Intraventricular Hemorrhage
Bresney Crowell and David J. Annibale

I. Overview
A. An intraventricular hemorrhage (IVH) is an intracranial hemorrhage that begins in the subependymal germinal matrix with subsequent entrance of blood into the ventricular system. (See Fig. 15-1.)
B. Predominately found in preterm infants, IVH is associated with an increased risk of adverse neurodevelopmental outcomes. The associated risks increase with severity.

II. Pathophysiology
A. Pathogenesis of grades I–III IVH (see Section IV.D.) is multifactorial and the reasons for the preterm infant’s vulnerability to IVH are both anatomical and pathophysiological.
B. IVH largely originates in the germinal matrix located in the subependymal region around the lateral ventricles. Origination of IVH in this region is related to the fragility of the germinal matrix vasculature, the disturbance of cerebral blood flow (CBF), and coagulation and platelet disorders.
   1. Intrinsic vascular fragility of the germinal matrix
      a. The germinal matrix produces new glial cells early in gestation, requiring a rich blood supply due to increased quantities of substrate and energy. Glial fibers develop with increasing maturation.

FIGURE 15-1
Intraventricular Hemorrhage (IVH)

An IVH begins in the subependymal germinal matrix with subsequent entrance of blood into the ventricular system. Predominately found in preterm infants, IVH is associated with increased risk of adverse neurodevelopmental outcomes.
b. This area lacks muscular layers or supporting structures, leaving the small, fragile, immature vessels susceptible to rupture.

c. The vessels in this capillary bed do not resemble arterioles or venules and are sometimes called channels. They do not become real capillary beds until the germinal matrix disappears.

d. The region’s microvasculature and poor connective tissue results in a poor blood-brain barrier due to an abundance of blood vessels that have paucity of pericytes, immature basal lamina, and a deficiency of tight junctions, as well as glial fibrillary acidic protein in the astrocyte endfeet.

e. It is thought that the venous system that drains the fragile capillary network is prone to venous congestion and stasis, which contributes to germinal matrix IVH.

f. The greatest risk period for IVH is the first three days of life, after which the germinal matrix vessels are believed to become less fragile.

2. Increased risk of the germinal matrix to hypoperfusion injury

a. The cellular elements of the germinal matrix are rich in mitochondria and metabolically active, making them more susceptible to hypoxic insult.

b. The vulnerability of the germinal matrix in the first three days is compounded by the physiological instability after birth of a preterm infant.

c. In the preterm brain, autoregulatory and cerebral vasoreactivity mechanisms are poorly developed. Infants have limited control of cerebral perfusion pressure and CBF during periods of low systemic pressure, and limited protection to cerebral circulation during periods of elevated systemic pressure.

d. The range of arterial pressures over which a premature infant can maintain autoregulation is narrow and abrupt changes in blood pressure can overwhelm the neonate’s ability to protect cerebral circulation.

e. Poor autoregulatory mechanisms result in a pressure-passive cerebral circulation in which CBF is determined by moment-to-moment changes in systemic blood pressure.
f. Pressure-passiveness is directly correlated with lower gestational age and birth weight and most often identified in medically unstable, ventilated infants.

g. Physiologic and non-physiologic states, such as sleep cycles, spontaneous movements, positive-pressure ventilation, noxious stimuli, rapid volume infusion, and others may result in rapid fluctuations in CBF and IVH, secondary to alterations in arterial blood pressure.

h. Alterations in carbon dioxide also disrupt cerebral autoregulation:
   (1) Hypercarbia: vasodilatation
   (2) Hypocarbia: vasoconstriction

3. Exposure to biochemical and mechanical disturbances
   a. Fluctuations in CBF can be related to hypotension, hypoxemia, hypercapnia, acidosis, patent ductus arteriosus, and restlessness. Increases in CBF can cause IVH as well as reperfusion injury after periods of decreased CBF.
   b. Elevations in cerebral venous pressure (CVP) during mechanical ventilation, pneumothorax, and positive-pressure ventilation can cause decreases in cerebral perfusion.

4. Intrinsic disturbance in coagulation
   a. Multiple studies have shown that thrombocytopenia is a risk factor for IVH, but the role of coagulopathy in the pathogenesis of IVH has not been completely elucidated.
   b. Drugs that affect coagulation may also contribute to increased risk for IVH.

5. Genetic predisposition: Conflicting data regarding mutations of hemostasis genes and predisposition to IVH in preterm infants

6. Prenatal hemorrhage
   a. Relatively rare
   b. Maternal risk factors
      (1) Von Willebrand disease
      (2) Anticoagulation therapy
      (3) Cocaine abuse
      (4) Seizures
      (5) Abdominal trauma
      (6) Amniocentesis
      (7) Febrile illness
(8) Chorioamnionitis

c. Fetal risk factors
(1) Immune thrombocytopenia
(2) Congenital tumors
(3) Clotting factor deficiencies
(4) Fetomaternal hemorrhage
(5) Twin-twin transfusion
(6) Co-twin death

C. Pathogenesis of grade I, II, and III hemorrhages appears to be related to a disruption in autoregulation that leads to a pressure-passive CBF that is determined entirely by blood pressure.

1. Fluctuation in blood flow results in disruption of the capillary rete in the germinal matrix, resulting in a local hemorrhage.
2. A germinal matrix hemorrhage can result in local edema and vascular congestion in the region, leading to increasing venous pressure in the terminal vein.
3. The veins take a very sharp turn where the terminal vein in the germinal matrix and the internal cerebral vein meet. This narrow area is sensitive to high pressure.
4. Bleeding can extend into the ventricles.

D. Pathogenesis of grade IV hemorrhage appears to be related to anatomical characteristics of the cerebral venous circulation and increased cerebral pressure that results from lower-grade hemorrhage.

1. Increased cerebral pressure in the region of a germinal matrix hemorrhage results in increased venous pressure within the germinal matrix.
2. Blood flow is impaired in the medullary veins, which drain the cerebral white matter into the terminal vein.
3. The increased venous pressure is transmitted in a retrograde direction along the venous drainage of the periventricular white matter.
4. Increased venous pressure results in a periventricular hemorrhagic infarction (also known as grade IV IVH) with destruction of periventricular white matter.
5. The hemorrhagic venous infarction tends to be most concentrated near the ventricular angle where the medullary veins drain the cerebral white matter.
III. Incidence
A. Although incidence of IVH in very low birth weight (VLBW) infants (<1,500 g) has declined to 20%–25% from ~40%–50% in the early 1980s, it remains a major complication.
B. In extremely low birth weight (ELBW) infants (<1,000 g), the incidence of IVH increases to ~45%.
C. There are ~12,000 new cases of IVH diagnosed in preterm infants each year in the United States.
D. 10%–15% of VLBW infants suffer from more severe grades of hemorrhage and about three-fourths of these infants suffer from mental retardation and/or cerebral palsy.
E. Overall incidence is inversely related to gestational age.

IV. Diagnosis
A. Timing
1. Approximately 90% of IVH occurs within the first five postnatal days.
2. 50% occur within the first day, 25% in the second, and 15% in the third.
3. Most extensions of a lesion occur 3–5 days after the initial hemorrhage.
B. Clinical presentation
1. Silent syndrome occurs in 25%–50% of cases and is diagnosed by routine brain sonography.
2. Saltatory syndrome can evolve over hours or days and is characterized by an altered level of consciousness, hypotonia, and subtle changes in eye movement and positioning.
3. Catastrophic presentation is the least common and can develop within minutes or hours of injury.
   a. This presentation includes coma or stupor, irregular respirations (apnea/hypoventilation), seizures, or posturing.
   b. Other features include bulging fontanel, hypotension, bradycardia, and anemia. Metabolic acidosis, as well as inappropriate antidiuretic hormone secretion, can occur.
C. Screening
1. Cranial sonography
   a. Procedure of choice for diagnosis
      (1) High resolution
      (2) Portable
      (3) Non-radiating
b. Screening guidelines from the American Academy of Neurology and the Practice Committee of Child Neurology Society
   (1) Routine cranial ultrasound on infants <30 weeks gestational age or <1,500 g
   (2) Should be performed at 7–14 days and repeated at 36–40 weeks postmenstrual age

2. Lumbar puncture
   a. Used if cranial ultrasonography is not available.
   b. Cerebrospinal fluid (CSF) with IVH typically includes numerous red blood cells and elevated protein levels.

D. Grading system
   1. Described by Papile
   a. Grade I IVH: Hemorrhage subependymal and confined to germinal matrix (Figs. 15-2A and 15-2B)
   b. Grade II IVH: Hemorrhage in lumen of lateral ventricle(s) without ventricular distention (Fig. 15-3)
   c. Grade III IVH: Hemorrhage within lumen of lateral ventricle(s) with dilation of ventricle (Figs. 15-4A and 15-4B)

**FIGURE 15-2A**
*Neonatal Cranial Sonogram*

Images courtesy of J. Hill, MD, Department of Radiology and Radiological Science at the Medical University of South Carolina.

Grade I IVH, left sagittal view. Note the hemorrhage is subependymal and confined to the germinal matrix.
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d. Grade IV IVH: Combination of blood within lateral ventricle(s) and an echogenic area in periventricular tissue (Fig. 15-5)

2. Modified by Volpe

   a. Grade I IVH: Germinal matrix hemorrhage with no or minimal intraventricular blood (Figs. 15-2A and 15-2B)
   b. Grade II IVH: Hemorrhage with intraventricular blood occupying 10%–50% of ventricular volume (Fig. 15-3)
   c. Grade III IVH: Hemorrhage with intraventricular blood occupying >50% of ventricular volume (Figs. 15-4A and 15-4B)
   d. Grade IV IVH: Periventricular hemorrhagic infarction (Fig. 15-5 and Section VI.A.)

V. Management

A. Treatment of IVH is mostly supportive. Care should be aimed toward preventing further injury, preserving cerebral perfusion, and detecting associated complications.

1. Maintain blood pressure to preserve cerebral perfusion.

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FIGURE 15-2B
Neonatal Cranial Sonogram

Images courtesy of J. Hill, MD, Department of Radiology and Radiological Science at the Medical University of South Carolina.

Coronal view of grade I IVH.
2. Ensure adequate oxygenation and ventilation.
3. Provide efficient nutritional and fluid support.
4. If seizures present, initiate treatment to avoid impairments of cerebral oxygenation or perfusion.
5. Detect and manage associated complications.

B. Follow-up care is important for outcomes and developmental intervention programs are indicated for patients with IVH.

VI. Associated lesions and complications

A. Periventricular hemorrhagic infarction (PHI)
   1. PHI was initially described as an extension of a germinal matrix hemorrhage (GMH). It is now known that PHI is a direct complication, affecting 10%–15% of preterm infants with GMH.
   2. PHI is a large region of hemorrhagic necrosis in the periventricular white matter.
   3. It is usually unilateral (asymmetrical).
   4. PHI occurs when pressure is exerted on the periventricular terminal drain, leading to venous congestion and subsequently causing ischemia and further hemorrhage.

Coronal view of grade II IVH. Note the intraventricular blood can occupy 10%–50% of the ventricle (Volpe), but the ventricle is not distended (Papile).
Coronal view of grade III IVH, which shows ventricular dilation.
B. Periventricular leukomalacia (PVL)
   1. PVL refers to the necrosis of the white matter in the brain. It has a characteristic distribution and consists of periventricular focal necrosis with cystic formation and more diffuse gliotic cerebral white matter injury. (See Figs. 15-6, 15-7A, and 15-7B.)
      a. Non-hemorrhagic
      b. Usually symmetrical (bilateral)
      c. Necrosis of all cellular elements
      d. Watershed injury due to vascular insults

**FIGURE 15-5**

**Neonatal Cranial Sonogram**

Grade IV IVH, coronal view. Note the combination of blood within the lateral ventricle(s) and the echogenic area in the periventricular tissue (Papile). PHI (Volpe) is a large region of hemorrhagic necrosis in the periventricular white matter.
2. While PVL and IVH may occur independently, they can be associated and are often found in the same patients. The association might be related to similarities in pathogenesis and/or the initiation of pathological mechanisms such as perfusion abnormalities and reperfusion injury.

3. PVL has been associated with maternal chorioamnionitis, possibly due to cytokines, inflammatory damage, and perfusion.

4. PVL is associated with increased development of cerebral palsy, intellectual impairment, and visual disturbances.

C. Posthemorrhagic hydrocephalus (PHH)

**FIGURE 15-6**

*Neonatal Cranial Sonogram*

Early PVL, which refers to necrosis of the white matter. PVL is usually non-hemorrhagic and symmetrical. Although PVL and IVH may occur independently, they may be associated and found in the same patients.
1. PHH occurs in ~50% of infants with IVH and can present within 1–3 weeks after the initial hemorrhage. It appears to be most common in neonates with severe-grade IVH, found in as many as 75% of infants with grades III or IV IVH.

2. Infants with PHH usually present with rapidly increasing head circumference, ventricular dilatation on ultrasound, and signs of increased intracranial pressure (ICP). Symptoms of PHH may not be evident for weeks after the initial hemorrhage due to brain compliance in the neonate.

3. Effects of PHH are believed to be caused by injury to the periventricular white matter.

4. Communicating PHH is the most common form and is caused by the inability to reabsorb CSF due to inflammation of the subarachnoid villi.

5. Some patients may develop non-communicating hydrocephalus due to an obstruction from a clot or subependymal scarring within the ventricular system.

6. PHH may be non-progressive or resolve spontaneously without intervention.

**FIGURE 15-7A**

**Neonatal Cranial Sonogram**

Images courtesy of J. Hill, MD, Department of Radiology and Radiological Science at the Medical University of South Carolina.

Cystic PVL, sagittal view. Periventricular focal necrosis with extensive cyst formation.
7. Some treatment options have significant drawbacks, especially in VLBW infants.
   a. Close surveillance
      (1) Monitor head growth (>2 cm/week).
      (2) Monitor for signs of increasing ICP (agitation, decreased responsiveness, coma).
      (3) Consider neurosurgery consult for infants with rapidly increasing head growth or changes on head ultrasound.
   b. Lumbar and ventricular taps
      (1) Most common short-term therapeutic approach for early stages of slowly progressing, communicating hydrocephalus.
      (2) Drawbacks include procedure failure, which may enhance the risk for clot formations and lead to non-communicating hydrocephalus. There is also a significant rate of infection associated with taps (7%–27%).

**FIGURE 15-7B**
**Neonatal Cranial Sonogram**

Images courtesy of J. Hill, MD, Department of Radiology and Radiological Science at the Medical University of South Carolina.

Coronal view of cystic PVL with bilateral cyst formation.
(3) Hyponatremia may also occur with the removal of CSF.

c. External ventricular drainage (EVD)
   (1) This involves placement of an intraventricular catheter that is connected to an external drainage system. CSF drainage is adjusted by the level of the external system.
   (2) Associated problems include over-drainage and the possible development of subdural hygromas. EVDs have low infection rates.
   (3) The rate of needing a permanent shunt after an EVD is ~64%–68%.

d. Subcutaneous reservoir (SC)
   (1) This is a temporary treatment. Taps are performed through an SC, thereby preventing the need for ventricular taps with needle tracking and possible further brain injury.
   (2) These reservoirs are accessed as many as 2–3 times per day, depending on the ICP. Drawbacks include the rise of the ICP in between taps. Infection and skin necrosis are ongoing problems.
   (3) Permanent shunting is required in 75%–88% of patients with SC.

e. Ventriculoperitoneal (VP) shunting
   (1) This is the most common long-term treatment of PHH, usually for infants >2 kg.
   (2) There are multiple problems associated with this method of treatment.
      (a) The surgery is complicated and has a high revision rate. Shunts may need to be adjusted or replaced to account for changes in pressures as the child ages.
      (b) Due poor immune systems in preterm infants, the infection rate is ~5%–15%.
      (c) Shunt failure is common due to obstructions caused by increased CSF protein levels.

VII. Outcomes

A. Each year, there are >3,600 new cases of mental retardation related to IVH in the United States, according to data from the U.S. Census Bureau, the NICHD Neonatal Network, and the Centers for Disease Control.

B. Lifetime care costs exceed $3.6 billion for these children.
C. Long-term outcomes are inversely associated with birth weight and gestational age and are correlated with the location, extent, and laterality of the lesion. For example, in IVH associated with PVI, bilateral lesions spanning frontal-temporal-occipital regions carry the worst prognosis. Small, unilateral, frontal, white matter lesions have the best prognosis.

1. Severe IVH is associated with an increased mortality rate (~20%). Approximately 75% of survivors develop PHH, which increases the mortality rate to 55%.

2. With mild IVH, mortality rates drop to 5%, with only 7% of infants developing PHH.

3. 45%–85% of preterm infants with moderate to severe IVH have major cognitive deficits.

4. 90% of infants with severe IVH and PHI develop neurological sequelae.

5. Studies have shown an increase in cerebral palsy to 24% in ELBW infants with grade II IVH, vs. 6% in infants who had grade I IVH or no IVH.

D. Major predictors of poor outcome include PVI, cystic PVL, need for VP shunt placement, and shunt infections and revisions.

1. The mortality rate for infants with PHH requiring VP shunt placement is ~25%. Of these infants, 20% have severe neurological abnormalities, with only ~30% having a normal outcome.

2. 87% of infants with severe PVL or PVI have major deficits and 75% have impaired cognitive function.

3. Epilepsy develops in 50% of infants with PVL.

VIII. Prevention

A. Prenatal and delivery-room intervention: Prevention of preterm delivery most effective

1. Antenatal corticosteroids are known to reduce risk of respiratory distress syndrome (RDS) associated with increased risk for IVH.
   a. Most beneficial with completed course
   b. Protective effect in regard to IVH

2. Recent studies suggest that administration of magnesium sulfate may have a protective effect against IVH.

3. Delayed cord clamping increases hematocrit at birth, decreasing the need for transfusions and thereby decreasing the risk for IVH.
B. Postnatal management

1. Promptly and appropriately resuscitate, avoiding hemodynamic instability or conditions that impair cerebrovascular autoregulation.
   a. Synchronize ventilation.
   b. Limit suctioning.
   c. Prevent pneumothorax.
   d. Maintain neutral head position (midline).

2. Avoid hypotension or hypertension; if present, correct while avoiding large bolus infusions. Manage fluid carefully.

3. Avoid metabolic abnormalities.
   a. Hyperosmolality
   b. Hyper/hypoglycemia
   c. Acidosis or alkalosis-bicarbonate therapy associated with increased risk


5. Studies have looked at the use of prophylactic indomethacin to reduce the incidence of IVH. These studies resulted in clear short-term benefits with a decrease in IVH in preterm infants. Although research supports indomethacin for the reduction of IVH, this is not the current standard of care. More research is indicated to identify optimal dosing regimen as well as optimal patient population in regard to gestational age, birth weight, and illness severity.

IX. Conclusion

A. Despite research and developments in medicine, prevention of IVH remains an unsolved problem affecting preterm infants.

B. Careful assessment and observation with timely and appropriate treatment may reduce the long-term effects of IVH.

C. More research is needed to implement therapies that may reduce the incidence of IVH.

D. Infant follow-up clinics and early referrals to intervention programs may also improve neurological and developmental outcomes.
References


