 - Neonatal Chronic Lung Disease (oxygen dependency at 36 weeks postmenstrual age)
 - Apnea of prematurity
 - Pulmonary hemorrhage (most commonly in extremely preterm infants)

Respiratory abnormalities: treatment

- Assisted ventilation
 - Noninvasive: Nasal CPAP and nasal ventilation
 - Invasive: Conventional ventilation, high frequency oscillation
 - NAVA (neurally adjusted ventilatory assist): invasive and noninvasive modes
- Surfactant therapy
- Supportive care

- Patent Ductus Arteriosus (PDA)
 - Symptomatic PDA occurs in ~30% of VLBW infants
 - The PDA shunts blood flow from left to right, increasing blood flow to the pulmonary circulation and decreasing perfusion to the systemic circulation
 - Physiologic consequences depend on shunt size and response of heart and lungs to shunt
 - The management of PDA in preterm infants includes the following strategies
 - Conservative management with general supportive measures alone.
 - Pharmacologic closure using cyclooxygenase (COX) inhibitors (e.g. indomethacin, ibuprofen) or acetaminophen (paracetamol).
 - Prophylactic COX inhibitor therapy to prevent PDA.
 - Surgical ligation.

It remains unclear which approach is most advantageous for preterm infants, as there have not been large randomized controlled trials comparing these different strategies.



Cardiovascular abnormalities: PDA

Cardiovascular abnormalities: Hypotension

- Low blood pressure
 - Low BP without evidence of shock is commonly observed, especially in ELBW infants
 - Do these infants have worse outcomes?
 - Is intervention for low BP without evidence of shock beneficial?
 - What BP threshold should be used?
 - What is the optimal therapy?
- Determine primary factor leading to low BP with management based on cause
 - Manage hypotension due to hypovolemia (acute blood loss) with volume expansion
 - Manage hypotension due to myocardial dysfunction with inotropic therapy'
 - Manage hypotension due to infection with inotropic therapy (and treat the infection)

Central Nervous System: Hemorrhage

- IVH: Intraventricular hemorrhage (germinal matrix hemorrhage and intraventricular hemorrhage)
 - **germinal matrix** is a highly cellular and highly vascularized region in the brain from which cells migrate out during brain development. The germinal matrix is the source of both neurons and glial cells and is most active between 8 and 28 weeks gestation.
 - Severity of hemorrhage in preterm infants is based on the extent of bleeding (confined only to the germinal matrix region or extending into the adjacent ventricular system), involvement of the white matter (intraparenchymal), and/or with the presence of ventricular distension

Intraventricular hemorrhage (IVH)

- IVH occurs most frequently in very low birth weight (VLBW) infants (BW <1500 g) and/or very preterm (VPT) infants (GA <32 weeks).
- General preventive measures:
 - Prompt and appropriate resuscitation
 - Manage hemodynamic instability
 - Avoid conditions that impair cerebral autoregulation (hypoxia, hyperoxia, hypocarbia, hypercarbia)
- No specific therapy exists to limit the extent of IVH after it has occurred.
- Treatment is supportive, directed towards preservation of cerebral perfusion, minimization of any further brain injury, and early detection of complications
- Posthemorrhagic hydrocephalus is a major complication of severe IVH

Severity of germinal matrix and intraventricular hemorrhage on cranial ultrasonography

Grade	Description on parasagittal view
I	Germinal matrix hemorrhage (GMH) only or germinal matrix hemorrhage plus intraventricular hemorrhage less than 10% of ventricular area
II	GMH and intraventricular hemorrhage; 10 to 50% of ventricular area
III	GMH and intraventricular hemorrhage involving more than 50% of ventricular area; lateral ventricles are usually distended
IV	Hemorrhagic infarction in periventricular white matter ipsilateral to intraventricular hemorrhage (also called periventricular hemorrhagic infarction)

Adapted from: Papile LA, et al. *J Pediatr* 1978; 92:529 and Inder TE, et al. *Preterm Intraventricular Hemorrhage/Posthemorrhagic Hydrocephalus*. In: *Volpe's Neurology of the Newborn*, 6th, Volpe JJ (Ed), 2018. p.637.

Feeding the preterm infant

- Feeding problems
 - Immaturity of bowel function (lax esophageal sphincter, small gastric capacity, decreased motility)
 - Inability to coordinate suck and swallow (< 33 -34 weeks)
 - Complicating medical illness
 - Complicating medical interventions
- Approaches
 - Early introduction of enteral feeds
 - Exclusive use of human breast milk for VLBW infants
 - Use of feeding protocols, with feeding advancement based on weight categories
 - Lactation service support

Necrotizing enterocolitis (NEC)

- NEC is one of the most common gastrointestinal emergencies in the newborn infant (2-10% of VLBW infants).
- There is ischemic necrosis of the intestinal mucosa, with associated severe inflammation, invasion of enteric gas forming organisms, and dissection of gas into the bowel wall and portal venous system. NEC accounts for substantial long-term morbidity in survivors of neonatal intensive care, particularly in preterm very low birth weight (VLBW) infants (BW below 1500 g).
- Ten (10) percent of preterm infants with NEC will have long term gastrointestinal difficulties.



Necrotizing enterocolitis (NEC)

Management:

- Antenatal corticosteroids, primarily used to reduce the risk of neonatal respiratory distress syndrome
- Human milk feeding
- Use of a standardized feeding protocol, including administration of colostrum.
- Avoidance of unnecessary and prolonged antibiotic use.
- Avoidance of agents that reduce gastric acidity (e.g., histamine 2 [H2] blockers).
- Avoidance of severe anemia.
- Probiotics – Although there is good evidence that probiotic therapy reduces NEC, there remain challenges regarding the choice of agent, dosing, and duration of therapy and product safety

Infections

- Infection
 - Late onset sepsis is a common complication in preterm infants
 - One or more episodes of sepsis (positive blood culture + clinical signs of infection) occurs in 20% of VLBW infants who survive more than three days
 - Central line-associated blood stream infections
 - Coagulase negative Staphylococcus in 48% of cases
 - Fungal infection (candidiasis) accounts for 9% of cases and has a high mortality rate (28%)
 - Management and Prevention
 - Hand-washing
 - Appropriate staffing ratios
 - Antibiotic stewardship

Retinopathy of Prematurity

- Retinopathy of Prematurity (ROP)
 - Developmental vascular proliferative disorder that occurs in the incompletely vascularized retina of preterm infants.
 - Incidence and severity increase with decreasing gestational age and birthweight
 - Infants with birthweight ≤ 1500 grams or gestational age ≤ 30 weeks are screened
 - Maintain SpO₂ target ranges
 - Treatment is based on disease severity
 - laser photocoagulation
 - intravitreal injection of an anti-vascular endothelial growth factor (VEGF) agent (e.g. bevacizumab)
 - Choice is determined by experience and preference of the treating ophthalmologist

Prognosis

- Is related to gestational age at birth and birthweight
- With the advancements in neonatal intensive care, the survival rate for infants born at 24 weeks gestation is 40%.
- 5-10% of infants with birthweight less than 1500 grams have major disability such as cerebral palsy, developmental delay, blindness or deafness
- Risk increases with decreasing gestational age and weight

Long term complications

- Long term pediatric complications
 - Recurrent hospitalizations
 - Common causes include respiratory disorders (RSV infection and pneumonia)
 - Neurodevelopmental disabilities
 - Fine or gross motor delay, cerebral palsy
 - Sensory impairments (vision or hearing loss)
 - Behavioral and psychological problems
 - Impaired cognitive skills.
 - Growth impairment
 - Chronic health issues

Shared decision-making

- Prenatal considerations
 - Counseling should include discussion regarding survival rates and both short- and long-term complications
 - Determining parental wishes when delivery is anticipated near the limit of viability
 - Approximately 0.5% of all births occur before the third trimester of pregnancy
 - There early deliveries result in the majority of neonatal deaths and more than 40% of infant deaths
 - Family and health care teams are presented with complex and ethically challenging situations
 - Parents should be able to state their preferences, that hopefully have been Informed by information about complications and survival rates
 - Need for caregiver and parent teamwork

Counseling parents

“In formulating a plan of care for periviable neonates, clinicians should discuss with parents whether their goal is optimizing survival or minimizing suffering. The approach to antenatal and postdelivery care may differ dramatically depending on parental preferences regarding resuscitation.”

<https://www.acog.org/clinical/clinical-guidance/obstetric-care-consensus/articles/2017/10/periviable-birth>

Estimate survival and disability outcomes for extremely preterm infants (22 - 25 weeks)

<https://www.nichd.nih.gov/research/supported/EPBO/use>

* Indicates required field

*Gestational Age

(Best estimate in completed weeks)

25

*Birth Weight

(from 401-1000 grams)

725

*Infant Sex

Male Female

*Singleton Birth

Yes No

*Antenatal Steroids

Yes No

Clear

Submit

Infants Receiving Active Treatment

Average Survival: 76%
Hospital Range: 63 - 85%

All Infants, Including Infants Not Actively Treated

Average Survival: 76%
Hospital Range: 63 - 85%

Outcomes At 18-26 Months' Corrected Age Among Infants Who Survive: (About the Data)

Profound
Neurodevelopmental
Impairment

1 - 3%

Moderate-Severe
Neurodevelopmental
Impairment

21 - 32%

Blindness Deafness

< 1%

1%

Moderate-Severe
Cerebral Palsy

4 - 6%

Cognitive
Developmental
Delay

19 - 31%

Estimate survival and disability outcomes for extremely preterm infants (22 - 25 weeks)

<https://www.nichd.nih.gov/research/supported/EPBO/use>

* Indicates required field

*Gestational Age

(Best estimate in completed weeks)

23

*Birth Weight

(from 401-1000 grams)

600

*Infant Sex

Male Female

*Singleton Birth

Yes No

*Antenatal Steroids

Yes No

Clear

Submit

Infants Receiving Active Treatment

Average Survival: 40%
Hospital Range: 27 - 55%

All Infants, Including Infants Not Actively Treated

Average Survival: 33%
Hospital Range: 21 - 49%

Outcomes At 18-26 Months' Corrected Age Among Infants Who Survive: (About the Data)

Profound
Neurodevelopmental
Impairment

5 - 6%

Moderate-Severe
Neurodevelopmental
Impairment

37 - 52%

Blindness Deafness

< 1%

2 - 5%

Moderate-Severe
Cerebral Palsy

9 - 15%

Cognitive
Developmental
Delay

35 - 46%



Family-Centered NICU Care

- Practice principles
 - Parents are a natural part of the team
 - Parents are present as care-givers
 - Requires welcoming atmosphere
 - Supportive unit policies
 - Parents participate in rounds
 - Improves empowerment
 - Increases transparency
 - Kangaroo care (skin-to-skin)
 - Rooming-in