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A birthday tribute to the pediatrician, Professor Dilip R Patel

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Introduction

Dilipkumar Rambhai Patel was born in 1956 in the Gujarat State, India and during childhood influenced to become a physician by his beloved parents (Dr. Rambhai and Pushpa Patel) and also from having a powerful role model in his physician father. Dilip was always an outstanding student and received his BS degree at the VP & RPTP Science College, Sardar Patel University, Vallabh Vidyanagar in India with a concentration in organic chemistry. He received his Bachelor of Medicine and Bachelor of Surgery (MBBS) at Jawaharlal Nehru Medical College, Karnataka University, Belgaum, Karnataka State, India. Afterwards Dilip completed a medical internship at the SSG Hospital, Baroda Medical College, Maharaja Sayajirao University, Vadodara, Gujarat State, India. So it is easy for us to coin the following quote to the childhood of Dilip:

(Mawtar vave ne viya vadhe)
Children reap what their parent’s sow

After this superb undergraduate medical training and internship Dilip arrived in the United States and obtained a medical externship in cardiology at the Oak Forrest Hospital, Oak Forest in Illinois. He then landed a very competitive pediatric residency at the Newark Beth Israel Medical Center, Newark, New Jersey under the direction of its PICU Director, Barry Evans, MD. Dilip then was a fellow in ambulatory pediatrics under the direction of the Department’s Chair, the well-known Jules A Titelbaum, MD in Newark, New Jersey.

The first author had the great fortunate to have Dilip as a fellow in adolescent medicine from 1989 to 1991 starting out first in Des Moines, Iowa and then in Kalamazoo, Michigan. He was a remarkable fellow absorbing all the fellowship could offer and then some more! He was clearly a most inspirational
fellow and was simply beloved by all in both cities. When the first author left Des Moines to move to Michigan, the Iowa leaders wanted him to stay and work with them, but luckily he came to Michigan to complete his fellowship. Of all the remarkable things he did, Dilip was the only fellow the first author ever had who truly understood the joys and importance of scholarship that the first author tried to teach all fellows. Dilip comprehended this concept in medical education and was able to match anyone and surpass all in his milieu in many areas! All fellowship directors want to have a fellow leave and become well-known and beloved in the world outside of one’s fellowship—indeed, Dilip Patel was able to do this in a superb way!

He then returned to Newark to work with Jules A. Titlebaum MD again, but the first author was able to lure him back to Michigan as a faculty member in 1995, but only after Dr. Titlebaum was assured that Dilip would be “taken good care of.” His Newark colleagues as others in his past, were very reluctant to see him leave and a few tears were shed by his former colleagues in the process and he has always been welcomed back with honor as a visiting professor in his “place of residency birth.”

Kalamazoo, Michigan

Dilip returned to Kalamazoo and quickly distinguished himself as a faculty member with a meteoric rise to full Professor in the Michigan State University College of Human Medicine (East Lansing, Michigan) and now at the Western Michigan University Homer Stryker MD School of Medicine (Kalamazoo, Michigan). Dilip is also a Clinical Professor in the Department of Pediatrics at Michigan State University College of Osteopathic Medicine (East Lansing, Michigan) and an Adjunct Professor in the Department of Speech Pathology and Audiology at Western Michigan University (Kalamazoo, Michigan).

Because of his brilliance and extensive scholarship, he was able to become board certified in general pediatrics, adolescent medicine, sports medicine, developmental-behavioral pediatrics, and neurodevelopmental disabilities. The sports medicine certification is a conjoint board with the American Board of Pediatrics (ABP) and the American Boards of Internal Medicine, Family Medicine, Emergency Medicine, and Physical Medicine / Rehabilitation. The adolescent medicine certification is a conjoint board with the ABP, Internal Medicine, and Family Medicine. The neurodevelopmental disabilities certification is co-jointly with the ABP and the American Board of Psychiatry and Neurology.

His penta-board certifications are truly unique by any standard and reflective of Dilip’s knowledge and capabilities. He continues to absorb information at a truly remarkable rate. In 2011 he became a certified physician executive (CPE) — Certifying Commission in Medical Management from the American College of Physician Executives. He had an another banner year in 2012 becoming certified in Medical Quality (CMQ) from the American Board and American College of Medical Quality; in addition he became a CPHQ (Certified Professional in Healthcare Quality) — Healthcare Quality Certification Commission from the National Association for Healthcare Quality (NAHQ). In 2013 obtained his MBA degree from the University of Massachusetts Isenberg School of Management (Amherst, Massachusetts) with a concentration in medical management. The first author is a proud fellowship director and can brag as few fellowship directors can!

It is fortunate for Kalamazzo that Dilip has stayed and he has become the medical director in the Department’s General Pediatrics Outpatient Service as well as Associate Pediatric Residency Director in the Department of Pediatric and Adolescent Medicine, Western Michigan University Homer Stryker MD School of Medicine. Graduate medical education has entered the Next Accreditation System (NAS) as of July 1, 2013 with new changes and requirements. He was also a college health physician at Western Michigan University for many years providing a special service in sports medicine. Dilip has been a remarkable faculty member as he actively seeks out this new movement and help the Department “grab the reins”, while entering this GME new era with confidence and progress.
Recognition

Of course such a stellar performance has led to many certificates of professional recognition and awards. He received the Gateway Maternal and Child Health Consortium Certificate of Appreciation (Newark, NJ) in 1995, and the Award for Excellence in Research and Scholarly Activities from the Michigan State University Kalamazoo Center for Medical Studies (Kalamazoo, MI) in 2003 and 2005. In 2009 Dilip received the prestigious William B Weil Jr, MD Endowed Distinguished Pediatric Faculty Award from the Department of Pediatrics and Human Development at Michigan State University College of Human Medicine (East Lansing, MI). Dr. Weil was the founding Chair of that department and was a nationally recognized academician and scholar in pediatrics. In 2010 Dilip was awarded the Adele D. Hofmann Visiting Professorship Award in Adolescent Medicine from the Society for Adolescent Health and Medicine. Adele Dellenbaugh Hofmann (1926-2001) was a leading force and icon in the development of adolescent medicine in the 20th century in the United States. In 2012 Dilip received the Western Michigan University Homer Stryker MD School of Medicine Pediatric resident teaching award.

Dilip is a member of many professional societies including the American Academy of Pediatrics, the American Academy of Cerebral Palsy and Developmental Medicine, the American College of Sports Medicine, the American College of Physician Executives, the American College of Physician Executives, the American Medical Informatics Association, the Healthcare Information Management Systems Society, and others.

He is a sought-after reviewer for many journals. Dilip was an International editorial advisory board member for the Indian Journal of Pediatrics (1999-2009). He has lectured in many countries of the world and in many parts of the United States. For example, he was co-course director in Postgraduate Course in Sports Medicine for the Indian Academy of Sports Medicine (Jaipur, India in 2000) and the co-course director for the International Training Program in Adolescent Health for the Indian Academy of Pediatrics in 2002 (New Delhi, India). In 2005 he was co-course director for the Donets Regional Maternity and Child Care Center Comprehensive Course in Adolescent/Youth Health (Svyatogorsk, Ukraine).

Dilip is a Charter member as well as Advisory Board/Medical Consultant for the Association of Adolescent and Child Care in India (NGO). He was on the editorial boards for Adolescent Medicine Clinics, the Indian Journal of Pediatrics, and the Asian Journal of Paediatric Practice.

Dilip has been active in his many fields both nationally and in his now home State of Michigan. For example he has been a medical consultant in the Children’s Special Health Care Services (Department of Community Health) since 2008 as well as a member of the advisory committee for the Early Hearing Detection and Intervention Program for the Department of Community Health in the State of Michigan. He has been the leader of a state-wide, annual conference in Developmental Disabilities for many years. From 2007 to 2012 he was a member of the American Academy of Pediatrics: PREP:DBPeds: Pediatrics in Review and Education Program: Developmental Behavioral Pediatrics Self Assessment Program.

He has been a volunteer at many local activities including being a tournament physician since 1996 for the United States Tennis Association 16-18 Boys National Championships Annual Event held in Kalamazoo, Michigan. Dilip has been interviewed by various journals and television programs over the years, because of his vast knowledge as well as experience in pediatrics.

His many research projects cover a vast array of pediatric topics including surveys of primary care physicians (various topics), use of depo-medroxyprogesterone acetate in adolescents, sports medicine education in pediatric residency programs, use of dexamethasone suppression testing in adolescents with depression, knowledge of sports medicine personnel (i.e., high school coaches, physical education instructors, athlete trainers) on asthma management for children and adolescents, prevalence of nutritional supplement use among American high school students, prevalence and patterns of breast injuries in female collegiate athletes, referral patterns for consultations to pediatric orthopedic clinic practices, survey of nutritional supplement advertisements in lay public magazines, audiological profile of children with fetal alcohol syndrome, and others. These projects were presented at various local
and national meetings usually with one or more of his trainees.

**Publications**

His publication output has been truly prodigious and includes over 21 books, over 24 edited journal issues, over 124 book chapters, over 163 journal articles, over 30 non-referenced publications (i.e., editorials, prefaces, book reviews, others), over 30 special research presentations/abstracts (local, national, international), over 26 case studies presented at the national American College of Sports Medicine (with his residents), over 30 international presentations around the world, over 25 national presentations, over 25 regional/local presentations, over four formal board review courses, and over 52 pediatric grand round lectures. With Professor Dilip R Patel, one has to say “over…” because once this tribute is published, there will have been more and more produced!

Thus, as Professor Dilip R. Patel MD turns 60 in 2016 it is fitting and proper to ponder on the life and contributions of this amazing and outstanding person. There have been and will be many remarkable Patels coming from the Gujarat State, India. Like many others, Dilip speaks Gujarati in addition to Hindi and English. Gujarati is an Indo-Aryan language, which is part of the Indo-European languages and spoken by over 65 million persons in the world. Dilip is certainly one of the most remarkable of these Gujarati-speaking Patels from the Gujarati state in India. He has passed the MD mantel received from his father on to his son Neil Patel, MD, who is in training to become an outstanding surgeon in the United States. His loving wife, Ranjan, has been with Dilip for many years guiding both men in her life toward amazing successes.

**Collaborator and friend**

The first author has had the unique and serendipitous privilege in guiding and then working with Professor Dilip R Patel for the past quarter of a century. He was a most outstanding fellow in adolescent medicine who has taught me more than I ever taught him. He made my fellowship directorship most rewarding and allowed me to “tongue-in-cheek” say to all, as he achieved one amazing accomplishment after another, that “I taught him all he knows!” Many of his publications have been with me and it has been a most rewarding and happy partnership. He is admired by countless former and current medical students, residents, staff, and faculty for his spectacular accomplishments in teaching, education, and patient care. Professor Dilip R Patel has become my younger brother in academic pediatrics and adolescent medicine. It is with great joy and wonderment that I wish Professor Dilip R. Patel a joyous happy birthday and a wish for many, many more as you enter the sexagenarian decade of your accomplished life.

**International friendship and collaborator**

The second author through his friendship with Hatim A Omar, MD, FAAP, Professor of Pediatrics and Obstetrics/Gynecology, Children's Miracle Network Chair and Chief of the Division of Adolescent Medicine and Young Parents Program at the Kentucky Children’s Hospital in Lexington, became a friend with the first author of this editorial and therefore over the past decade or more also a collaboration and friendship with Dilip.

In addition to joint publications and work, where we over the past year have been working very closely together on the mammoth international textbook project on health care for people with intellectual and developmental disabilities (1), we have also enjoyed time spend both in Israel and the United States and hopefully many more years together in friendship and health.

We therefore both of us wish a happy birthday to Dilipkumar Rambhai Patel, MBBS, MD, MBA, CPE, CPHQ, CMQ, FAAP, FACSM, FSAHM, FAACPDM with many years of friendship together and health.

Janam divas ni shubhechchha (Best wishes for birth day!)

Velo uthe veer, Bal buddhi vade ane sukhiyu rahe anu shareer (Early to bed, early to rise, makes a man healthy, wealthy, and wise or early rising: A natural, social, and religious duty from Benjamin Franklin, 1706-1790) (2)
References


REVIEW ARTICLES
Development: The human nervous system

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Abstract
An understanding of the basics of neurological development is important for optimal care of newborns, since it helps re-assure the provider when a child is developing within normal limits or alerts to abnormal patterns of development and the need for early intervention. This discussion reviews the most current understanding of the complex processes of development of the human nervous system, with emphasis on making the material readable and easier to comprehend without losing vital content. The pediatrician, the general practitioner or the mid-level provider who cares for newborns and infants will benefit from this summary, but the material will also be a good resource for the neurodevelopmental pediatrician and other experts who need a succinct refresher and update on this topic.

Keywords: Development, nervous system, pediatrics, newborn

Introduction
Traditionally, human nervous development has been studied or grouped into three broad chronological categories, namely embryogenic period, fetal period, and post-natal period. Recognized stages in pre-natal brain development include induction, proliferation, migration, differentiation, and synaptogensis while post-natal development can be further divided into the early childhood, childhood and adolescent/young adult stages.

The development of the human nervous system is arguably the most fascinating of known life processes. Brain development is guided by both intrinsic and extrinsic factors. The intrinsic genetic codes predominantly determine form and symmetry and stimulate the neural circuitry for function while extrinsic factors starting early in-utero and continuing throughout life, modulate final brain form, adaptability and function for good or bad. The lengthy process of human brain development begins as early

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as the third week of gestation when neural progenitors differentiate. It continues through late adolescence and to some extent, throughout our lifespan, with continuous synaptic extensions and pruning.

Broadly, primary neurulation (formation of neural tube, excluding those regions caudal to the lumbar region) occurs at week 3 to 4 post-conception, prosencephalic development occurs at 2 to 3 months post-conception, neuronal proliferation and migration between 3 and 5 months, canalization at 3 to 7 weeks; myelination take years to complete while neuronal/synaptic pruning peaks in adolescence but goes on for life. Simply outlined:

- The bilaminar (epiblast and hypoblast) embryo becomes trilaminar through gastrulation
- The ectoderm from the epiblast gives rise to two types of progenitor cells including neuroectodermal cells and epidermal ectodermal cells.
- A complex cascade of molecular signaling is involved in the differentiation of the embryonic stem cells into neural and other progenitors.
- The notochord and somites form under the ectoderm and are involved with signaling and patterning of neurulation but do not form any intrinsic part of the nervous system.
- Next the neural plate forms from a primitive neural area (first seen at about embryonic day 18) in the ectoderm at 3 to 4 weeks post-conception
- The neural plate then folds into a neural groove and neural crest
- Next, the neural groove curls into a neural tube, with the neural crest still beside it
- The neural tube then differentiates into distinct regions (primary vesicles); the forebrain (Prosencephalon), midbrain (Mesencephalon), hindbrain (Rhombencephalon), and the spinal cord.
- Recent fetal gene expression studies strongly suggest that the regional differentiation of the CNS occurs in response to a genetically determined gradient of signaling by pathways such as the sonic hedgehog. In other words, the amount of signaling and its receptors vary according to the regions of neural tube resulting in differential expression of secondary pathways and key neural characteristics.
- The three primary vesicles of the brain later give rise to five secondary vesicles as follows:
  - Prosencephalon: (i) telencephalon - “endbrain, forms cerebral hemispheres, and (ii) diencephalon - “between brain”, forms optic outgrowth
  - Mesencephalon: mesencephalon
  - Rhombencephalon: (i) metencephalon - behind brain and (ii) myelencephalon – “medulla brain”
- The neural crest migration and derivatives occur
- Ectodermal placodes form components of the special senses, including lens placode, otic placode (otocyst), and nasal placode
- The forebrain becomes di-hemispheric, expands to cover the midbrain, and by weeks 28 to 40 expands greatly in surface area via the formation of sulci and gyri.
- The spinal cord forms with alar and basal plats respectively developing into the dorsal (sensory) and anterior (motor) horns.
- The canal, ventricles, CSF and blood supply systems form and reorganize

Molecular events, such as gene expression and environmental inputs are essential for normal brain development, which happens within a tightly controlled but continually adapting genetically programmed context. However, neither genes nor environment is believed to bode determinative or definitive outcomes but disruption of either can significantly alter the final neural product. Instead, brain development follows a complicated succession of active, adaptive and neuroplastic processes, which act to promote the appearance and differentiation of new neural structures and functions.

Some sources propose that inflammatory and endocrine stress mediators are major factors that influence fetal brain development, by altering key signaling critical pathways, such as the mammalian target of rapamycin, Sonic hedgehog, Wnt (wingless), and reelin signaling.
Spanish histologist Santiago Ramon y Cajal (1852-1934) is credited with much of the basics we know about neurons. Cajal described neurons as the basic elements of the nervous system and laid out the life history of cells: birth, differentiation and growth, migration, maturation and death. He also initiated our understanding of their overproduction, pruning in development and interconnection into circuits.

### Table 1. Eight stages of development

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Mitosis / Proliferation</td>
</tr>
<tr>
<td>2.</td>
<td>Migration</td>
</tr>
<tr>
<td>3.</td>
<td>Differentiation</td>
</tr>
<tr>
<td>4.</td>
<td>Aggregation</td>
</tr>
<tr>
<td>5.</td>
<td>Synaptogenesis</td>
</tr>
<tr>
<td>6.</td>
<td>Neuron Death / Apoptosis</td>
</tr>
<tr>
<td>7.</td>
<td>Synapse Rearrangement</td>
</tr>
<tr>
<td>8.</td>
<td>Myelination</td>
</tr>
</tbody>
</table>

There are 8 stages of development, which are sequential for each neuron (see Table 1). However, when considering the entire brain, these stages are all happening concurrently throughout fetal development period. Production of neurons in humans starts at 42 days post-conception (Embryonic Day 42) and is almost done by week 20 (mid-gestation). Freshly made neurons do not have axons or dendrites. As they are produced, the migrating neurons are guided by radial neuroglia, maturing as they migrate. On reaching their destinations in different regions of the brain, they make associations, via axons and dendrites, with other neurons resulting in elementary neural networks. Growth cones with their filopodia on the tips of these axons crawl forward as they ramify the axons training behind them in response to chemical cues by chemoattractants and chemorepellants.

The major fiber pathways, including the thalamocortical pathway, are complete by the end of the prenatal period. Upon completion, the human brain is realistically estimated to contain:

- With each nerve cell capable of making 10,000 connections with other nerve cells
- Estimated 3 trillion connections

### Embryogenic period (conception through 8 weeks gestation)

#### Primary neurulation

The early stages of the central nervous system (CNS) have been traced to the period of the zygote. Approximately day 18 to 21 post-conception, the notochord and chordal mesoderm induce the formation of the CNS by signaling a group of cells in the ectoderm at the dorsal portion of the embryo to form a thick and flat structure called the neural plate. Continuing induction by the chordal mesoderm causes the lateral margins of the neural plate to curl dorsally towards each other until a tubular structure called the neural tube emerges. The first part of the tube to fuse is around the medulla. This happens on about day 22. Fusion then progresses in both rostral (cephalic) and caudal directions, with closure of cephalic end (anterior neuropore) occurring on approximately day 24.

The caudal end (posterior neuropore) of the neural tube closes at the upper sacral level on about day 26 as part of a different process called canalization and regressive differentiation, which also features formation of the caudal segments of the spinal cord from the caudal 1/3 of the neural tube. The dura mater and axial skeletal elements result from continuing interaction between the neural tube and neighboring mesoderm. Neural crest cells also appear at the time of the tube closure and later give rise to:

- Sensory ganglia of cranial nerves
- Dorsal root ganglia
- Parasympathetic and sympathetic ganglia
- Schwann cells
- Cells of arachnoid and pia mater
- Cardiac neural crest
- Craniofacial bones and connective tissue
- Tooth primordial
- Enteric plexi
- Thymus, parathyroid, thyroid glands
• Melanocytes
• Cells of the adrenal glands

Details of molecular events involved in the processes above are still being investigated. For the sake of simplicity they include microfilaments (involved in tube formation), cell adhesion molecules (involved in cell-cell and cell-extracellular matrix recognition), signaling by regional patterning genes (especially sonic hedgehog – SHH), homeobox genes, transcription factors, surface receptors and second messengers.

Until closure, the lumen of the neural tube, called the neural canal, communicates with the amniotic fluid. As the walls of the neural tube forms the brain and the spinal cord, the neural canal evolves into the ventricular system of the brain and the central canal of the spinal cord.

Secondary neurulation/formation of the caudal tube

Secondary neurulation takes place following closure of the posterior (caudal) neuropore and involves the lower sacral and coccygeal regions. It occurs between week 4 and week 7, starting with canalization and progressing to retrogressive differentiation. On about day 28 to 32, the caudal cell mass (a yet undifferentiated mass of cells at the caudal end of the neural tube) becomes vacuolated, coalesces and then enlarges. Soon they come in contact with the central canal. Retrogression of much of the caudal mass starts at about 7 weeks and continues until a little after birth, giving rise to the ventriculus terminalis in the conus medullaris and the filum terminale.

Clinical implications of neurulation

Perturbations of the processes involved in primary and secondary neurulation result in neural tube closure defects such as anencephaly and spinal dysraphisms, often with associated axial skeletal aberrations. Pre-natal diagnosis of these defects has become routine, especially with the combination of screening maternal serum alpha fetoprotein (AFP) levels (best done at 16 to 18 weeks) and ultrasonography. Ultrasound could be confirmatory but fetal MRI is assuming greater prominence for confirmation and characterization.

Alpha fetoprotein is used as marker because it is the major fetal protein in humans and it can be detected from about day 30 post-conception, peaking in the amniotic fluid by about week 9 to 13. AFP levels will be elevated both in the amniotic fluid and in maternal serum with open neural tube defects as with any open lesion (such as gastroschisis).

Early fetal period (8 weeks to 20 weeks of gestation)

Initially, the neural tube is a single layer of cells called germinal epithelium. These neural stem cells are pluripotent and give rise to both the glia and the neurons as interactions with notochord and prechordal mesoderm continue under the influence of strong molecular signaling cascades/pathways, which must maintain dorsal-ventral polarity in the neural tube.

Induction

The “inductive cascades” can be summarized as follows:

• Segmental - along the length of the neural tube: Hox/Lim gene expression
• Dorsal identity: nodal pathway involving bone morphogenetic proteins (BMP) from epidermis: roof plate cells in neural tube
  – TGF-B cascade: cell differentiation (dorsal, sensory neurons)
  – Dorsalin
• Ventral identity: Shh pathway involving Sonic hedgehog (Shh) from notochord and retinoic acid from somites: floor plate cells of neural tube
  – Shh gradient, Patch receptor: cell differentiation (ventral, motor neurons)
  – BMP-7/chordin interactions.

Unequal rates of growth and migration of cells result in constrictions, flexures, thickenings, invaginations, and evaginations. Three dilations and
Human nervous system

The appearance of the pontine flexure opens the lateral walls of neural tube out like a book, generating the fourth ventricle and causing the sulcus limitans (shallow groove separating the alar and basal plates on either side of the tube) to lie in its floor while the alar plate changes position in this region, from a dorsal to a more lateral orientation. A process called segmentation, which is crucial for the development of several structures and nuclei of the CNS, starts at the 5-vesicle stage of brain development.

Segmentation

Segmentation of the three anterior portions of the brain (telencephalon, diencephalon and mesencephalon) is driven by outward growth from the ventricles. The cortex is the first to grow, but not the first to differentiate. Then follows growth of the limbic areas in a mainly radial direction from the mesencephalon, which at this time, has folded into an inverted U figure. Structures of the telencephalon and diencephalon grow further faster and completely encase the mesencephalon (mid brain) and the anterior portions of the metencephalon (caudal hind brain). The cortex thus ends up the only outer brain structure in the anterior of the head.

Segmentation in the hindbrain structures and spinal cord does not occur from the ventricles but from various specialized structures neighboring the neural tube.

Cells derived from the neural crest aggregate into eight distinct segments called rhombomeres, which surround the hindbrain (metencephalon and myelencephalon). These segments are believed to determine the organization of the innervation of cranial nerves and nuclei in the hindbrain as well as surrounding non-neural tissues.

Segmentation of the spinal cord is determined by non-neural tissues surrounding that section of the neural tube. At about 19 days of gestation, mesodermic tissue forms into a segment grid on each side of the developing and curling tube. These segments, known as somites, proceed to develop into the ribs and vertebrae. They also determine the development and aggregation of neurons into the motor ganglions of the spinal cord.

In addition to paired telencephalic evaginations seen about day 29, which later form the cerebral hemispheres, the prosencephalon also gives rise to three other evaginations that develop into the specific structures in the brain:

- Optic vesicles, which form the optic nerve and retina. The optic vesicles are first to appear, before the anterior neuropore closes, but becomes more prominent on day 29 at a position just caudal to where the telencephalic evaginations will appear.
- A midline evagination in floor of forebrain which forms the posterior pituitary gland.
- Another midline evagination in caudal part of roof of forebrain forms the pineal gland.

The telencephalic evaginations are recognizable as developing cerebral hemispheres by the end of the embryogenic period (week 8). Their outer surface remains smooth until about week 12 when gyri formation is evident, starting from their sagittal portions closest to the falk cerebri.

The CNS meninges result from a primordial meninx formed by mesenchymal condensation around
the neural tube. The primordial meninx is initially 2-layered: the dura and leptomeninges. Later, a fluid-filled layer forms within the leptomeninges, resulting in the arachnoid and pia maters. The fluid-filled layer is the sub-arachnoid space. Meninges are mostly from mesoderm but parts of the leptomeninges surrounding the forebrain and midbrain are of neural crest origins. All brain structures and nuclei are differentiated between the third and seventh months. See Table 2 for adult derivatives of fetal brain structures.

### Table 2. Adult derivatives of early fetal structures of the human CNS

<table>
<thead>
<tr>
<th>Neural Tube</th>
<th>Primary Vesicles</th>
<th>Secondary Vesicles</th>
<th>Major Adult Structures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>Prosencephalon</td>
<td>Telencephalon</td>
<td>Rhinencephalon, Amygdala, Hippocampus, Cerebrum</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(cerebral cortex), Basal Ganglia, lateral ventricles</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diencephalon</td>
<td>Epithalamus, Thalamus, Subthalamus, Hypothalamus, Pituitary gland, Pineal gland, third ventricle</td>
</tr>
<tr>
<td></td>
<td>Mesencephalon</td>
<td>Mesencephalon</td>
<td>Tectum, Cerebral peduncle, Pretectum, cerebral aqueduct</td>
</tr>
<tr>
<td></td>
<td>Rhombencephalon</td>
<td>Metencephalon</td>
<td>Pons, Cerebellum, fourth ventricle</td>
</tr>
<tr>
<td></td>
<td>Myelencephalon</td>
<td></td>
<td>Medulla Oblongata, fourth ventricle</td>
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</table>

#### Cell migration and differentiation

As the gross CNS structures are forming, histologic changes are also taking place in the respective regions of the developing CNS. Upon closure of the anterior neuropore of the neural tube, neuroepithelial cells begin to differentiate into the periventricular germinal layer. This layer will generate both the neuroblasts and glioblasts. Neurons and glia have the same early embryonic origins before undergoing a lengthy multifaceted developmental process of growth, differentiation, interaction and maturation.

Neurons appear first as neuroblasts and migrate towards the cortical plate. spongioblasts (glioblasts), which will become the supportive glia, appear a little later except for a special type of developmental glial cell called radial glia, which extend processes from the periventricular layer to the pia matter, thus providing the channels for neuroblasts to migrate out from the proliferating ventricular layer. The radial glial cells are also involved in the ensuing columnar organization and lamination of the CNS. They have been shown by immunohistochemical staining of glial fibrillary acid protein (GFAP) as early as 12 weeks of gestation.

The several different types of neuroglia, like radial glia, astroglia (fibrous and protoplasmic), oligodendroglia, microglia (phagocytic glia) and Schwann cells appear at different times in CNS development and have varying functions in the development and maintenance of the central and peripheral neural networks. The multiplying neuroblasts form a layer, peripheral to the neuroepithelial cells, called the mantle layer. Neuronal processes from these neuroblasts extend peripherally from the mantle layer. This collection of fibers forms the marginal layer. Mantle neuroblasts do not migrate but become the corpus striatum of basal ganglia in the brain and the gray matter of the spinal cord.

#### Spinal cord architecture

As the mantle layer neuroblasts proliferate, they organize into dorsal (called alar plates) and ventral (called basal plates) columns on either side. The basal plates differentiate into somatic motor neurons of the ventral horn, whose axons exit the spinal cord as the ventral roots of spinal nerves, which innervate voluntary muscles. The alar plate neuroblasts differentiate into association neurons/interneurons, which interconnect the motor neurons of the basal plate and the neural-crest-derived sensory neurons of the dorsal root ganglia. Neuroblast collections between the dorsal and ventral horns in the regions T1 to L2/3 and S2 to S4 form the intermediate/lateral horns and differentiate into the sympathetic and
parasympathetic preganglionic neurons. The marginal layer subsequently myelinating and in the spinal cord, becomes the white matter.

Cerebral architecture

The periventricular germinal layer remains a dense continuous layer until it begins to slim out at about gestation week 30, after which it becomes a layer of cell islets, which are evident from about 36 weeks of gestation to about 12 months beyond birth. Recent gene expression studies strongly suggest that the capacity for producing neurons from progenitor cells is preserved in the hippocampal region of the human brain, even in adults.

This is an area of intense research. In the brain, the 5-layered cerebral cortex is formed when the marginal layer of the 3-layered neural tube is invaded by neuroblasts, which assemble on the outer surface to develop into layered cortical grey matter in an inside-out laminar pattern. In other words, the deepest cells of cortex are the earliest to form while the neurons arising later migrate to more superficial areas. This also explains why the cerebral grey matter is peripheral to the white matter. The basic ventral-basal and dorsal-alar columnar transformation of the neural tube is maintained in the brainstem but is modified significantly elsewhere. In the forebrain, alar plates become more lateral instead of dorsal, the roof of the neural tube thins out and widens, and in the prosencephalon, the basal plates virtually involutes while alar plates grow. Thus the telencephalon is formed almost entirely from alar plate. Some differentiating neuroblasts, migrate and organize into groups within the brain. These groups are called nuclei and are either motor or sensory depending on whether they originate from basal or alar plates. These include specialized cranial nerve nuclei and other nuclei, which act as relays. The organization and depth of the cerebral hemispheres change over time and structures like the corpus striatum (basal nuclei), temporal lobes and hippocampus become identifiable.

The internal capsule (IC) is formed by many of the nerve fibers running from cerebral neurons through the corpus striatum (caudate nucleus and lentiform nucleus), to the thalamus and lower CNS. Each IC lies lateral to the thalamus and medial to the lentiform nucleus.

The corpus callosum consists of commissural nerve fibers joining the cerebral hemispheres. The structure that becomes the corpus callosum can be traced back to the dorsal lamina terminalis a small commissure constituting the most rostral midline structure of neural tube. It undergoes a caudal expansion during cerebral hemispheric growth. Also, the hippocampi apparently regress somewhat and the cerebral fissures form. Other commissural structures (linking the hemispheres) include the optic chiasm, the fornix, and the anterior and posterior commissures.

The olfactory bulbs are formed by anterior projections from the telencephalon. The floors of the cerebral (telencephalic) vesicles are fused with the diencephalon by a thin roof plate, which will give rise to the choroid plexi of lateral ventricles.

As in the telencephalon, the basal plates of the diencephalon do not contribute much. As a result, most of diencephalic structures derive from the alar plates. The third ventricle increases in size with growth of the diencephalon. The alar plate is displaced laterally in this process. Neuroblasts from the most dorsal regions of alar plate form the thalamus while those from the ventral regions form the hypothalamus. Hypothalamic nuclei are mainly involved in the regulation of homeostasis and the management of pituitary gland function. The thalamus is essentially a complex relay of information (including auditory, olfactory and visual) from the lower parts of the CNS and other specialized brain centers to the cerebral cortex.

The optic vesicles (developed much earlier, becoming CN II), the infundibulum (forms pituitary stalk and posterior pituitary), and the pineal gland (from a conjoined pair of buds), are all outcrops of the third ventricle. A choroid plexus also forms on the roof of the third ventricle.

The typical basal and alar arrangement of the neural core in is largely unmodified in the mesencephalon. A pair of superior and a pair of inferior colliculi, which serve as sensory (visual and auditory, respectively) relays to the cortex, form within the alar plates and are collectively called the tectum. The basal plate of the mesencephalon becomes the tegmentum, in which somatic afferents
of the CN III motor nuclei form, along with a smaller nucleus that innervates the sphincter of the pupil. CN IV motor nuclei are formed by neuroblasts which migrated from the metencephalon. The origin of the substantia nigra and red nuclei are uncertain but it is known that they relay visual and auditory information between the tectum and the cerebral cortex.

Packs of fiber tracks develop from the marginal layer of the mesencephalon. These are the peduncles, which interconnect the cerebral cortex with the cerebellum and the spinal cord. Unlike in other segments of the brain, the central canal in the mesencephalon does not undergo morphogenic change, except that it narrows significantly due to growth of surrounding structures. This is the aqueduct of Sylvius, relatively prone to congenital stenosis causing obstructive hydrocephalus.

Neuroblasts in the myelencephalon develop the somatic afferents of cranial nerves (CN) V to VII in a lateral to medial pattern; special visceral afferents also arise to the taste buds; and the heart and GI tract sensory nuclei. The major relay pair called olivary nuclei are also formed by neuroblasts, which migrate anteromedially. General visceral efferents arise from the basal plate to innervate the involuntary muscles of lungs, heart and GI tract. The special visceral efferents of CN IX to CN XI and somatic efferent of CN XII also form from the myelencephalic basal plates.

Maintaining the general basal-to-motor and alar-to-sensory or alar-to-relay organization, the alar and basal plates in the metencephalon develop the special visceral efferents of the CN V to VII and somatic efferent of CN VII. Three basic motor nuclei, which supply the caudal organs like the submandibular and sublingual glands also arise from basal plates in this region. Three main sensory nuclei are formed from the metencephalic alar plates, including trigeminal and vestibule-auditory afferents as well special and general visceral afferents. The metencephalon also gives rise to the pons and the cerebellum.

The formation of the cerebellum derives in large part from the rhombic lips of the pontine flexure. The cerebellum grows significantly towards the end of the embryonic period and by the end of the first trimester, the cerebellar hemispheres are well defined; their surfaces are still smooth and the vermis can be seen developing in the medial raphe. Foliation of the cerebellum starts around week 14 and by week 28, the surface area of the cerebellum has increased 2000-fold, covering the pons and the fourth ventricle in the process.

Histologic changes in the cerebellum begin with an internal granular layer formed from germinal cells of the pontine flexure rhombic lip. During weeks 20 to week 30, purkinje cell precursors form a lean lamina separated from the internal granular layer by a clear zone called lamina dessecans, which disappears at about week 30 to 32. Neuroblast proliferation and peripheral migration results in a five-layer cerebellum starting with the formation of the outer granular layer by neuroblasts from the mantle layer of the 3-layer precursor. The outer granular contains cells that multiply the most, differentiate into diverse neuron types and form the cerebellar cortex.

Other cell layers also form including the outermost molecular layer, the intermediate Purkinje layer and the innermost granular layer. During proliferation, some neuroblasts form the dentate nuclei and other deep cerebellar structures. Overall morphogenesis of the cerebellum is not finished until about 2 years after birth.

### Ventricular and CSF system

As highlighted in Table 1, the diamond-shaped lumen of the neural develops into the ventricular system as the respective structural regions of the CNS are formed. The lumen of spinal cord is the central canal, the cavity of the rhombencephalon is the fourth ventricle, and the cavity of the diencephalon is the third ventricle, while the cavities of the cerebral hemispheres are the lateral ventricles. The lumen between the third and fourth ventricles is the narrow aqueduct of sylvius, the lateral ventricles communicate with the third ventricle via the foramina of monro while the fourth ventricle opens into the subarachnoid space through the midline foramen of magendie and the bilateral foramina of luschka. In a normally developed human CNS, the central canal and the ventricles are continuous, allowing the cerebrospinal fluid (CSF) to flow freely within the brain and between the brain and the spinal cord.
CSF is produced by the choroid plexi found all through the ventricular system, except that none exists in the frontal or occipital horns of the lateral ventricles or within the cerebral aqueduct (aqueduct of Sylvius). The choroid plexi are essentially a blood-CSF barrier and filtration system made up of a network of blood capillaries and modified ventricular ependymal cells, the ependymal cells having originated from neuroepithelial cells. CSF is absorbed by arachnoid granulations found mainly in the superior sagittal sinus. The rate of CSF absorption matches or slightly exceeds the rate of production to maintain normal CSF pressures. Arachnoid granulations are small outcrops of the meningeal layers into the lumen of the venous sinus. CSF returns from the subarachnoid space into the venous system due to the mechanism of differential fluid pressure, whereby pressure within the subarachnoid space is higher than that within the venous system.

Functions of the CSF include: shock absorption/protection, transportation of nutrients, hormones and waste, maintenance of intracranial pressure (ICP) and homeostasis. CSF volume auto-adjusts to maintain a normal ICP, until this natural capacity is exceeded.

**CNS blood supply development**

The blood supply and venous drainage of the CNS goes through several changes before maturation. Discussion of the detailed development is beyond the scope of this chapter.

In the adult brain, the arterial blood supply is derived from two arterial systems: the carotid system and the vertebra-basilar system. The circle of Willis is a series of anastomotic channels found at the base of the brain, which allows inter-flow between the two systems.

Also in adults, the arterial blood supply to the spinal cord comes from two branches of the vertebral artery, which run the length of the spinal cord and form an irregular plexus around it. These are the single anterior spinal artery and two posterior spinal arteries. For the sake of simplicity, the venous drainage generally mirrors the arterial supply.

**CNS growth in the third trimester**

Advanced image-processing studies have applied complex algorithms and three-dimensional magnetic resonance imaging (3-D MRI) to estimate total brain volumes, along with cerebral gray matter, myelinated/unmyelinated white matter and cerebrospinal fluid in a normally developing brain between gestation weeks 29 and 41. Some studies have involved premature and mature newborns in the same age-range.

The studies show that the volume of total brain tissue grew linearly over this period at an average rate of 22 ml/week, with the total grey matter also increasing linearly at a rate of 15 ml/week. Relative to the total intracranial volume, the grey matter grew at approximately 1.4% extra. This rapid growth in total grey matter is equates to a fourfold increase in cortical grey matter over the third trimester. However, both intraventricular and extracerebral CSF volumes did not change significantly during the same period.

<table>
<thead>
<tr>
<th>Phase</th>
<th>Age</th>
<th>Major Development</th>
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</thead>
<tbody>
<tr>
<td>Prenatal</td>
<td>Conception to birth</td>
<td>Organogenesis, morphogenesis and Rapid size increase</td>
</tr>
<tr>
<td>Infancy</td>
<td>Birth to 2 years old</td>
<td>Motor and language development</td>
</tr>
<tr>
<td>Childhood</td>
<td>2 to 12 years</td>
<td>Abstract reasoning</td>
</tr>
<tr>
<td>Adolescence and Early adulthood</td>
<td>13 to 25 years</td>
<td>Identity, judgment (related directly to maturation of the “Prefrontal Cortex”)</td>
</tr>
</tbody>
</table>
Post-natal development

Brain development in the child is a complex process, which includes both linear and non-linear development in structure and function (Table 3). Normal development and function of the CNS requires proper synaptic formations between neurons and adequate timely myelination of their nerve fibers. Extensive neural network extension and synaptogenesis takes place during the fetal period but a significant amount occurs in the post-natal period. Most myelination occurs after birth, especially during the first two years. Significant positive correlation have been found between cognitive function measures, such as intelligence quotient (IQ), and the volume of regional gray matter in several regions of the brain, including the prefrontal cortex, orbitofrontal cortex, and cingulate gyrus.

Lifestyle and brain development - breakfast habits

Since the brain continues to develop throughout childhood and adolescence, proper nutrition, including appropriate breakfast habits diet during these periods affect brain development and cognitive function.

Recent studies have revealed that eating breakfast has an instant positive effect upon the cognitive function in children studied. It was also shown that skipping breakfast adversely affects the subjects’ short-term memory, problem solving, and attention. Studies of school breakfast programs have also demonstrated the long-term effects of breakfast on cognitive performance, which was overall better in well-nourished children, adjusting for known confounders.

Furthermore, a correlation has been found between breakfast staple type, gray matter volume in children and several cognitive functions. Taki and Kawashima recently used advanced imaging to study a large group of healthy children aged 5–18 years and reported that gray matter volume was not only related to daily breakfast habits but also depended on the glycemic index (GI) of the breakfast staple. They posited that foods with low GI when consumed in sufficient amounts were better at providing a more stable supply of glucose to the brain versus high GI foods, which are easily digested low-fiber carbohydrates that provided a rapid peak glycemic rush followed by overall lower circulating blood glucose two hours later.

A major fraction of the glucose consumed by the brain is used to maintain the neuronal membrane resting potential. Moreover, cerebral rates of glucose consumption are approximately two times higher in children than in adults, especially in pre-adolescence when the mean number of synapses per neuron increases. As such, stable and efficient supply of glucose, determined by breakfast type, is considered vital for brain maturation in children.

Lifestyle and brain development - sleep habits

Although the role of sleep in brain development remains debatable, recent studies strongly suggest that sleep is associated with hippocampal function and structure. One major school of thought is that memory consolidation happens mainly during sleep, when the hippocampus transfers information from the memory to the neocortex for long-term storage.

Studies in rat have shown suppression of neurogenesis and decreased proliferation of cells in their hippocampus as result of sleep deprivation.

A reduction in hippocampal volume has also been found in human patients who suffer primary insomnia. At least one study reports significant correlations between sleep and hippocampal gray matter volume based on MR images of healthy children aged 5–18 years. The study found the volume of the bilateral hippocampal bodies to correlate positively with the length of sleep by each child during weekdays, after adjusting for brain size, gender and other factors.

While the mechanism underlying this significant positive correlation is yet to be explained, it is best to apply this finding to clinical practice and ensure adequate sleep in the pediatric patient, noting that this is the period of increased neurogenesis and synaptic reorganization in the human hippocampus.
Conclusion

The last half-century has witnessed remarkable insights into this area, a growth in knowledge, which derives from the human genome project, recent advances in neuroimaging, computational neurobiology and simulation, and also progress in the time-honored disciplines of histology, cell studies and molecular biology. Dynamic and interactive models of nervous system development are replacing previously-held rigid models. The nervous system continues to develop after birth, significantly depending on the environmental stimulation it receives.

A strong persuasion for the potential role of the environment in human brain development is the fact that the human brain volume at birth is only about 35% of an adult brain. Compared to apes, the human baby is about 12 months less developed cognitively at birth but this soon changes as the brain grows and an adult brain ends up with about three to five times the brain capacity of apes, mainly due to an overall increased number of neurons and a larger cerebral cortex (encephalization). Twin-twin and adoption studies support the role of the environment but they also confirm the predominance of genetic factors.

Update on the fundamental role of genetic signaling is provided and the impact of environmental influences is emphasized, including intra-partum factors and events as well as post-partum nutrition, home environment, education, toxicology, and early intervention. The steady rise in average performance on intelligence tests over the past few decades, called the Flynn effect, is arguably an environmental effect.

The clinician who understands the basics of these complex but critical interactions is better positioned to guide families to the best neurologic outcome possible in each child, in health as well as in disease. As a specific example, understanding brain development in healthy children not only improves our understanding of the progress of brain maturation but also facilitates early evaluation and diagnosis of developmental disorders, including autistic spectrum disorders.

References


Neonatal neurology

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Abstract

Neurology of the newborn is an expanding field. The available evidence-based data still have “gaps,” and practical approaches are changing rapidly. There are significant advances in neonatal neurology, reflecting an enormous progress that was made over the past decades in identifying and treating newborn brain diseases. There are still un-answered questions, and newly emerging data is rather the rule than the exception. The explosion of knowledge and interest in basic science and clinical management issues has impacted all the many practitioners involved in newborn care. There are still enormous opportunities for new knowledge through well designed longitudinal descriptive studies and multicenter clinical trials. These complicated situations require cooperation between neonatologists and neurologists. In this discussion we cover relevant sections in newborn neurology that are supposed to serve as a useful tool for professionals with special interests in neurology of the newborn.

Keywords: Pediatrics, Neonatology, Neurology, Brain Development

Introduction

Neonatal neurology requires an interdisciplinary approach that integrates maternal, placental, fetal, and neonatal perspectives into diagnostic and treatment algorithms concerning fetal/neonatal brain disorders (1-3). Most preterm newborns need neonatal neurology care. But they are not the only group. Term babies born with congenital disorders, those who were born to sick mothers or after complicated pregnancies are also in such a need. Four million babies are born per year in the United States and 11% of those are born premature. One percent of term infants have significant illnesses at birth that also require care in the neonatal intensive care unit (NICU) (1).

Ante-partum, peri-partum, and postnatal strategies for diagnosis and therapeutic intervention must adjust to the multiple time points and etiologies...
that define neonatal neurology disorders. Therefore, neonatal intensive care has grown extensively over the past 40 years (1). Currently, neonatology is a cost-efficient mode of intensive care (4). A greater number of infants at smaller gestational ages and weight are now surviving to discharge but this is only one step in a long journey for these small and often medically fragile infants (2). Newborn patients’ brain disorders are unique. The synthesis of historical, clinical, and laboratory data implicate ante-partum, intra-partum, or postnatal time periods when brain damage occurred or was exacerbated.

Although the focus during the past decades has been on the saving of lives, it is also important to look beyond survival to issues of reducing morbidity and long-term neurological disabilities, as well as improving long-term developmental outcomes. There are promising interventions that can benefit survival as well as human development, and there is a huge public health needs to integrate these. Linking the agenda for maternal and newborn health with the emerging issues of long-term development, may well be the most appropriate strategy to ensure that we stay the course in solving one of the most important moral dilemmas of our times (3).

In this review we discuss the main issues most relevant in newborn neurology care.

**Neurologic examination of the newborn**

A comprehensive neurologic assessment should be performed in any newborn suspected to have a neurologic abnormality either based upon history or a physical finding detected during the routine neonatal assessment. Neurologists and neonatologists must frame the neurologic profile of the neonate in the context of the developmental niche (gestational maturity) during which an acquired or developmental disorder evolves. Therefore, every examination should start with estimation and mention of gestational age of the newborn.

Several authors have reported assessment of neurological functions in newborn infants (4,5). Some of these assessments have been adapted and validated for both infants born prematurely or at term. There have been number of publications that describe the newborn neurologic examination in different gestational ages aimed for different aspects (6). As in other age groups, the most relevant aspects of the newborn examination are: mental status, cranial nerves, motor and sensory examination, and the assessment of primitive reflexes (5).

These assessments can be easily and reliably used in both term preterm infants. Previously published data can help as a reference when examining newborn infant to see where the individual child stands compared with age-matched newborn infants and to identify signs that may be outside the reported range.

These assessment methods should be used routinely in the neonatal unit, at least in infants at risk of neurological abnormalities, since these examinations have been used and showed that they can reliably identify infants at risk of developing neurological abnormalities (6, 7).

Identifying early neurological abnormalities will allow early intervention, protection, and referral of these infants for rehabilitation and appropriate support for the families (5). A detailed systematic examination method is described in “Neurology of the newborn” textbook by Volpe (4).

**Neurology of the sick newborn**

Across the human lifespan, an individual faces the greatest risk of mortality during birth and the first 28 days of life, the neonatal period. Each year, nearly 4 million newborns die during this period – equivalent to around 10,000 per day. Three quarters of these deaths take place within one week of birth, and 1–2 million die during the first day following birth. Millions more suffer severe illness each year, and an unknown number are affected with lifelong disabilities (8).

Among survivors, small groups of people account for a large proportion of health care costs. Many of these were sick newborn babies. There has been a growing focus on understanding these “high utilizers” because it is thought that improving aspects of care could improve their outcomes, reduce unnecessary health care utilization, and hopefully begin to bend the cost curve trends in health care (9).

Complications during the neonatal period can be fatal or result in long-term injuries or disability. The
early post-natal period (the first seven days of life) is the critical period for initiating treatment, help and appropriate care. Providing effective care for newborns during the early post-natal period has the potential to generate the greatest gains in survival and health of any period in the continuum of care (8). In the next pages we discuss the most common and/or important medical aspects concerning the sick newborn.

Birth injuries

Birth injuries (BI) are defined as injuries sustained by the newborn during the course of labor (10). There is a wide spectrum of BI, ranging from self-limiting minor problems such as scalp injuries, to severe injuries that may lead to significant morbidity and mortality. The most common types of BI are scalp injuries and clavicle fractures (11). Linder et al. have reported an overall incidence of 24.3 per 1000 live newborns, in a retrospective study of 118,000 singleton newborns over 23 years (10). They reported several risk factors for BI including lower maternal age, lower parity, higher gestational age, higher birth weight, head circumference and length and a higher rate of instrumental deliveries and occipito-posterior position of the fetal head (10). A large cross-sectional study of 890,582 in-hospital birth discharges in the Unites States, estimated an incidence 29 per 1000 births.

Scalp injuries

Caput succedaneum is edema of the fetal head caused by pressure against the uterine cervix or the bony pelvis. This leads to an obstruction of venous return to the scalp and consequent extravasation of fluid into the interstitial tissue (12). On examination there is pitting edema that shifts with gravity and resolves within 48-72 hours after birth.

Cephalohematomas

A cephalohematoma is a collection of seroanguinous fluid under the periosteum of the skull bones (13). The hemorrhage is confined by the sutures. The swelling is usually not present at birth, and develops within the first 24-48 hours afterwards. Cephalohematomas complicate 0.2–2.5% of all deliveries (14). Higher birth weight, parity and instrumental deliveries (both vacuum extraction and forceps deliveries) have been correlated with cephalohematomas. The main complication of cephalohematomas is hyperbilirubinemia (10) but in rare cases cephalohematomas may become infected, which could lead to osteomyelitis, sepsis and meningitis.

Subgaleal hematoma (SGH)

SGH are caused by rupture of the emissary veins, connecting the dural and scalp veins. Blood accumulates between the epicranial aponeurosis and the periosteum. This space extends from the orbital ridge to the nuchal ridge and laterally to the temporal fascia, and can hold up to 260ml of blood in a term newborn. SGH is therefore a potentially life threatening condition which can lead to hypovolemia, hypotension and DIC, and is associated with up to up to 25% mortality in infants requiring intensive care (15).

The incidence of moderate to severe SGH is estimated at 1.5/10000 births (15). It is most often associated with instrumental deliveries, but may occur also in spontaneous vaginal deliveries. Optimizing outcome of a newborn with SGH requires early diagnosis; close monitoring of head circumference, blood pressure, hematocrit and coagulation studies and supportive care with fluids and blood products as required. Figure 1 below demonstrates the anatomical layers of the scalp and skull. Please refer to this when reviewing the head injuries discussed above.

Brachial plexus injuries

Erb’s palsy, also known as brachial plexus paralysis, results from damage to the cervical roots C5-C8, and T1 resulting in weakness or paralysis of the deltoid, infraspinatus muscles and the flexor muscles of the forearm. The affected arm is held straight and internally rotated with finger function usually left...
intact. When T1 is involved the infant may also exhibit Horner’s syndrome (16). Incidence of Erb’s palsy is increasing and is estimated at 0.5-4.4/1000 live births (16). Risk factors for Erb’s palsy include macrosomia, shoulder dystocia, gestational diabetes mellitus, maternal obesity, and instrumental vaginal delivery (16, 17). Most injuries are transient, with 80-92% recovery (17), however global lesions (C5-T1) have only 40% recovery, and may cause severe disability (16).

Figure 1. Anatomic layers of the scalp and skull.

**Facial nerve palsy**

Neonatal asymmetric crying facies, is a clinical phenotype resembling unilateral partial peripheral facial nerve paralysis, with an incidence of approximately 1 per 160 live births (18). Causes include perinatal trauma, intrauterine posture, intrapartum compression, and congenital aplasia of the nucleus (most commonly bilateral). Usually the cause is either facial nerve compression or faulty facial muscle and/or nerve development (18). Spontaneous resolution is expected with the former, but not necessarily with the latter etiology. Approximately 10% of the developmental cases have associated major malformations (18). Mandibular asymmetry and maxillary-mandibular non-parallelism of the gums are frequently overlooked visual clues to nerve compression. Ultrasound imaging of facial muscles and electro-diagnostic testing may be useful for differential diagnosis and management (18).

**The floppy newborn**

In the majority of newborns, hypotonia is often noticed at or soon after birth. The assessment of muscle tone is subjective (19). Neonatal hypotonia can be defined as a decrease of resistance to passive range of motion in joints versus weakness, which is a reduction in the maximum muscle power that can be generated in a newborn.

Identifying the underlying cause of neonatal hypotonia remains difficult, despite advances in diagnostic laboratory and imaging techniques.

Clinical evaluation strategies and standardized developmental tests can assist in differentiating hypotonia resulting from primary involvement of the upper motor neuron (central hypotonia) versus that involving the lower motor neuron and motor unit (peripheral hypotonia). The underlying pathology of infantile hypotonia can be divided into four broad categories: the central nervous system (CNS), the peripheral nerves (motor and sensory), the neuromuscular junction, and the muscle (20).
Usually the examination helps in the precise localization of lesion in the pathway for motor control (19). In the newborn, the differential must include acute illnesses and systemic diseases such as sepsis and congestive heart failure. To construct a meaningful differential diagnosis and eventually arrive at an appropriate diagnosis, the clinician must ascertain whether the patient is hypotonic or hypertonic and weak together. These may seem to be straightforward determinations but, in fact, are among the more difficult clinical determinations clinicians are called on to make, requiring careful history and examination plus serial examinations to be confident of the result.

Based on research evidence, central hypotonia accounts for 60% to 88% of cases of hypotonia, whereas peripheral origins or unknown causes accounting for the balance (21). Disorders causing hypotonia often are associated with a depressed level of consciousness, predominantly axial weakness, normal strength accompanying the hypotonia, and hyperactive or normal reflexes (21).

In addition, several congenital disorders that are characterized by hypotonia have both central and peripheral origins. Examples include congenital muscular dystrophy (in which infants have abnormalities of brain formation and central white matter abnormalities on magnetic resonance images), and congenital disorders of glycosylation, which can include cerebellar abnormalities as well as peripheral neuropathy. It is also worth noting that some infants may demonstrate ‘transient’ hypotonia, e.g., those born preterm, those with prenatal drug exposure, or those with acute infectious diseases.

Approximately 50% of patients who have hypotonia are diagnosed by history and physical examination alone. To aid in the early diagnosis of hypotonia in the newborn, especially for disorders in which definitive laboratory or imaging tests are not available, clinicians should include a detailed history of the infant, as well as the family’s history, and clinical and developmental assessments. The continued value of clinical assessment of infants with hypotonia, despite the many technological diagnostic advances, cannot be overstated.

An appropriate medical evaluation of hypotonia in infants also includes a karyotype, DNA-based diagnostic tests, cranial imaging, serologic tests, electroneuromyography, and muscle biopsy. Several studies state what should be done and what kind of tools and tests are included in the appropriate algorithm (19, 21). Treatment of the infant who has hypotonia must be tailored to the specific responsible condition. In general, therapy is supportive. Rehabilitation is an important therapeutic consideration, with the aid of physical and occupational therapists (21).

**Neonatal hypertonia**

Hypertonia refers to abnormally increased resistance to externally imposed movements around a joint (22). Newborns with brain disorders commonly exhibit abnormalities of muscle tone and posture (23). Hypertonia can be an integral component of many chronic motor disorders. These disorders can result from dysgenesis or injury to developing motor pathways in the cortex, basal ganglia, thalamus, cerebellum, brainstem, central white matter, or spinal cord (4). Unlike discussions of hypotonia, a comprehensive approach to neonatal hypertonia is rare. Recognition of specific presentations of hypertonia at the bedside can guide the clinician down a more accurate diagnostic path (23).

At least three descriptive terms are associated with different forms of childhood hypertonia: “spasticity,” “dystonia,” and “rigidity” (22). When the injury occurs in children before 2 years of age, the term cerebral palsy is often used. These general phenotypes can be helpful for the clinician when serial examinations are performed on neonates at successively older ages after birth. Some neonates can initially express hypotonia during the acute phase of encephalopathy and then later evolves into a hypertonic expression (23).

Pathophysiologic mechanisms resulting in hypertonia may also contribute to suboptimal voluntary motor performance or involuntary muscle contractions, and therefore strength, dexterity, coordination, or involuntary movements must be separately assessed. Assessment of deep tendon and tactile reflexes must be carefully recorded. This evaluation is limited for the newborn, but descriptions of motor tone and posture should be compared over serial examinations since the documentation of neonatal hypertonia can assist in a more complete
differential diagnosis based on etiology, localization, and timing of injury (23).

Several authors have provided a set of definitions and differential diagnosis for the purpose of identifying different components of childhood hypertonia (4, 22, 23). It is clear that physical and neurological examination, combined with laboratory and electrophysiological assessments can provide a more accurate clinic-pathologic correlation with respect to the timing, character, and etiology of injury.

**Neural tube defects**

Neural tube defects (NTDs) result from failure of the neural tube to close during the third or fourth week of gestation (24). During embryogenesis the central nervous system develops as a flat sheet of cells, which subsequently rolls up and fuses to form the neural tube. Disruption of this process causes NTDs. NTDs are of the most common birth defects (along with congenital heart anomalies and genitourinary defects, with a worldwide incidence of 1/1000 live births, ranging from 0.2 to 10/1000 in specific geographical locations.

Clinical severity of NTDs varies greatly, depending on lesion type and location. Open lesions affecting the brain (anencephaly, craniorachischisis) are invariably lethal before or at birth. Encephalocele can also be lethal depending on the extent of brain damage during herniation. Open spina bifida is generally compatible with postnatal survival, although the resulting neurological impairment below the level of the lesion can lead to absence of sensation, inability to walk, and incontinence.

Associated disorders include hydrocephalus, which often needs CSF shunting, Arnold Chiari type II malformation, vertebral deformities, and genitourinary and gastro-intestinal disorders. Closed spinal lesions are generally less severe and can be asymptomatic, as with spina bifida occulta. However, lumbosacral spinal cord tethering can be present in spinal dysraphism, and can lead to lower-limb motor and sensory deficits and a neurogenic bladder (24).

Both genetic and environmental factors have been implicated in the pathogenesis of NTDs. Although there is an increased recurrence risk for siblings (2-5% risk vs. 0.1% in the general population, most cases are sporadic. Decades of research, including randomized and community based trials demonstrated that exogenous periconceptional maternal folic acid supplementation was found to reduce risk of NTD in the offspring (25). However, as maternal folate levels in most affected cases is within the normal range, NTDs are not the result of a simple vitamin deficiency disorder (26). Studies exploring candidate genes, within and outside of the folic acid pathways, as well as studies of epigenetics are looking at the environmental – genetic combination in NTD pathophysiology.

**Anencephaly**

An invariably lethal condition characterized by absence of the cranial vault and severe defects of the cerebral hemispheres. The cerebellum is usually absent and the brain stem may be hypoplastic. Anencephaly comprises 40% of NTD’s, and is 3 times more common in females. It has been associated with gestational diabetes (24).

**Craniorachischisis**

Anencephaly continuous with complete open spina bifida, an invariably lethal condition, which comprises 3% of NTD and was found to be highly prevalent in north China (24).

**Encephalocele**

Encephalocele is a result of herniation of the meninges, with or without brain tissue through a skull defect. This defect is usually sporadic and comprises 7% of all NTD’s, with a female dominance. Clinical presentation of encephalocele includes a meningeal sac with or without brain tissue protruding from the skull, most commonly located in occipital, parietal or frontoethmoidal regions. Surgical repair is the main treatment, along with treatment of epilepsy and learning disorders, which are common sequelae (24).

**Myelomenigocele**

This most common type of NTD, (50% of NTDs), is mostly sporadic and with no gender predominance
There are two main types. A meningocele is a cystic dilatation of the meninges associated with spina bifida and a defect in the overlying skin. The spinal cord and neural roots are normal in structure and there are typically no neurologic deficits. A myelomeningocele is an abnormality in the structure and position of the spinal cord (27).

Myelomeningoceles are most commonly thoracolumbar, lumbar or lumbosacral and frequently associated with hydrocephalus (24). The extent of neural tissue involvement determines the severity of the deficit. Typically children with lesions, at L1-L2 or higher will be completely paraplegic (27). Surgery should be performed early, within the first 72 hours after birth, or in utero in some centers. The treatment includes surgical closure of the defect and insertion of a ventriculoperitoneal (VP) shunt. Supportive lifelong non-surgical treatment for associated anomalies and deficits is required (24, 28).

**Spinal dysraphism**

Non-fusion of one or more of the posterior arches of the spine most commonly found in the lumbosacral region. This lesion, also called spina bifida occulta, is covered by skin, and an overlying hair tuft, lipoma, hemangioma or other cutaneous lesions may coexist. The defect can be detected radiographically (24). There are no neurological consequences for spina bifida occulta per se, but underlying cord tethering may exist and requires surgery as growth will create traction of the cord.

**Neonatal encephalopathy - Hypoxic ischemic encephalopathy**

The term ischemia refers to the lack of appropriate blood supply to the tissues. Hypoxia is a decrease in oxygen supply (29). Insufficient gas exchange may result in hypoxemia and hypercapnea. The combination of hypoxia and ischemia results in a cascade of biochemical changes including activation of inflammatory mediators, accumulation of oxygen free radicals, extracellular glutamate accumulation. That opens N-methyl-D-aspartate (NMDA) gates and allows an influx of calcium into the cell, therefore causing irreversible neuronal damage.

This leads to neuronal cell death and brain damage, and with ongoing exposure and also to multisystem failure (29). Gestational age plays an important role in the changing susceptibility of the cerebral structures to hypoxia and ischemia. While a hypoxic ischemic insult in a preterm infant (up to 36 weeks gestation) will result in mainly white matter damage causing periventricular leukomalacia (PVL), the same insult in a term infant will result in deep grey matter damage; particularly posterior putamen and ventrolateral nucleus of the thalamus.

The prevalence of hypoxic ischemic encephalopathy (HIE) in term infants is estimated at 1-6/1000 live births. As the definitions are not clear, this estimate includes perinatal asphyxia, HIE and neonatal encephalopathy (30).

Neonatal hypoxic ischemic encephalopathy is a clinical syndrome of abnormal neurological behavior in the neonate, which is frequently associated with multi-system dysfunction and follows severe injury before or during delivery. Diagnosis of perinatal asphyxia is based on low Apgar scores (31) (<6 at 5 minutes), umbilical cord pH and base deficit (pH < 7 and BE <-12) as well as the infants responsiveness after birth.

There have been several consensus statements on diagnosis of intra-partum asphyxia, as this is a legal issue as well as a clinical one. The affected infant may experience trouble initiating and maintaining respiration, depressed tone and reflexes, abnormal level of consciousness, seizures and multi organ failure including renal failure and elevated liver enzymes (29). Clinical severity is classified by Sarnat’s criteria (32) which is based on the infants responses to stimuli, changes in tone, reflexes and consciousness and the presence of seizures (32). See Table 1. Most authorities now prefer the term neonatal encephalopathy (NE) and then specifying if the encephalopathy is associated with intra-partum injury.

**Treatment**

During the last two decades evidence from experimental and clinical trials suggests therapeutic hypothermia reduces cerebral injury and improves neurological outcome (33, 34).
Hypothermia reduces cerebral metabolism and down regulates intracerebral processes, thereby inhibiting apoptosis (27). Two different cooling strategies have been utilized in asphyxiated infants; head cooling with a cap perfused by a coolant solution at 10°C, reducing brain temperature to 34.5°C (35), and whole body cooling when the infant is laid on a cooling mattress or under a cooling blanket reducing rectal temperature to 33.5°C.

Current systematic reviews (34) report that when initiated within 6 hours of birth, both methods of therapeutic hypothermia are beneficial in reducing mortality (34) and increase survival with normal neurological function in asphyxiated term and late preterm infants. These results come from a large body of evidence; with the last Cochrane collaboration update (34) including over 1,500 infants from 11 randomized controlled trials (RCT’s).

**Magnesium sulphate**

During asphyxia, there are high concentrations of glutamate, which open NMDA channels and allow calcium influx into the cell, creating neuronal damage. Magnesium ion gates the NMDA channels in a voltage dependent manner and may protect the developing brain from NMDA receptor mediated injury. A recent systematic review (36) of the efficacy of postnatal magnesium therapy in term infants with HIE within the first 24 hours after birth, reported an improvement in short-term outcomes (up to 18 months). However, they reported an insignificant trend towards increased mortality in the magnesium group. As this review has not reported long term outcomes, and included only 182 participants from 5 RCT’s, larger studies are required before applying
magnesium to routine treatment protocols for asphyxiated infants.

**Prognosis and outcome**

Outcome of infants sustaining a cerebral hypoxic-ischemic injury is influenced by duration and severity of the insult to the brain, gestational age, presence of seizures and multi-organ involvement (27). Van Laerhoven et al. (37) conducted a meta-analysis including 29 studies, describing 13 prognostic tests performed 1631 in 1306 term asphyxiated infants. They reported the most promising tests for an accurate prognostic evaluation were MRI, amplitude-integrated- electroencephalography, EEG and visual evoked potentials (37). In a review of 13 studies (29), adverse developmental outcomes, including death, cerebral palsy and cognitive and sensory impairments were found in over 50% of post asphyxia infants. Using the Sarnat grading system (32) adverse outcomes were rare in grade I, and very high in grade III. Outcome varied in HIE Sarnat grade II (29).

**Congenital CMV infection**

Human cytomegalovirus (CMV) is the most common cause of congenital infection, with vertical transmission causing congenital viral infection in up to 0.3-2% of all live births worldwide. Current estimates indicate about 8000 new children in the US are affected by some neurologic sequelae related to congenital CMV every year. This makes in utero CMV infection the most common cause of birth defect and childhood disability in the United States.

**Diagnosis**

The gold standard for detection is virus isolation from urine or saliva in the first 2 weeks of life. Clinical manifestations

Congenitally infected infants are asymptomatic at birth in 85-90% of cases. In symptomatic infants clinical presentation may vary from mild to severe disseminated life threatening disease with up to 20% mortality. Obvious symptoms of congenital CMV infection include jaundice, hepatosplenomegal and petechiae in a growth-retarded infant. Neurological involvement can include microcephaly, seizures, hypotonia and lethargy.

Long-term disabilities may include mental retardation, autism, cerebral palsy and epilepsy. Long term visual impairment and strabismus are common in children with symptomatic congenital CMV infection and may be caused by chorioretinitis, pigmentary retinitis, macular scarring, optic atrophy and central cortical defects. Visual impairment is unusual in an asymptomatic infant.

Most children (60-90%) with symptomatic CMV infection and 10-15% of children born asymptomatic develop one or more neurologic sequelae, such as mental retardation, psychomotor retardation, progressive sensorineural hearing loss (SNHL) and ophthalmic abnormalities. It is important to note that although long term sequelae occurs 3-4 times more in symptomatic infants, and is often more severe, more children with long term sequelae were asymptomatic at birth (38).

**Brain structural abnormalities**

The most common lesions are due to chronic infection, and include ventricular dilatation, white matter gliosis, volume loss, parenchymal and ependymal cysts, calcifications and cortical malformations. Symptomatic infants have higher rates of structural brain abnormalities; the most frequent of these is the presence of intracranial calcifications appearing in up to 50% of the cases.

**Auditory abnormalities**

CMV is the leading cause of non-hereditary SNHL. CMV related SNHL may be manifested at birth or may be progressive in nature, with deterioration occurring over the first few years of life. Hearing loss is more frequent among children with symptomatic CMV infections (30-65%), than in the asymptomatic group (7-15%).
Treatment

A synthetic acyclic nucleoside analogue, structurally similar to guanine, which requires phosphorylation by a CMV produced enzyme for activation (39). There is evidence that short-term treatment with gancyclovir ameliorates CMV related progressive SNHL (40). No effect on long-term neurodevelopmental outcome has been reported, and brain malformations are obviously irreversible.

Neonatal seizures

Seizures are the most frequent clinical manifestation of central nervous system dysfunction in the newborn (41). The neonatal period is one of the highest-risk periods for seizures during the human life span. The overall incidence rate of neonatal seizures in several population-based studies varies from 1.8 to 3.5 per 1,000 newborns (42). Very low–birth-weight infants are particularly at risk, with rates ranging from 19 to 57.7 per 1,000 (41, 43).

Pathophysiology

Neonatal seizures usually reflect a serious underlying derangement of the brain, most of which are triggered by an acute illness such as HIE, stroke, or infection; rarely are they triggered by epilepsy per se (41). Because neonatal seizures could portend a significant illness (hypoxia–ischemia, hemorrhage, or infection), it is essential to ascertain their etiology. About 60% of the neonatal seizures are believed to result from primary hypoxia–ischemia; ~15% result from intracranial hemorrhage; ~10% result from cerebral dysgenesis, transient metabolic disturbance, inborn error of metabolism, or infection; and the remaining 10-15% have an unknown etiology. It is assumed that these remaining patients have genetic encephalopathies.

Seizures are the most common and important sign of acute neonatal encephalopathy and are well recognized as a major risk factor for death or subsequent neurologic disability. Controversy exists as to whether neonatal seizures themselves cause damage to the developing brain, or if the damage is primarily due to the underlying cause of the seizures. Not long ago, it was believed by many that neonatal seizures themselves were relatively innocuous, but there is growing evidence (mainly from research in animal models) that neonatal seizures per se contribute to the adverse neurodevelopmental outcomes. However, evidence in human newborns is scant. As a result of this controversy there is ongoing discussion whether all seizures (clinical and subclinical) should be treated.

Diagnosis

Making a confident, clinical diagnosis of seizures in the neonate can be difficult. In the search for the correct diagnosis, a thorough history, clinical examination, laboratory work-up, neurophysiological and neuroradiological investigations are all essential. When considering the diagnosis of neonatal seizures, objective evidence of a true epileptic condition is required because as jitteriness, apneic spells, autonomic alterations, and other phenomena are sometimes attributed to neonatal seizures without proper justification (41). At this age, seizures are often disorganized, multifocal, or subtle, likely reflecting the inability of the immature brain to sustain organized epileptiform activity. Moreover, immaturity of myelination leads to slow and unusual patterns of seizure propagation.

Furthermore, many neonates manifest seizure-like behavior without electrographic change or, conversely, may show electrographic seizure activity without any clinical manifestation. Neonatal seizures can be classified as tonic, clonic, myoclonic, and subtle. A clinical diagnosis is not easy as seizures are usually subtle in neonates. Moreover, in the majority of newborn infants seizures are subclinical. On the other hand, not all abnormal movements identified by clinicians as clinical seizures are accompanied by electroencephalographic seizure discharges in the EEG.

Customary clinical practice includes visual monitoring of high-risk neonates for seizures, performance of a routine electroencephalogram (EEG) for suspicious clinical seizure activity, and sometimes-empirical treatment with anti-epileptic drugs. Electro-clinical dissociation is common in
neonatal seizures. As a result, detection and identification of seizures by visual clinical observation alone is insufficient and unreliable in neonates (44).

Neonatal seizures should be evaluated using electroencephalogram (EEG) monitoring. However, long-term EEG monitoring is not available or employed at most centers in ordinary clinical practice. Customary clinical practice now includes visual monitoring of high-risk neonates for seizures, performance of a routine (30-minute) bedside EEG for suspicious clinical seizure activity, and often empiric treatment when seizures are clinically recognized or confirmed by EEG (43, 45).

Therefore, the use of continuous amplitude integrated electroencephalogram (aEEG) recordings neonatal populations have enjoyed increasing popularity. The aEEG has been employed with the goal of early identification and more aggressive treatment of neonatal seizures. The aEEG technique makes use of ongoing EEG amplitudes in single or double channels. In brief, the raw EEG signals from bi-parietal electrodes are amplified, filtered, and compressed over long periods of time to obtain a simplified EEG waveform that enables evaluation of long term trends in electrocortical background activity. Moreover, neonatal aEEG features of background pattern, cyclicity, and seizure activity were significantly associated with the neurodevelopmental outcomes at the age of one year.

**Treatment**

As a consequence of the growing body of evidence that neonatal seizures per se contribute to adverse neurodevelopmental outcome, clinicians are more focused on treatment of neonatal seizures. The question, however, still remains how aggressively neonatal seizures should be treated. Unfortunately, data from randomized controlled trials to support the choice of anticonvulsants are limited and there are no definite recommendations or evidence-based guidelines for the pharmacologic management of neonatal seizures (46). On the other hand, expert opinion supports use of pharmacologic treatments with a goal of abolishing electrographic seizures in neonates, even those without clinical correlation (46).

Usually most NICUs have a therapeutic approach for the first, second and third-line anticonvulsants. First generation, older anti-epileptic drugs (AED) (Phenobarbital, Benzodiazepines, lidocaine) are still the drugs of first choice because of extensive clinical experience, despite their limited clinical effectiveness (45). However, other newer medications (levetiracetam, topiramate, lamotrigine, vigabatrine) are gaining reputation though the number of studies in the newborn age group is still limited.

Since current therapeutic options to treat neonatal seizures are relatively ineffective, there is an urgent need for prospective, randomized, controlled trials to assess the efficacy and safety of AEDs in neonates. One of the most significant barriers for performing such studies is the fact that AEDs are among the most common causes of fetal malformations.

AEDs not only induce widespread apoptotic neurodegeneration in the developing brain, but can also impair cell proliferation and differentiation, synaptogenesis and synaptic plasticity, and cell migration as well as axonal arborization. A disruption of these developmental processes may potentially account for neurological deficits seen in humans exposed to AEDs pre or post natailly. Unfortunately, the effect of AEDs on these processes in the developing brain has not been systematically analyzed (43, 45).

**Prognosis**

Neonatal seizures were mentioned as associated with a 55- to 70-fold increased risk of cerebral palsy, a 5.3-fold increased risk of mental retardation, and an 18-fold increased risk of epilepsy (4). Preterm infants fare most poorly, with normal outcome occurring in only 35% of those less than 2,500 g and in 19% of those less than 1,500 g (4). Much of the disability is because of the actual cerebral insult causing the seizures and underlying etiology is a strong predictor of outcome (4, 41). Favorable outcome is generally associated with familial neonatal seizures, hypocalcemic seizures, or primary subarachnoid hemorrhage, whereas poor outcome is the rule with severe hypoxic-ischemic encephalopathy, central nervous system malformations, and massive intraventricular/periventricular hemorrhage (4, 41).
Although the prognosis of neonatal seizures has improved over the past several decades, approximately one third of survivors are still left with neurologic sequelae including motor deficits, mental handicap, and epilepsy (4).

Abnormal head growth

Microcephaly is an important neurologic sign but there is non-uniformity in its definitions, early measurements, and evaluation. Microcephaly is usually defined as a head circumference (HC) more than 2 SDs below the mean for age and gender. However, some authors have advocated for defining severe microcephaly as an HC more than 3 SDs below the mean. Microcephaly may result from any insult that disturbs early brain growth and can be seen in association with hundreds of genetic syndromes.

Few data are available to inform evidence-based recommendations regarding diagnostic testing. The yield of neuroimaging ranges from 43% to 80%. Genetic etiologies have been reported in 15.5% to 53.3%. The prevalence of metabolic disorders is unknown but is estimated to be 1% (47). Children with severe microcephaly (head circumference lower than 3 SD) are more likely to have imaging abnormalities and more severe developmental impairments than those with milder microcephaly (47). Coexistent conditions include epilepsy, cerebral palsy, mental retardation, and ophthalmologic disorders.

According to the subcommittee of the American Academy of Neurology and the practice committee of the Child Neurology Society neuroimaging may be considered useful in identifying structural causes in the evaluation of the child with microcephaly. Targeted and specific genetic testing may be considered in the evaluation of the child with microcephaly who has clinical or imaging abnormalities that suggest a specific diagnosis or who shows no evidence of an acquired or environmental etiology. Screening for coexistent conditions such as cerebral palsy, epilepsy, and sensory deficits may also be considered (47).

Neonatal macrocephaly

Two terms are discussed here: Macrocephaly, defined as an occipito-frontal circumference (OFC) greater than the 98th percentile, and Megalencephaly defined as a brain weight/volume ratio greater than the 98th percentile for age (or more than 2 standard deviations above the mean for age and gender). Megalencephaly results from true hyperplasia or overproduction of central nervous system parenchyma, and its actual prevalence is unknown.

Megalencephaly is generally accompanied by macrocephaly; however, macrocephaly may occur in the absence of megalencephaly because of underlying hydrocephalus, cerebral edema, neoplasia, fluid collection, or thickened calvarium.

Megalencephaly is divided into: an anatomic type (developmental), which most often occurs as an isolated clinical finding (as in benign familial megalencephaly), and a metabolic type, refers to various storage and degenerative encephalopathies. Large head circumference is determined not only by brain size, but includes any malformations and space occupying lesions, cerebrospinal fluid, cranial blood volume, presence of subdural fluid, thickness of skull bones and overlying tissue scalp.

Macrocephaly is used when the head size exceeds the mean by more than two standard deviations of age and gender. Macrocephaly is associated with many genetic disorders and is a frequent cause of referral to the clinical geneticist. Because identification of macrocephaly can lead to correct syndrome identification, the careful assessment of the OFC remains a crucial part of the clinical evaluation. Several authors emphasized the genetic conditions where macrocephaly is likely to be one of the presenting clinical symptoms or a predominant aspect of the clinical presentation. The prognosis depends mainly on the cause and associated conditions (48).

Newborn screening for inborn errors of metabolism

Inborn errors of metabolism (IEMs) are phenotypically and genetically heterogeneous group of disorders of intermediate (carbohydrate, amino acid, and lipid) metabolism that are caused by
dysfunction of an enzyme encoded by a single gene, leading to malfunctioning metabolism and/or the accumulation of toxic intermediate metabolites (49).

IEMs have wide phenotypic variation and can present with static encephalopathy but may be suspected on the basis of historical features (affected family members, parental consanguinity, episodic decompensation, developmental regression), physical findings (coarse facial features, organomegaly), or neuroimaging findings (abnormal myelination, striatal necrosis) (49). All IEM are rare diseases, and collectively they pose a substantial burden to affected individuals, their families and the health care system, because of the severity of their manifestations, and the large numbers of such disorders (estimated at 7,000, affecting a total of 30 million people in the US alone).

Within this group, those disorders that affect the nervous system represent the most dramatic challenges to researchers and clinicians. Patients have severe and often life-shortening disabilities, and there are few, if any, tools to measure the progression of their neurologic disease or its response to therapeutic interventions. A systematic literature review, updated in 2013, identified 89 IEMs, which present with intellectual disability as prominent feature and are amenable to causal therapy.

There may be greater suspicion for IEMs in children whose parents either are consanguineous or have had children with similar problems or unexplained death or fetal demise. Children with IEMs may have multiple organ system dysfunction, failure to thrive, dietary selectivity, unusual odors, hearing loss, or episodic symptoms, including seizures or encephalopathy. The importance of considering IEMs requires emphasis, because for some entities specific dietary or metabolic treatments may improve neurologic symptoms (49).

To date, more than 1000 different IEM have been identified. While individually rare, the cumulative incidence has been shown to be upwards of 1 in 800. Clinical presentations are protean, complicating diagnostic pathways. IEM are present in all ethnic groups and across every age. Some IEM are amenable to treatment, with promising outcomes. However, high clinical suspicion alone is not sufficient to reduce morbidities and mortalities.

In the last decade, due to the advent of tandem mass spectrometry, expanded newborn screening has become a mandatory public health strategy in most countries. The technology allows inexpensive simultaneous detection of more than 30 different metabolic disorders in one single blood spot specimen at a relatively low cost, with commendable analytical accuracy and precision. Metabolomics for example measure global sets of low molecular weight metabolites (including amino acids, organic acids, sugars, fatty acids, lipids, steroids, small peptides, vitamins, etc.), thus providing a “snapshot” of the metabolic status of a cell, tissue or organism. The use of metabolomics appears to be a promising tool in newborn medicine.

The management of sick newborns might improve if more information on perinatal/neonatal maturational processes and their metabolic background were available. Urine as well, can be particularly suitable for metabolic analysis in newborn medicine, because it may be collected by using simple, noninvasive techniques and because it may provide valuable diagnostic information. Biologically, the brain poses specific problems related to the difficulty of delivering therapeutic agents across the blood brain barrier, and targeting them to very specific neuronal populations and networks. Although the brain contains stem cells, its potential for self-regeneration is limited, in contrast to most other tissues.

As potential disease-modifying therapies have emerged in recent years, the need for reliable and valid instruments to measure neurologic function, and for validated biomarkers, has become more pressing. Therapeutic effects for IEMs include improvement and/or stabilization of psychomotor/cognitive development, behavior/psychiatric disturbances, seizures, neurologic and systemic manifestations. Cost-effectiveness studies have confirmed that the savings achieved through the use of expanded newborn screening programs are significantly greater than the costs of implementation. The adverse effects of false positive results are negligible in view of the economic health benefits generated by expanded neonatal screening and these could be minimized through increased education, better communication, and improved technologies.

The development of biochemical genetics is closely linked with expanded neonatal screening. With ongoing advancements in nanotechnology and
molecular genomics, the field of biochemical genetics is still expanding rapidly. The potential of tandem mass spectrometry is extending to cover more disorders. Indeed, the use of genetic markers in T-cell receptor excision circles for severe combined immunodeficiency is one promising example. There is a need for evaluative outcomes research to support effective and appropriate care for IEM.

Diagnostic algorithms support the clinician in early identification of treatable IEM allowing for timely initiation of therapy with the potential to improve neurodevelopmental outcomes. There is a need for future studies to determine yield and usefulness of these recommendations, with subsequent updates and improvements to developments in the field. It was suggested that research should consider interventions at both the level of the health system (e.g., early detection through newborn screening, programs to provide access to treatments) and the level of individual patient care (e.g., orphan drugs, medical foods).

A practice-based evidence framework was developed to guide outcomes research for IEM. Focusing on outcomes across the triple aim, this framework integrates three priority themes: tailoring care in the context of clinical heterogeneity; a shift from “urgent care” to “opportunity for improvement”; and the need to evaluate the comparative effectiveness of emerging and established therapies. Metabolic newborn screening programs warrant systematic healthcare service delivery across the pre-analytical, analytical, and post-analytical phases. There should be a comprehensive reporting system entailing genetic counseling as well as short-term and long-term follow-up. It is essential to integrate existing clinical IEM services with the expanded newborn screening program to enable close communication between the laboratory, clinicians, and allied health parties.

**Conclusion**

Our understanding of the pathophysiology, etiology, and timing of brain injury to the newborn has dramatically evolved. Animal models have been advanced to provide clarification around the mechanisms of brain injury in the newborn and platforms for the investigation of therapeutic interventions. Tremendous advances in imaging of the newborn brain have dramatically contributed to our understanding of the underlying etiology, timing, and prediction of neurodevelopmental outcome, with increasing refinement predicted for this field over the coming years. Recently, biomarkers are being investigated, helping us to identify and treat those infants at risk for injury.

Advances in the care of high-risk newborn babies have contributed to reduced mortality rates for premature and term births, but the surviving neonates often have increased neurological morbidity (50). We are beginning to experience safe, efficacious, and age-specific interventions that provide meaningful improvement to the life and future of those newborns injured near birth. Therapies aimed at reducing the neurological sequelae of birth asphyxia at term have brought hypothermia treatment into the realm of standard care. However, this therapy does not provide complete protection from neurological complications and a need to develop adjunctive therapies for improved neurological outcomes remains.

In addition, the care of neurologically impaired newborns, regardless of their gestational age, clearly requires a focused approach to avoid further injury to the brain and to optimize the neurodevelopmental status of the newborn baby at discharge from hospital. This focused approach includes, but is not limited to, monitoring of the patient’s brain with amplitude-integrated and continuous video EEG, prevention of infection, developmentally appropriate care, and family support (50).

The combination of increased survival and earlier discharge has added to the number of sick newborn infants needing complex post hospital care and close follow-up. Some of the infants have a much higher rate of hospital readmission and death during their first year of life as compared with healthy infants. A single study showed that access to comprehensive follow-up care from highly experienced caregivers in neonatal medicine has shown to reduce life-threatening illnesses and total days of pediatric intensive inpatient care by more than 40% among high-risk inner city infants (1). Provision of dedicated neurocritical care to newborn babies requires a collaborative effort between neonatologists and neurologists, training in neonatal neurology for nurses and future generations of care providers, and the
recognition that common neonatal medical problems and intensive care have an effect on the developing brain (50).

Since neonatal neurology is a growing subspecialty area and given the considerable amount of neurologic problems present in the newborn, a neurologist with expertise in neonates is becoming more important. The neonatologists on their side usually express appreciation for having a dedicated neurologist available.

Including a dedicated neurologist in the department of neonatology may represent an improved model of care. The neurologist can play an integral part in evaluating known or suspected neurologic processes, the daily management regarding these conditions, and in communicating with the family about test results, brain imaging, and their newborns’ neurodevelopmental prognosis. An increased focus on the brain at an early age might lead to improved outcomes for the youngest neurology patients.

References


Cardiology and the newborn

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Abstract

Approximately 8 out of every 1,000 newborns have a congenital heart abnormality, ranging from mild to severe. This discussion provides a review of these conditions beginning with an overview of cardiac embryology as well as fetal and transitional circulation. Then there is consideration of newborn cardiac evaluation and principles of newborn cardiac testing. Disorders covered include cyanotic heart defects, persistent pulmonary hypertension of the newborn, acyanotic defects, congestive heart failure as well as cardiogenic shock, associated congenital heart defects of the the dysmorphic newborn, and finally, neonatal arrhythmias. An appreciation of cardiology of the newborn is an important component for the clinician in caring for the newborn.

Keywords: Pediatrics, neonatology, newborn, cardiology

Introduction

Approximately 8 out of every 1,000 newborns have a congenital heart abnormality, ranging from mild to severe. Congenital cardiac defects can be divided into two major groups based on the presence or absence of cyanosis, which can be determined by physical examination aided by pulse oximetry. Congenital heart disease (CHD) generally occurs because of incomplete or abnormal development of the fetal heart during the first 7 weeks of pregnancy. Some defects are associated with genetic disorders but the cause of most congenital heart defects is unknown.

The workings of the human heart are the profoundest mystery of the universe. Charles W Chesnutt (1858-1932)

An estimated 85% of children diagnosed with CHD will survive into adulthood. Survival rates vary by disease complexity: Long-term (survival over 20 years) rates are estimated to be 95% for simple CHD (e.g., isolated semilunar valve disease, atrial and
ventricular septal defects), 90% for moderate-severity CHD (e.g., coarctation of the aorta, atroventricular septal defect, ventricular septal defect with comorbidities, tetralogy of Fallot), and 80% for CHD of great complexity (e.g., single ventricle, truncus arteriosus, complex transposition of the great arteries. Although specific types of complex CHD (e.g., hypoplastic left heart syndrome) may have lower survival rates, overall rates have increased for even the most complex defects (1).

Since the first open-heart surgery for congenital heart defects over 60 years ago, there have been exciting improvements in outcomes from both surgical and catheter-based interventions. The first successful intracardiac correction of a congenital heart defect using hypothermia was in 1952 by Drs. C Walton Lillehei and F John Lewis at the University of Minnesota. In 1954 Dr. Lillehei performed a series of open-heart operations using cross-circulation with the patient's parent. Laying the groundwork for this was the 1945 JAMA paper by Alfred Blalock and Helen Taussig reporting the anastomosis of a systemic artery to the pulmonary artery to improve oxygen saturation in 3 cyanotic children.

In the US about 40,000 babies are born each year with a heart defect including about 4,800 with a critical heart defect. Despite improved detection by fetal ultrasound and surgical advances, CHD remains one of the most important causes of death in infancy. The detection rate by fetal ultrasound is between 15 and 50%. Critical CHD is a potentially life-threatening cardiac abnormality; this term implies that either the systemic or pulmonary circulation is dependent on a patent ductus arteriosus and/or that an invasive procedure is necessary within the first month of life. Stated another way, critical CHD includes heart defects that would result in demise unless neonatal intervention to palliate or correct the defect is undertaken.

CHD can be associated with an underlying chromosomal disorder, and many syndromes are associated with cardiac lesions. Approximately 25% of all infants with CHD have at least one associated extracardiac malformation. Conversely, extracardiac malformations can be associated with cardiac defects. For example, a newborn with a cleft palate has a 20% chance of having a heart defect. For the infant with Down syndrome the risk of CHD is 50%. It is often up to the pediatric provider to connect the dots.

Fetal echocardiography has become a vital tool in the diagnosis of CHD. Prenatal diagnosis of critical CHD avoids the hemodynamic compromise often accompanying postnatal diagnosis. The recommended timing for a fetal echocardiogram is 16-20 weeks gestation. Indications include cardiac or other significant abnormalities noted on prenatal ultrasounds, along with a host of fetal, maternal and familial risk factors. Some cardiac anomalies, such as coarctation of the aorta, small ventricular septal defects, atrial septal defects and anomalous pulmonary venous return may be difficult to detect prenatally.

Advances over the past 20 years have resulted in a dramatic decline in mortality and morbidity for infants requiring early open-heart surgery. The developmental progress of these new survivors remains a concern. Causes contributing to brain injury may include prenatal, preoperative, intraoperative, and postoperative events. Long-term studies suggest that subtle neurological deficits and developmental delay are not uncommon. Exciting areas of focus are early detection, surgical advances, advanced imaging techniques and optimization of developmental outcomes.

### Embryology overview

The cardiovascular system is the first major organ system to develop. It is fully formed and functioning by the eighth week of gestation. Similarities of aspects of heart development across phylogeny have helped elucidate principles underlying cardiac development and cardiac anomalies. Figure1 below depicts cardiac development.

During the first 20 days post-conception the embryo is without a cardiovascular system. Over the next month, the heart and great vessels develop. Angiogenic cells are transformed into a four-chambered structure. The heart tube starts beating at 23 days. By 30 days blood circulates throughout the embryo.
The heart is a mesodermal structure, with precursor cells originating in the lateral plate mesoderm. These precursor cells migrate towards the midline to form a single heart tube. The heart tube differentiates into several fusiform structures. From cranial to caudal, these dilatations include the truncus arteriosus, the bulbus cordis, the primitive ventricles, the primitive atria and the sinus venosus.

The tubular heart undergoes rightward looping and grows into a complex, three-dimensional structure with asymmetry along its axes resulting in an asymmetric multi-chambered heart. Rightward looping is essential for proper orientation of the developing cardiac chambers, chamber septation and the development of inflow and outflow tracts. Figure 2 demonstrates cardiac looping.

The primitive heart tube, containing both myocardial and endocardial layers, starts pumping blood through a primitive circulatory system at about 4 weeks. Blood leaving the lower ventricles enters the truncus arteriosus. Rightward- or d-looping aligns cardiac chambers for morphogenesis into a four-chambered structure.

As the embryo grows and folds on itself, the heart tube undergoes a series of foldings. As a result the atria align posterior and superior to the ventricles. Septation of atria and the ventricles begins at 27 days. The atrioventricular canal leads to cardiac septation. A spiral septum grows within the truncus arteriosus, dividing it into the pulmonary artery and aorta.
Disruptions of cardiac development are well-recognized. Failure of migration of precursor cells can lead to dextrocardia or situs inversus. Abnormal septation can lead to atrial and ventricular septal defects. Atrioventricular septal defects or tricuspid atresia can result if the endocardial cushion fails to provide normal septation. Failure of the spiral septum to divide the truncus arteriosus into the pulmonary artery and aorta can result in conotruncal defects such as truncus arteriosus, tetralogy of Fallot or transposition of the great arteries (2).

Fetal and transitional circulation

After birth the pulmonary and systemic vascular systems are in series and the systemic vascular resistance is higher than the pulmonary vascular resistance. In utero the low vascular resistance of the placenta and the high vascular resistance of the fluid-filled fetal lungs result in right-to-left shunting characteristic of the fetal circulation. Figure 3 depicts fetal circulation.

Fetal circulation

A single umbilical vein transports oxygenated blood from the placenta towards the heart via the ductus venosus (bypassing the liver). To bypass the collapsed lungs the foramen ovale allows for shunting into the left atrium and the ductus arteriosus allows for shunting into the descending aorta. Two umbilical arteries transport deoxygenated blood back to the placenta.

Fetal circulatory anatomy is designed to transport oxygenated blood from the placenta to the fetus while bypassing the lungs. Fetal oxygenation and nutrient exchange occurs at the placenta, and blood is returned to the right atrium through the ductus venosus after bypassing the liver. Most of this oxygen-rich blood is shunted across the foramen ovale into the left atrium and is then transported to the body via the aorta.

Some of this oxygen-rich blood, however, travels from the right atrium into the right ventricle and enters the main pulmonary artery, mixing with venous return from the head. The lungs are collapsed and the pulmonary vascular resistance is therefore high. Because of this high pulmonary vascular resistance most of the blood in the main pulmonary artery
crosses the ductus arteriosus and mixes with blood in the aorta supplying the body. In this manner the right ventricle provides approximately 60% of the total cardiac output.

The fetal circulation results in 1) oxygenated blood from the placenta preferentially flowing through the foramen ovale to allow the left heart to pump oxygenated blood into the aortic arch and therefore the brain, and 2) oxygen-poor blood returning from the superior vena cava preferentially flowing into the right ventricle, pulmonary artery, and ductus arteriosus pathway to enter the descending aorta. From the descending aorta blood can flow back to the placenta, via the umbilical arteries, where carbon dioxide and waste products are released in exchange for oxygen and nutrients.

In the right atrium about one-third of the total inferior vena caval blood enters the left atrium via the foramen ovale; the remaining two-thirds mix with the superior vena caval blood to enter the right ventricle. Blood reaching the left atrium via the right atrium mixes with the small amount of blood returning through the pulmonary veins and passes into the left ventricle. The left ventricle pumps this blood into the ascending aorta. Thus the ascending aorta provides relatively oxygenated blood to the head, myocardium, and upper body, via the carotid, coronary, and subclavian arteries; a small portion travels across the aorta to the descending aorta. Intrauterine oxygen tension is low, mostly between 20 and 30 mmHg. The highest oxygen tension is found in the umbilical vein with a PO2 of only about 55 mmHg. Blood returning to the placenta has a PO2 between 15 and 25 mmHg.

Because most of the blood pumped by the right ventricle bypasses the lungs into the descending aorta, the two ventricles are operating in-parallel in utero, rather than in-series as occurs after delivery. The right ventricle is dominant, pumping about twice the output of the left ventricle.

Transitional circulation

Changes in the fetal circulation occur immediately after birth, beginning with the first breath and the clamping of the umbilical cord. With the clamping of the umbilical cord, there is loss of the low resistance placental circulation, leading to a sudden increase in the systemic vascular resistance. The left ventricular systolic pressure rises in response.

Umbilical cord clamping also leads to a sudden loss of flow through the ductus venosus, which then closes. This results in decreased venous return to the right atrium and a drop in the right atrial pressure while the left-sided pressures are rising. An approximation of the septum primum with the septum secundum and functional foramen ovale closure follows. Anatomic closure of the foramen ovale occurs over a period of months to years. In about a third of adults it never completely closes.

When the newborn takes the first few breaths, there is a sudden expansion of the lungs with a fall in pulmonary vascular resistance and increased blood flow through the pulmonary vessels. By then the pressure in the aorta exceeds the pulmonary artery pressure, leading to a reversal in the blood flow across the ductus arteriosus. The musculature of the ductus arteriosus is sensitive to oxygen. As the oxygen saturation of the blood increases the ductus arteriosus constricts and functionally closes during the first few days of life. The pulmonary vascular resistance continues to drop, with the maximal drop occurring within the first few weeks of life.

Newborn cardiac evaluation

Symptoms: In young infants, metabolic demands are highest during feedings. The infant with low cardiac output, most commonly from excessive pulmonary blood flow, will tire easily during feeding, as an older child would with exercise. With congestive heart failure caloric intake is decreased by the difficulty of coordinating the suck-swallow mechanism in the presence of tachypnea and general fatigue. Increased sympathetic discharge leads to tachycardia and diaphoresis, especially during feeds. Suboptimal weight gain in infants with congestive heart failure thereby results from both decreased intake and increased caloric demands.

Vital signs

Heart rate: When assessing heart rate it is important to consider the newborn’s activity level, which can
result in elevations of heart rate. Resting rates outside the normal range for age should be assessed for normal or abnormal variability or fixed rate, suggesting an underlying dysrhythmia. The newborn heart rate averages about 100 beats per minute, ranging between about 70 and 180 beats per minute. Term newborns may have a resting heart rate towards the lower end especially when sleeping.

More important than the actual heart rate is whether it varies appropriately with activity or stimulation. For newborns with abnormally low heart rates and whose heart rate variability seems blunted an electrocardiogram may help to exclude complete heart block, as can occur with maternal lupus (diagnosed or undiagnosed). Because neonates have smaller stroke volumes, cardiac output is maintained by higher heart rates. Over time, stroke volume increases and contributes more to the overall cardiac output. Compared with the adult heart, neonatal myocardium has fewer contractile myofilaments and is relatively stiff. Newborns therefore rely primarily on increases in heart rate to increase cardiac output.

Respiratory rate: Tachypnea above 60 breaths per minute with or without retractions suggests a cardiac abnormality. Tachypnea can of course also be seen with pulmonary or metabolic abnormalities. In addition to tachypnea, respiratory distress in the newborn, from cardiac or other causes, may be accompanied by apnea, cyanosis, grunting, stridor, nasal flaring and poor feeding.

Blood pressure: Documentation of blood pressure is essential when assessing the cardiovascular system. Before considering if values are abnormal, record the blood pressures several times when the baby is quiet. For noninvasive measurement, automated Doppler or oscillometric equipment is preferred, along with using the appropriate size cuff.

In newborns conventional sphygmomanometry is not recommended because the Korotkoff sounds cannot be heard reliably. The same BP cuff selection method as is used in older children applies (bladder length covering 80% of the arm circumference and inflatable bladder width covering at least 40% of the arm circumference).

An Australian study of 400 term infants showed median systolic, diastolic and mean blood pressures on day 1 of 65 mmHg, 45 mmHg, and 48 mmHg, respectively (3). (The ranges were 46 - 94, 24 -57, and 31 – 63, respectively.) By day 4, these values had increased slightly to 70 mmHg, 46 mmHg and 54 mmHg.

In the newborn the systolic arm and leg pressures are expected to be the same (4). In older children systolic amplification in the legs, due to reflected waves, is felt to account for higher pressure in the legs than arms. This absence of a higher systolic pressure in the leg in the newborn may be related to the presence of a normally narrow aortic isthmus. In any case, an arm systolic blood pressure more than 10 mmHg above the leg blood pressure suggests an aortic coarctation, aortic arch hypoplasia, or an interrupted aortic arch. If the ductus arteriosus is widely patent, however, a blood pressure difference between upper and lower extremities may not be present with these defects.

**Physical examination**

Inspection: The newborn cardiac exam does not start with a stethoscope. It begins with a careful inspection of the infant with these questions in mind: What is the heart rate, respiratory rate, blood pressure? Is the baby unusually small, e.g., from intrauterine growth retardation, or unusually large, e.g., from maternal diabetes? Is s/he dysmorphic? Is s/he comfortable or working to breathe? An infant with comfortable tachypnea may have an underlying heart defect, most often a cyanotic defect. If the infant is dysmorphic or syndromic an underlying heart defect is more likely.

Palpation: The cardiac exam begins with palpation to assess precordial activity and pulses. Increased precordial activity may be from an increased right or left ventricular stroke volume, as can be seen with anemia or sepsis. As the weeks go by, the pulmonary vascular resistance, which is high initially, drops. By a month of age increased precordial activity from a left-to-right shunt may be noted. At this age heart failure symptoms may develop, as from an atrial or ventricular septal defect or a patent ductus arteriosus.

If the murmur is prominent a thrill may be present. If a thrill is not felt on initial palpation it is advisable in the presence of a loud murmur to go back and palpate the area where the murmur is loudest. The ball of the hand (at the base of the fingers) is the most
sensitive for detecting thrills. If a thrill is detected, the murmur is at least a Grade IV/VI; if there is no thrill, the murmur is by definition a Grade III/VI or less.

Pulses: Palpation of the brachial and femoral pulses should be performed simultaneously. If the timing and intensity of these are similar then a coarctation of the aorta is unlikely. Diminished pulses indicate poor cardiac output, peripheral vasoconstriction, or left-sided heart defects. These include hypoplastic left heart syndrome, critical aortic stenosis and an interrupted aortic arch.

Femoral pulses may be difficult to palpate; patience and gentleness are important. If an infant is crying, it’s best to try again after the infant relaxes. Absent or diminished femoral pulses suggest a coarctation of the aorta. Sometimes in the presence of a coarctation the left radial pulse will be difficult to palpate, along with the femoral pulses, depending on the location of the aortic narrowing.

Auscultation: When listening to the heart sounds one should be aware of where they are best heard. With dextrocardia the heart sounds are louder over the right chest, even if audible over the left chest as well. The precordium should be addressed methodically, encompassing: 1) upper right sternal border, 2) upper left sternal border, 3) mid-left sternal border, 4) lower left sternal border, and 5) the apex. The diaphragm of the stethoscope is best for mid and high-pitched sounds and the bell is best for low-pitched sounds. S1 is due to closure of the mitral and tricuspid valves and is normally single. It is best heard at the lower left sternal border. S2 comes from closure of the aortic and pulmonic valves and is best heard at the upper left sternal border.

The splitting of S2 should increase with respiration although this is often difficult to appreciate in newborns with their relatively fast heart rates. This splitting occurs because inspiration pulls more blood into the right heart and right ventricular ejection is thereby prolonged, leading to delayed closure of the pulmonary valve. A single S2 may be heard with transposition of the great arteries as the aorta is directly anterior and obscures pulmonary valve closure or with pulmonary atresia when the pulmonary valve is missing.

Systolic ejection clicks are high-pitched sounds that occur with maximal opening of the aortic or pulmonic valves. They are heard best with the diaphragm, just after S1 along the mid-left sternal border. These can occur with a bicuspid or stenotic aortic or pulmonic valve. Aortic valve ejection clicks are constant, i.e., they do not vary with respiration. Pulmonary valve clicks are heard best during expiration.

A murmur does not always signify a heart defect, nor is the absence of a murmur reassuring. 60% of normal newborns can have a murmur. Small ventricular septal defects are common and are not clinically important. Soft systolic flow murmurs (Grade I-III/VI) may occur during the transition from fetal to neonatal circulation, as with transient tricuspid regurgitation.

The most common newborn murmur is a peripheral pulmonic stenosis murmur. The murmur is a soft mid-systolic long ejection murmur heard over the pulmonary area radiating across both sides of the chest and to the axilla and back. This murmur reflects the relative hypoplasia of the branch pulmonary arteries compared to the well-developed main pulmonary artery, and also to the branches’ sharp angle of origin. There is little flow of blood through the branch pulmonary arteries in utero; as they stretch to accommodate the normal pulmonary blood flow over the first few months of life, this murmur will gradually become softer.

Still’s murmurs, more common in school-age children, can be heard in infancy. These systolic murmurs have a vibratory or musical quality (like a rubber-band twang) thought to perhaps be from vibrations of the papillary muscle apparatus of the mitral valve. Pathologic murmurs associated with specific cardiac lesions are discussed separately.

Systolic murmurs are graded on a 6-point scale and diastolic murmurs on a 4-point scale. Systolic murmurs can be characterized as harsh, as from high-velocity gradients, ejection (diamond-shaped), best heard at the upper sternal border overlying stenotic pulmonary or aortic valves, or blowing or regurgitant (plateau-shaped), from a ventricular septal defect or mitral or tricuspid regurgitation, each of which is best heard at the mid- or lower- left sternal border. Diastolic murmurs in the newborn are rare in isolation. Continuous murmurs, most commonly occurring in association with a patent ductus arteriosus, are long systolic murmurs that continue
into diastole. Three generalizations concerning auscultatory findings in newborns are:

- Innocent murmurs are heard less frequently in neonates than in older children; if a murmur is heard take it seriously.
- If a harsh systolic murmur is heard in the first 3 days the baby may have an obstructive lesion.
- The murmur of a ventricular septal defect may not be present until a few days of age, appearing only after the pulmonary vascular resistance falls. Parents may wonder why the murmur wasn’t detected in the nursery (5).

Liver size: Use the fingertips to work up from right lower quadrant of the abdomen, pressing gently upward. The liver edge is normally 1–2 cm below the right costal margin. If it is enlarged, in the absence of hyperinflated lungs displacing the liver into the abdomen, this suggests heart failure, which may be either right or left sided. Unlike in older children this is a relatively easy marker to measure. Peripheral edema and rales are rare in infants with heart failure. Although respiratory distress and tachypnea may be present, subtler signs such as poor feeding and hepatomegaly may be the only manifestations of heart failure. Assessment of the liver edge is thus a critical portion of the physical examination in infants.

Newborn cardiac testing

The hyperoxia test is one way to distinguish cyanotic congenital heart defects from pulmonary disease. Newborns with cyanotic CHD are usually not able to raise their arterial PaO₂ significantly during administration of 100% oxygen. If the PaO₂ rises above 150 mm then an intracardiac right-to-left shunt can usually be excluded (although some patients may be able to increase their PaO₂ to >150 mm Hg due to intracardiac streaming patterns). In patients with pulmonary disease on the other hand, PaO₂ generally increases significantly in 100% oxygen, as abnormalities in ventilation-perfusion equilibrate. Further, hypoxia with many of the cyanotic heart lesions is consistent, whereas for respiratory disorders and persistent pulmonary hypertension of the newborn (PPHN), arterial oxygen tension varies with time or changes in ventilator settings.

Pulse oximetry screening

In 2011 screening for critical congenital heart disease (CCHD) was added to the Recommended Uniform Screening Panel for newborns in the United States. CCHD is often patent ductus arteriosus (PDA)-dependent but is also defined more generally as requiring heart surgery within the first month. Many newborns with CCHD, especially left-sided CCHD, will appear entirely well at the time of routine hospital discharge only to become critically ill within the next few days. Studies have shown that compared to the physical examination alone, universal neonatal screening with pulse oximetry improves identification of patients with CCHD.

A large Swedish study showed that universal pulse oximetry screening was better than the physical exam at detecting both infants with mild oxygen desaturation and those with CCHD. Six of 16 infants with pulse oximetry saturation between 90 and 94% were not detected by physical examination but were by pulse oximetry. Also noted was a lower rate of missed diagnoses of CCHD in places with universal pulse oximetry screening compared to places without routine oximetry (8 vs 28%).

In addition, no newborn died from a ductal-dependent lesion in places utilizing routine pulse oximetry versus 5 deaths in places without routine oximetry. The investigators concluded that screening seems cost-neutral in the short-term, but it will likely prove cost-effective in the long term, through the prevention of neurological morbidity and a reduced need for pre-operative neonatal intensive care (6).

In a 2012 meta-analysis of 13 studies with data for almost 230,000 newborn infants the overall sensitivity of pulse oximetry for detection of CCHD was 76% and the specificity was 99.9%, with a false-positive rate of 0.14%. The false-positive rate was particularly low when newborn pulse oximetry was done after 24 hours of age compared to before 24 hours. In contrast, sensitivity is not affected by the timing of the pulse oximetry test. A cutoff SaO₂ <95% is generally used (7). A number of practical points to consider include:
• Pulse oximetry fails to identify all patients with left-sided obstructive lesions dependent on a PDA and will not detect acyanotic heart defects, such as ventricular septal defects.
• Other conditions, such as transient tachypnea of the newborn, can result in low oxygen saturation readings.
• If the infant is crying or moving the accuracy of the test will be reduced.
• Training of health care personnel improves reliability and accuracy.
• Post-ductal probe placement is optimal because defects with right-to-left shunting of desaturated blood through the PDA are less likely to be detected with pre-ductal placement only.

Newborn screening is directed towards identifying seven specific lesions. Of note, the undiagnosed conditions most likely to lead to death soon after discharge from hospital are hypoplastic left heart, interruption of the aortic arch and coarctation of the aorta. The seven lesions that are statistically most likely to be detected, however, include only hypoplastic left heart syndrome. The other six are cyanotic lesions. The seven lesions most likely to be detected are:

• Hypoplastic left heart syndrome
• Pulmonary atresia
• Tetralogy of Fallot
• Total anomalous pulmonary venous return
• Transposition of the great arteries
• Tricuspid atresia
• Truncus arteriosus

The following newborn pulse oximetry screening strategy has been endorsed by the American Academy of Pediatrics (AAP) and the American Heart Association (AHA) (8):

• Screening should be performed at about 24 hours of age, or as late as possible if early discharge is planned.
• A motion-tolerant pulse oximeter should be used, in the right hand and either foot, simultaneously or in direct sequence.
• Screening should be performed by qualified and trained personnel.
• A positive screening test fulfills one of the following three criteria:
  • \( \text{SaO}_2 \) measurement <90%
  • \( \text{SaO}_2 \) measurement <95% in both upper and lower extremities on three measurements, each separated by one hour
  • \( \text{SaO}_2 \) difference >3% between the upper and lower extremities
• Each birthing institution should establish a protocol to ensure a timely evaluation for newborns with a positive screening test. After a careful review of the newborn’s condition, medical history and physical exam, assessment of a positive screen most often includes the performance of high-quality echocardiography and interpretation by a clinician with expertise in the diagnosis of CHD. Access to these diagnostic services either at the center, via telemedicine, or via transport is essential.

**Electrocardiogram**

Note right axis deviation and right ventricular hypertrophy, both of which are normal for age. The negative QRS voltage in lead I, with an overall positive voltage in aVF places the QRS axis in the southwest corner, at about 150 degrees. Across the precordial leads V1 and V6 in particular show right ventricular dominance.

The right ventricle is thicker than the left ventricle in the fetus and newborn as a result of their higher pulmonary pressures. Therefore, the electrocardiogram (ECG) will show right ventricular dominance and right axis deviation. Across the precordium, the R wave amplitude is increased in leads V1 and V2 and decreased in leads V5 and V6. This is due to stronger right ventricular forces (anterior) compared to left ventricular forces (posterior).

In children the QRS axis is normally between about 0 and 90 degrees, with the QRS positive in leads I and aVF. In the newborn, however, the QRS axis is typically negative in lead I, as a result of right axis deviation. Although the PR and QRS intervals
tend to be shorter in infants, the corrected QT interval (QTc) is longer than in older children. When there is a question about a long QT interval the ECG can be repeated days or weeks later to see if it normalizes.

Finally, T wave morphology can be difficult to interpret in neonates and children. At birth, the T wave may be upright, flat, or inverted in V1. Within a few days after birth the T wave normally becomes inverted. Upright T waves after a few days of age may indicate right ventricular hypertrophy. Figure 4 demonstrates a normal newborn electrocardiogram.

![Newborn Electrocardiogram](image.jpg)

**Chest radiography**

A chest X-ray (CXR) in newborns with desaturation or respiratory distress is most helpful in differentiating between pulmonary and cardiac disease. CXR interpretation focuses on heart size, arch sidedness and abdominal situs, pulmonary vascularity and checking for bony abnormalities (e.g., abnormal vertebrae or ribs). In the case of suspected heart disease it shows whether pulmonary blood flow is increased, normal, or decreased; this can help narrow the cardiac differential diagnosis.

The mediastinum and cardiac shadow are relatively large in the newborn. Newborns may therefore appear to have cardiomegaly when in fact the thymus is contributing to the generous “cardio-thymic shadow.” The diameter of a normal heart may approach 60% of the thoracic transverse diameter.

A screening CXR for CHD in neonates has a low sensitivity (26–59%) and an even lower low specificity for detecting heart defects among neonates under 2 kg (9). Cardiomegaly can be from a congenital heart defect, cardiomyopathy or a pericardial effusion. The atrial and visceral situs can be assessed based on the position of the stomach bubble. If possible, both the side of the aortic arch and the bronchial anatomy can be noted. Vascular rings, although rare, usually occur in association with a right-sided aortic arch.

Regarding pulmonary vascularity, oligemia (dark lung fields) suggests decreased blood flow through the pulmonary circulation. This may result from a right-to-left shunt, as with right ventricular outflow obstruction. Congested pulmonary vasculature, conversely, can represent either increased pulmonary blood flow or increased pulmonary venous pressure from abnormal pulmonary venous return.

**Echocardiography**

Echocardiography has revolutionized the diagnosis and management of congenital heart disease (CHD), most notably in the neonatal period. It confirms anatomy and provides information regarding physiology and myocardial function. High-resolution
transducers, portability, good neonatal acoustic windows and its safety profile have meant that echocardiography is often the only modality needed to diagnose most neonates with CHD. Strides in fetal ultrasound technology have further improved neonatal management and outcomes. Specifically, echocardiography is useful to elucidate the following:

- Cardiac anatomy, including venous and arterial connections
- Presence and amount of shunting, for example through a patent ductus arteriosus or ventricular septal defect
- Presence and degree of valvar stenosis and regurgitation
- Atrial and ventricular sizes
- Systolic and diastolic function
- Estimation of right ventricular and pulmonary artery pressures

Echocardiography is the gold standard for diagnosing CHD, but it requires skilled personnel and is not readily available in all hospitals. It is operator-dependent. A sonographer with knowledge of CHD if available should obtain the images, ideally with a pediatric cardiologist at the bedside in cases of suspected congenital heart disease.

With advances in echocardiography technology and the addition of color Doppler in the late 1980s, most anatomic and hemodynamic information can be obtained from a thorough echocardiogram. This means that cardiac catheterization is reserved for times when 1) anatomic detail could not be fully delineated by echocardiography (e.g., distal pulmonary arteries, aortopulmonary collaterals, and aberrant coronary arteries) or 2) transcatheter therapeutic intervention is being considered.

Magnetic resonance imaging

Occasionally the information from echocardiography is insufficient, and cardiac magnetic resonance imaging (MRI) can provide detailed information regarding cardiac anatomy, ventricular function and characteristics of the myocardium. Currently, MRI is used as an adjunct to other imaging modalities, such as echocardiography and invasive angiography. MRI studies are typically directed to clarify specific questions about the morphology of known anatomy.

MRI offers advantages over other imaging modalities including lack of ionizing radiation, excellent soft tissue contrast and true three-dimensional imaging of anatomy. Imaging of infants is more demanding than imaging of older children and adults. Sedation is usually needed. Also required are increased spatial resolution because of the subject’s smaller size and inability to breath-hold, and increased temporal resolution because of their higher heart rates (10). Neonatal cardiac MRI has a number of advantages over echocardiography:

- Less operator-dependent, enhancing repeatability
- Provides direct visualization of all areas of the heart.
- More reliable flow measurements and markers of contractility.

Cyanotic heart defects and persistent pulmonary hypertension of the newborn

Cyanosis is a physical finding that is commonly seen in newborns. It is the appearance of a bluish color to the skin and mucous membranes. Newborn cyanosis has become easier to confirm or discount than in the past, as pulse oximeters have become ubiquitous.

True cyanosis, or central cyanosis, is best appreciated at the mucous membranes of the eyes and lips, and in the nail beds. Cyanosis represents an increased concentration of reduced hemoglobin. That which is within the red blood cells after the oxygen of oxyhemoglobin has been released to the tissues.

Cyanosis is generally perceptible when 5 g/100mL of reduced hemoglobin is present in the capillaries. The normal amount of reduced hemoglobin is about 2 g/100mL, although this varies based on the underlying total hemoglobin levels. A polycythemic newborn will have recognizable cyanosis at higher oxygen saturations, while an anemic newborn will not have cyanosis until there is lower oxygen saturation.

With a normal hemoglobin level, the degree of reduced hemoglobin (5 g/100mL) necessary to perceive cyanosis in a newborn corresponds to an
oxygen saturation of 75-80%. Milder degrees of hypoxemia are not often apparent. Hypoxemia is a biochemical phenomenon in which the systemic arterial partial pressure of oxygen is abnormally low; it is not synonymous with cyanosis for the reasons noted above.

Acrocyanosis (from the Greek akros meaning extreme or at the end) of the hands and feet is common in the days following delivery, while the circulation to the extremities transitions. It is considered benign. Pulse oximetry readings are reassuringly normal. Similarly, isolated circumoral cyanosis, i.e., around the mouth, is occasionally encountered in children with fair skin and is thought to represent vasoconstriction with resultant sluggish blood flow.

Approach to true cyanosis: When a newborn presents with true cyanosis and hypoxemia, confirmed by pulse oximetry, identifying the cause is paramount in order to initiate appropriate treatment. The first question to consider is whether the cyanosis is cardiac or non-cardiac (e.g., pulmonary, neurologic or hematologic, such as methemoglobinemia). A cardiac cause of cyanosis can be confirmed with an oxygen challenge or hyperoxia test (see newborn cardiac testing section above).

Because the fetus has low oxygen tension by virtue of placental exchange neonatal cyanosis is better tolerated than it would be without this adaptation. Nonetheless, in addition to tracking oxygen levels in infants with cyanotic heart defects it is important to monitor for developing acidosis.

Cyanotic heart defects: These can be divided according to whether pulmonary blood flow is decreased (tetralogy of Fallot, pulmonary atresia with an intact septum, tricuspid atresia and total anomalous pulmonary venous return with obstruction) or increased (transposition of the great vessels, some types of single ventricles, truncus arteriosus and total anomalous pulmonary venous return without obstruction). The chest radiograph is a valuable tool for initial differentiation between these two categories. Many of these defects start with the letter T, to which they may be referred as the “Terrible Ts.”

**D-transposition of the great arteries (d-TGA)**

The most common cardiovascular cause for cyanosis in the immediate newborn period is d-transposition of the great arteries (d-TGA). There is usually an accompanying patent foramen ovale or atrial septal defect and in one-third of cases there is a ventricular septal defect (as shown in Figure 5). D-TGA results from abnormal rotation and development of the truncus arteriosus with resulting ventriculo-arterial discordance. This means that the great arteries (aorta and pulmonary artery) arise from the inappropriate ventricles.

The aorta is anterior to the pulmonary artery and arises from the right ventricle (RV). This alignment results in a circulatory system with two parallel circuits, the systemic circuit being oxygen-poor and the pulmonary circuit being oxygen-rich, rather than in the normal “in-series” arrangement.

Because the 4-chamber views are usually normal, this defect can be difficult to identify prenatally. Along with significant central cyanosis, comfortable tachypnea is a common physical finding. Usually no murmur is present. The second heart sound (S2) is likely to be single, from the anterior aortic valve.

A chest x-ray may show narrowing of the superior mediastinum, related to the orientation of the great vessels, the” egg-on-a-string” shadow; more often the thymus overlies the mediastinum in the newborn, masking this finding that would be more common in older children. A chest x-ray would typically show either normal or increased pulmonary vascularity. The combination of the lack of a murmur and a relatively normal appearing chest x-ray in a significantly cyanotic newborn makes the odds of d-TGA high. Confirmatory diagnosis is made by echocardiogram with particular attention given to the atrial and ventricular septae, outflow tracts, coronary-artery anatomy and size of the PDA.
Delivery of oxygen to the tissues in a newborn with d-TGA depends on communication between the two parallel circuits that allows oxygenated blood to mix with deoxygenated blood; this is the role of the atrial septal defect or patent foramen ovale. If the atrial septum is inadequately small an emergent atrial septostomy can be performed as part of a cardiac catheterization to establish a more reliable communication between the two parallel circuits. The PDA helps by shunting systemic blood into the lower resistance pulmonary circuit. The PDA is usually kept patent using prostaglandin E1 (PGE1) to augment atrial mixing. This is followed by definitive repair with an arterial switch operation, usually done within the first week of life. Figure 5 depicts transposition of the great arteries.

**Tetralogy of Fallot**

Tetralogy of Fallot (TOF) has a slightly higher prevalence throughout the lifespan than d-TGA, making it the most common cyanotic congenital defect. TOF is a constellation of 4 cardiac abnormalities: large malaligned ventricular septal defect (VSD), aorta overriding the VSD, right ventricular outflow tract (RVOT) obstruction with pulmonary stenosis, and RV hypertrophy (see Figure 6).

TOF ranges from the “pink Tet” with minimal pulmonary stenosis to the most severe form of RVOT obstruction, which is pulmonary atresia. The degree of cyanosis in TOF is roughly related to the degree of antegrade flow across the native pulmonary valve. When the RVOT is more obstructed, less blood passes from RV to pulmonary artery and more “blue” blood is shunted across the VSD and out the overriding aorta.

Most forms of TOF do not require immediate intervention and can be monitored on an outpatient basis prior to surgical intervention at a few months of age. The physical exam may show some cyanosis with a harsh systolic ejection murmur produced by turbulent flow across a narrowed RVOT. A chest x-ray may show a “boot-shaped” heart due to uplifting of the cardiac apex by RV hypertrophy and an absent shadow of the main pulmonary artery. In newborns this may be masked by the overlying thymic shadow. The pulmonary vascularity on chest x-ray is usually reduced.
Diagnosis is made by echocardiography that includes detailing the malaligned VSD, RVOT, pulmonary valve leaflets and annulus size (11). A PDA may or may not be present but PGE1 is generally not needed in management of a “straight-forward” TOF newborn.

Parental education is important for recognizing hypercyanotic (“Tet) spells in the infant, which are more commonly seen after a few weeks of age. These spells can become refractory and life-threatening. They are characterized by paroxysms of hyperpnea (rapid and deep respirations), irritability and prolonged crying with increased cyanosis and decreased intensity of the heart murmur on exam.

The medical management of hypercyanotic spells aims to increase systemic vascular resistance, decrease impedance to pulmonary blood flow, and improve the relative balance between the systemic and pulmonary circulations. The knee-to-chest position increases the systemic vascular resistance. Administration of oxygen, intravascular volume expansion, and sedation are used to improve pulmonary blood flow acutely.

Similarly, vasopressor agents such as epinephrine, phenylephrine, or norepinephrine can be given acutely to increase systemic vascular resistance and blood pressure. Beta-blocking agents such as propranolol may be used to relax the RVOT obstruction acutely or over the longer term to decrease the occurrence of spells in infants awaiting surgery. The occurrence of hypercyanotic spells is considered an indication for planning surgical intervention, especially given the trend towards earlier surgery. Figure 6 depicts Tetralogy of Fallot.

**Tricuspid atresia**

Tricuspid atresia is characterized by absence of the tricuspid valve with resultant RV hypoplasia. The diagram resembles that of pulmonary atresia (below) except there are varying degrees of RV outflow tract obstruction and right ventricular hypoplasia. There is always an ASD or large PFO allowing for egress of blood from the right atrium. A VSD, if present, may mean that the infant is born with a normal-size right ventricle. That is, the RV is hypoplastic unless there is an associated large VSD.

Cyanosis is common, from decreased pulmonary blood flow. A murmur may or may not be heard depending on the presence of outflow tract obstruction. An ECG typically shows a superior QRS axis and a lack of right-sided forces. (This is a defect for which a newborn ECG may be helpful, as the typical newborn right axis deviation and right ventricular hypertrophy will not be present.)
Pulmonary vascularity on the chest x-ray is usually reduced.

Initial management for these infants, including the need for PGE1, depends on the amount of pulmonary blood flow. Surgical treatment aims to establish and control the amount of pulmonary blood flow. These patients will require surgical single-ventricle staged palliation with a Fontan procedure when they are older. The Fontan procedure directs blood flow from both vena cavae to the pulmonary arteries, thus separating the pulmonary and systemic circulations.

Figure 7. Pulmonary atresia with an intact ventricular septum – the lack of antegrade pulmonary blood flow in utero leads to underdevelopment of other right-sided structures.

**Pulmonary atresia with an intact ventricular septum**

Pulmonary atresia (PA) with an intact ventricular septum is characterized by complete RVOT obstruction, absence of a VSD (distinguishing it from TOF with pulmonary atresia), and varying degrees of RV and tricuspid valve hypoplasia. The cardiac exam may not be remarkable, other than the single S2, or there may be a systolic regurgitant murmur if there is tricuspid regurgitation. A chest x-ray typically shows a paucity of pulmonary vascular markings. A PGE1 infusion is necessary until a reliable source of pulmonary blood flow is surgically provided.

Depending on the adequacy of the tricuspid valve, size of the RV, and presence of RV-to-coronary-artery sinusoids, patients may undergo either a 2-ventricle repair or a staged Fontan procedure for single-ventricle type palliation (directing blood flow from both vena cavae to the pulmonary arteries). The Fontan procedure is generally completed by the time the child is 2-4 years of age. Figure 7 depicts pulmonary atresia with intact ventricular septum.

**Total anomalous pulmonary venous return**

Total anomalous pulmonary venous return (TAPVR) occurs when all four pulmonary veins drain into systemic veins or more directly into the right atrium, with or without pulmonary venous obstruction. Systemic and pulmonary venous blood mixes in the right atrium. Oxygenated blood reaches the systemic circulation only via an ASD or patent foramen ovale, which is essential for survival.

Embryologically, failure of the common pulmonary vein to connect with the pulmonary venous plexus leads to persistence of one or more earlier venous connections to either the superior vena cava, the left vertical vein (innominate vein), or the umbilicovitelline vein/portal vein (supracardiac,
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cardiac, infradiaphragmatic or mixed drainage patterns). TAPVR is isolated in two-thirds of patients, and occurs as part of a group of heart defects (e.g., heterotaxy syndromes) in approximately one-third of patients. All of the pulmonary veins frequently converge to a confluence that may sit behind the left atrium but does not communicate with the left atrium.

Whether or not there is a “vertical vein” to drain the confluence differentiates the forms of TAPVR. If the vertical vein is unobstructed, patients may have very mild or no cyanosis. Obstructed TAPVR occurs when the vertical vein flow is restricted, leading to pulmonary edema and pulmonary arterial hypertension. Although there is often not a murmur, the physical exam may show, along with cyanosis and tachypnea, a continuous murmur at the location of the obstructed vertical vein. If the pulmonary venous return is obstructed, the chest x-ray will usually show small cardiac silhouette and marked pulmonary edema.

Diagnosis of TAPVR is made by echocardiogram detailing all pulmonary veins and their courses. While PGE1 is generally helpful for defects with severe cyanosis, it should not be given to patients with TAPVR because it can increase flow into the pulmonary arteries and worsen pulmonary congestion. Obstructed TAPVR is now the only cyanotic congenital heart defect that cannot be aided by medical treatment and is a surgical emergency. Unfortunately, this defect is difficult to diagnose prenatally. Figure 8 depicts totally anomalous pulmonary venous return.

![Figure 8. Total anomalous pulmonary venous return (the supracardiac type is shown on the left and infradiaphragmatic on the right).](image)

**Truncus arteriosus**

Truncus arteriosus comprises only 0.7% of all CHD and 4% of all CCHD cases. One in four cases is associated with a 22q11.2 deletion, suggesting DiGeorge syndrome. In truncus arteriosus there is a common arterial trunk overriding a ventricular septal defect. The truncus arteriosus provides blood for the systemic and pulmonary circulation and coronary arteries. Aortic arch abnormalities are common, including a right aortic arch and an interrupted aortic arch. Cyanosis is relatively mild.

Physical exam findings may include a single and loud second heart sound. A systolic ejection click from the large truncal valve may be heard along the left sternal border. There is usually a systolic ejection murmur along the left sternal border. Peripheral pulses may be prominent and may become bounding because of runoff into the pulmonary vascular bed in diastole.

There is relatively little left-to-right shunting at birth. Over the first weeks of life, however, the pulmonary vascular resistance drops, left-to-right shunting increases and heart failure symptoms develop. Although the pathophysiology is similar to that of isolated ventricular septal defects, heart failure usually occurs earlier. This is because the systemic and pulmonary circulations are essentially in parallel; with pulmonary blood flow often at least 3-fold higher than systemic blood flow.
Surgical repair is often necessary in the first month. Survival rates are 80% or higher. During childhood re-intervention is often necessary, including replacement of the right ventricle to pulmonary artery conduit and/or truncal valve repair or replacement. See Figure 9 for truncus arteriosus.

**Ebstein’s anomaly**

Ebstein’s anomaly is characterized by abnormalities of the tricuspid valve and right ventricle. The tricuspid valve leaflets are malformed and are displaced downwards into the right ventricle, partly attached to the fibrous tricuspid valve annulus and partly to the right ventricular endocardium. The morphology of the tricuspid valve and the clinical presentation are highly variable.

Newborns with marked tricuspid leaflet displacement or abnormal leaflet attachment may have severe regurgitation, right-sided heart failure and significant right-to-left inter-atrial shunting resulting in marked cyanosis. Other physical findings may include a prominent “a” wave in the distended jugular veins and hepatomegaly. There may be a palpable prominent parasternal impulse. On auscultation, there may be a widely-split second heart sound from right bundle branch block. A prominent S3 and/or a loud S4 may give the impression of multiple heart sounds. A systolic murmur from tricuspid regurgitation is common. The chest x-ray in severe cases reveals massive cardiomegaly with diminished pulmonary vascularity (11).

In general, surgical therapy is avoided in the newborn period. Neonatal medical management is limited to supportive therapy until the pulmonary vascular resistance drops over time. In case of extreme cyanosis, a PGE1 infusion may be helpful to keep the ductus arteriosus open for pulmonary blood flow until the pulmonary vascular resistance drops. Inhaled nitric oxide may also help by reducing pulmonary vascular resistance and improving antegrade pulmonary blood flow. Ebstein’s anomaly is depicted in Figure 10.

**Persistent pulmonary hypertension of the newborn**

Persistent pulmonary hypertension of the newborn (PHN), as the name suggests, occurs when the pulmonary vascular resistance (normally high in the fetus and decreasing after birth), remains abnormally elevated after birth. This results in right-to-left
shunting through fetal circulatory pathways. The incidence is higher in term and near-term infants and may be as high as 1 in 500. Normally, the decrease in PVR after the first breath results in a 50% decrease in pulmonary artery pressure and in a 10-fold increase in pulmonary blood flow during the first few minutes of life (12).

Figure 10. Ebstein’s anomaly – note “atrialization” of the right ventricle but the downwardly-displaced tricuspid valve.

The term originally used to describe this syndrome was persistent fetal circulation. This was changed to PPHN to describe the pathophysiology more accurately. The delayed neonatal transition can lead to severe hypoxemia presenting at or shortly after birth, more often in neonates born at 34 weeks or more of gestation. Severity ranges from mild and transient respiratory distress to severe hypoxemia and cardiopulmonary instability requiring maximal support. Many cases are associated with lung parenchymal disease, such as meconium aspiration syndrome and respiratory distress syndrome, but some have idiopathic PPHN. There is an association with maternal non-steroidal anti-inflammatory agents during the third trimester causing constriction of the PDA.

On cardiac examination a prominent right ventricular impulse and a loud second heart sound are sometimes apparent. Occasionally, a systolic regurgitant murmur of tricuspid regurgitation may be heard at the lower left sternal border. Hypoxemia is universal and is typically unresponsive to 100% oxygen given by oxygen hood but may respond to hyperoxic ventilation. A PaO₂ gradient between a pre-ductal (right arm) and a post-ductal (umbilical artery or leg) site of blood sampling >20 mm Hg suggests right-to-left shunting through the PDA, as does an oxygenation saturation gradient >5% between pre- and post-ductal sites using pulse oximetry. Of course this pre- and post-ductal difference does not reflect shunting at the atrial level, but only across the PDA.

Echocardiography is the most reliable, convenient and noninvasive way to establish the diagnosis, to assess cardiac function, and to exclude an associated structural heart defect. Right-to-left shunting across a patent foramen ovale and/or a PDA may be noted. The right ventricle is usually enlarged, with a flattened ventricular septum that may be displaced into the left ventricle by the elevated right ventricular pressures.

It is important to establish that the aortic arch and pulmonary veins are normal, as structural anomalies can masquerade as PPHN. Specifically, a coarctation of the aorta can be associated with right-to-left PDA shunting and anomalous pulmonary venous return with right-to-left foramen ovale shunting. Tricuspid regurgitation may be noted with PPHN and pulsed Doppler interrogation of the tricuspid regurgitation jet velocity can be used to estimate the pulmonary pressure relative to the patient’s blood pressure.

Following the discovery of nitric oxide (NO) as the endogenous vasodilator released by blood vessels, it was shown to cause selective pulmonary vasodilation in a sheep model of pulmonary hypertension in 1991 (13). The introduction of inhaled NO therapy has been the most significant milestone in the era of vasodilator therapy for PPHN and is a remarkable example of bench-to-bedside translational advances.
The need for extracorporeal membrane oxygenation (a procedure that uses a machine to bypass the lungs and sometimes the heart) in these infants has declined by about 40% since NO therapy became available. NO is scavenged by hemoglobin (Hb) after diffusing into the blood and is rapidly inactivated. The vasodilatory effect of inhaled NO is therefore limited mostly to the lung. This is in contrast to formerly used intravenous vasodilators that caused systemic vasodilation and hypotension.

Survival of patients with PPHN varies by severity and underlying diagnoses. Newborns with mild PPHN who respond quickly to therapy have a good long-term outlook. Survival rates for PPHN in general exceed 90%. Infants with severe PPHN requiring extracorporeal membrane oxygenation have a 70-80% survival rate. These survivors are at risk for developmental delay, cerebral palsy and sensorineural hearing loss (14).

**Acyanotic defects**

After ventricular septal defects, an atrial septal defect (ASD) is the second most common congenital heart defect, accounting for 10-15% of all CHD. ASDs occur almost twice as frequently in girls. There are three types of atrial septal defects: ostium primum (10-15%) in the lower portion of the atrial septum near the mitral and tricuspid valves, ostium secundum (70-80%), central and in the region of the fossa ovalis, and sinus venosus (10-15%), posterior, near the orifice of the superior vena cava and frequently associated with partial anomalous pulmonary venous return. Right-sided chamber enlargement can develop after the newborn period.

The exam is characterized by wide and fixed splitting of the second heart sound and a soft pulmonary flow murmur. Even if the ASD is large, there are usually no symptoms during infancy and childhood. Symptoms resulting from increased pulmonary blood flow generally do not develop until the second or third decade.

Elective repair for ASDs with significant shunting is recommended at about 3-4 years of age. This can be done surgically. For many secundum ASDs device closure at that age or older is also an option. See figure11 for a demonstration of atrial septal defect.

**Ventricular septal defect**

A ventricular septal defect (VSD) is the most common congenital heart defect and accounts for 20-30% of CHD. Small VSDs often close spontaneously. Moderate and large defects are less likely to close and may result in congestive heart failure at about a month of age. The terms restrictive and non-restrictive describe whether or not the right ventricular pressure is the same as the systemic blood pressure.

VSDs may be muscular, perimembranous, inlet or outlet. Sometimes a ventricular septal aneurysm is seen on the echocardiogram. This thin flap of tissue may increase the chances that the defect will close spontaneously.

Symptoms from a large VSD are not seen before a few weeks of age, at which time diuretics may be used to control them and optimize weight gain.
Surgery may follow weeks or months later for larger defects especially if weight gain is compromised. Figure 12 demonstrates ventricular septal defect

**Atrioventricular septal defects**

The term atrioventricular septal defect (AVSD), also called endocardial cushion or atrioventricular canal defects) refers to a spectrum of lesions that have improper development of the atrioventricular junction as the underlying abnormality. An AVSD can be considered a failure of chamber septation. In these cases, the atrioventricular junction fails to undergo normal septation and formation of separate atrioventricular valves, leaving a common atrioventricular valve providing inflow to both ventricles. The atrioventricular cushion contributions to atrial and ventricular septation are abnormal, resulting in an ASD of the ostium primum type, and/or a VSD of the inlet type. Although AVSDs comprise only 7% of congenital malformations, they occur in about 40% of patients with Down syndrome. To date, no single gene on chromosome 21 has been implicated in causing AVSDs.

Figure 12. Ventricular septal defect - muscular type.

Figure 13. Atrioventricular septal defect – complete and balanced.
Surgical repair is necessary unless the defect is very small or is mostly occluded by aneurysmal valve tissue. Defects with significant ventricular shunting are typically closed at a few months of age. Those with only atrial shunting (so-called partial AVSDs) may be closed, in the absence of symptoms, at the recommended time for ASD closures, that is, at 3-4 years of age. See Figure 13 for a depiction of atrial septal defect.

**Patient ductus arteriosus (PDA)**

In infancy a PDA is most often seen in the setting of preterm delivery. Non-steroidal agents (ibuprofen, indomethacin) are effective in closing these in premature infants. Occasionally surgical PDA ligation will be necessary. In older children coil embolization is the method of choice. The PDA is thought to derive from the embryonic left sixth aortic arch. The aortic end of the PDA arises distal to the left subclavian artery and the pulmonary end inserts at the junction of the main and left pulmonary arteries.

The clinical manifestations of a PDA are determined by the degree of left-to-right shunting, which is dependent upon the size and length of the PDA, and the difference between pulmonary and systemic vascular resistances. Physical-exam findings include a continuous murmur and bounding pulses, including the presence of palmar pulses in the newborn. Precordial palpation may reveal a dynamic left ventricular impulse; an apical mid-diastolic rumble induced by increased flow across the mitral valve may also be present. Figure 14 demonstrates a PDA.

![Figure 14. Patent ductus arteriosus. A patent ductus arteriosus allows blood to flow from the aorta back into the pulmonary artery, to recirculate to the lungs. Left-sided dilatation may develop.](image)

**Left-sided obstructive lesions**

Coarctation of the aorta is a discrete narrowing of the aorta. It accounts for 4 to 6% of all CHD. On physical examination, a clinical diagnosis is made if the femoral pulses are absent or delayed (especially when compared with the right brachial pulse). Four-limb blood pressure measurements may show a higher systolic pressure in the right arm compared to the legs. The cardiac exam is usually otherwise unremarkable.

Prenatal diagnosis is challenging as the ductus arteriosus may overlie the narrowing and it provides much of the descending aortic flow. Because patients with Turner syndrome have about a 10% risk of coarctation, female patients with a coarctation should be examined for features of Turner syndrome. See Figure 15 that demonstrates coarctation of the aorta.
Interrupted aortic arch

The most extreme form of coarctation is an interrupted aortic arch. Complete interruption usually occurs between the left carotid and left subclavian arteries (as shown in the figure) but it can occur either distal to the left subclavian artery or between the innominate and left carotid artery. It is usually associated with a large ventricular septal defect. Surgical correction is required for both the arch obstruction and the ventricular septal defect. Figure 16 depicts interrupted aortic arch.
Hypoplastic left heart syndrome

Hypoplastic left heart syndrome (HLHS) and related functional single right-ventricle conditions remain the highest risk and costliest group of lesions among commonly-occurring CHD. Hypoplastic left heart syndrome accounts for 2 to 3% of all CHD. HLHS is characterized by hypoplasia of the left heart and the aorta, with compromised cardiac output. Untreated, 95% will die within the first few weeks of life.

Syndromes occurring with HLHS include Turner syndrome, trisomy 13, trisomy 18, Holt-Oram, Smith-Lemli-Opitz and Jacobsen syndrome. HLHS patients with a genetic disorder and/or extracardiac abnormality have a worse prognosis (15).

As the PDA begins to close and pulmonary vascular resistance decreases, infants become symptomatic from a decrease in systemic perfusion with diminished peripheral pulses and increasing pulmonary blood flow. They may appear tachypneic and poorly perfused. Usually there is no murmur but the second heart sound may be noted to be single. Untreated, infants soon develop hypotension, acidosis, and respiratory distress and finally cardiogenic shock. Hepatomegaly helps distinguish infants with this type of shock from infants in shock from sepsis or dehydration. Establishing a PDA with PGE1 can reverse this process. The PDA provides vital flow from the right ventricle to the systemic circulation.

While this is not considered a cyanotic defect, the degree of cyanosis is determined by the relative amount of pulmonary versus systemic blood flow. Infants with high pulmonary blood flow may have only minimal cyanosis.

Infants generally undergo a three-stage reconstruction culminating in the Fontan procedure. The first operation (stage I) is the Norwood procedure, in which the right ventricle is connected to a reconstructed aorta with the use of the proximal main pulmonary artery for systemic outflow. Pulmonary blood flow is reestablished using a shunt from the aorta or a conduit from the right ventricle, to the pulmonary arteries.

In the second operation (stage II), generally performed at age 3 to 6 months, the shunt is removed and pulmonary blood flow is supplied by an anastomosis between the superior vena cava and the pulmonary artery. The Fontan procedure (stage III) generally occurs when the child is age 2 to 4 years. In this operation, blood flow through the inferior vena cava is directed to the pulmonary artery, thus separating the pulmonary and systemic circulations.

Figure 17. Hypoplastic left heart syndrome - note underdevelopment of the left heart with hypoplasia of the left ventricle including atresia, stenosis or hypoplasia of the aortic or mitral valve (or both valves), hypoplasia of the ascending aorta and aortic arch and PDA-dependent systemic blood flow.
Mortality associated with the Norwood procedure remains the highest among common congenital heart procedures, ranging from 7 to 19% and is associated with the highest cost and the third longest length of stay. Between the Norwood procedure and the stage II procedure, 4 to 15% of infants die; this mortality rate is expected to improve with recent quality-improvement initiatives directed at outpatient interstage monitoring.

A newer option, called the hybrid approach, uses a combination of surgical and transcatheter techniques to accomplish the goals of the Norwood repair but without cardiopulmonary bypass and circulatory arrest (16). This approach also culminates in the Fontan procedure. See Figure 17 for hypoplastic left heart. A good review of acyanotic heart lesions is found in reference 17 by Marino, Bird, and Wernovsky(17).

**Congestive heart failure and cardiogenic shock**

Congestive heart failure (CHF) is a clinical syndrome that manifests as tachypnea, tachycardia, hepatosplenomegaly, and cardiomegaly. It represents a physiologic state where the heart is unable to adequately meet the metabolic demands of the body. The newborn with CHF frequently presents with tachypnea or diaphoresis during feeding leading to failure to thrive.

A chest x-ray may reveal pulmonary edema and cardiomegaly. Although generally less useful, an ECG may demonstrate an arrhythmia (if this is the cause) or chamber enlargement due to excessive volume load. An echocardiogram is helpful in confirming impaired ventricular function or structural heart defects that may cause of CHF. If CHF goes unrecognized and untreated, inadequate tissue perfusion may lead to hypoxemia and acidosis, with progression to cardiogenic shock. In most cases, repair or palliation of the underlying cardiac defect provides the most effective treatment for CHF.

Hydrops fetalis is the presentation of CHF in the fetus. It is characterized by abnormal amounts of fluid in two or more body spaces. Fluid accumulation can lead to skin edema, pericardial or pleural effusions, and ascites. Hydrops fetalis is classified as immune versus non-immune. Cardiovascular disorders represent about 20% of non-immune cases. In the fetus or immediate newborn period the most likely structural problems are severe atrioventricular valve regurgitation, Ebstein’s anomaly of the tricuspid valve, any type of severe atrioventricular valve regurgitation, and a large arteriovenous malformation.

CHF in the newborn period may be caused by non-structural heart disease. Non-structural causes include birth asphyxia with myocardial ischemia, hypoglycemia, hypocalcemia, hypothyroidism, severe anemia, sepsis, and arrhythmias. Myocarditis and different types of cardiomyopathy should also be considered in the differential of CHF in the newborn period.

An approach to evaluating CHF in the newborn is assessment of the age at presentation. While functional closure of the ductus arteriosus may happen by several hours, ductal-dependent lesions predominate in the newborn-to-one-week period. The most likely structural problems at this time are HLHS, interrupted aortic arch and a severe coarctation of the aorta. Patients with these defects may present with cardiogenic shock. Another cause of CHF that is more common in preterm infants is a PDA.

Arrhythmias such as complete heart block, supraventricular tachycardia, or much less often, ventricular tachycardia can cause hydrops fetalis or newborn CHF. Other causes include severe anemia and myocardial dysfunction such as from a cardiomyopathy or myocarditis.

By a month of age the pulmonary vascular resistance of a newborn reaches its nadir. This leads to a predominance of left-to-right shunt lesions causing CHF around that time, with the most likely lesions being VSDs and AVSDs.

**The dysmorphic newborn and associated congenital heart defects**

The percentage of heart defects related to an abnormal chromosome is estimated to be 5%, single gene defects about 4%, and environmental factors about 2%. In 85 to 90% of cases, however, there is no identifiable cause. Some genetic conditions, such as Down syndrome, Turner syndrome, and 22q11.2 deletion syndrome, result from changes in the number
or structure of particular chromosomes. Other conditions, including Noonan syndrome and Alagille syndrome, result from mutations in single genes. Potential environmental risk factors include exposures to maternal viral infections (e.g., rubella), diabetes and phenylketonuria.

Dysmorphic features in a newborn can lead to the diagnosis of CHD and addition congenital malformations. Nearly 25% of those with CHD have one or more extracardiac malformations. It is not uncommon for a cardiac defect to raise suspicion of an associated syndrome, such as pulmonary stenosis leading to a diagnosis of Noonan syndrome or fetal heart block revealing maternal lupus.

It is thus important to be familiar with frequently-encountered syndromes or teratogenic exposures and their associated cardiac defects. Patients often require a comprehensive and coordinated approach among various subspecialty areas. The following is a brief summary of major syndromes and exposures commonly associated with CHD.

**Down syndrome (Trisomy 21)**

Down syndrome is commonly associated with advanced maternal age and is the most frequently encountered chromosomal abnormality affecting live births. The estimated incidence is 1 in 1,000 live births. This syndrome is characterized by cognitive, motor, and growth delays.

Patients have a recognizable and abnormal flat facial appearance with slanted palpebral fissure, small eyes, small ears and macrognlossia. They also may have other findings such as hypotonia, short and broad necks, shortened limbs, single transverse palmar crease, Brushfield spots of the iris, and clinodactyly (a bend or curvature of the fifth finger). A karyotype analysis identifies cases due to translocation or mosaicism. Down syndrome is considered non-hereditary, except for rare cases of translocation. The majority of cases (95%), are caused not by translocation but by non-disjunction.

About 50% will have CHD, most often an atrioventricular septal defect (formerly called an endocardial cushion defect), ventricular septal defect, atrial septal defect and/or a patent ductus arteriosus. Due to the high incidence of CHD in this population, an echocardiogram is recommended at the time of suspected diagnosis (either in utero and/or in the newborn period).

An echocardiogram in an asymptomatic newborn with suspected Down syndrome is ideally done after 24-hours of age but before hospital discharge, to allow time for spontaneous patent ductus arteriosus and patent foramen ovale closure. Not all newborns will have undergone this transition by hospital discharge, but waiting to do the echocardiogram allows a day for this to occur. Similarly, a normal fetal echocardiogram does not rule out a patent ductus arteriosus or secundum atrial septal defect, both common in Down syndrome patients.

**22q11.2 deletion syndrome (DiGeorge syndrome)**

This syndrome is associated with microdeletions of chromosome 22 and has an estimated incidence of 1 in 4,000. It is the most common microdeletion syndrome and the inheritance pattern is autosomal dominant. The deletion occurs near the middle of the chromosome at a location designated q11.2. Over 70% have congenital heart defects with the most common defects being truncus arteriosus, interrupted aortic arch, and tetralogy of Fallot.

The presentation can be variable, even among members of the same family, and it can be subtle. Because the phenotype is so varied, different combinations of features were once identified by different names, including DiGeorge syndrome, velocardiofacial syndrome and CATCH 22 (Cardiac defects, abnormal facial features, Thymic hypoplasia, Cleft palate, and Hypocalcemia). DiGeorge syndrome was described in 1968 by a pediatric endocrinologist from Philadelphia, Angelo DiGeorge (1921-2009). The pattern of malformations was actually recognized as early as 1671, when the Danish scientist Nicolas Steno (1638-1686) described a patient with cleft palate and truncus arteriosus. Others had reported the association of the various findings with hypoplasia of the thymus and parathyroid glands.

DiGeorge syndrome has been used for patients with a cardiac anomaly, hypocalcemia and poor T-cell production. Confusion exists because there are those who have the deletion but not the clinical syndrome
and there are those considered to have DiGeorge syndrome who do not carry the deletion. The preferred term is 22q11.2 deletion syndrome.

Diagnosis can be confirmed with targeted FISH (fluorescent in situ hybridization) testing or chromosomal microarray analysis. Unique facial characteristics include a prominent nose, hypertelorism, short philtrum, downslanting eyes and auricular abnormalities. Infants may have palatal abnormalities, conduction hearing loss, feeding problems, developmental and growth delay, learning disabilities, hypoplasia or absent thymus and parathyroid, hypocalcemia and T-cell dysfunction. Later in life, they are at an increased risk for schizophrenia, depression, anxiety and bipolar disorder.

Associated cardiac defects are ventricular septal defects and conotruncal malformations. Conotruncal malformations include truncus arteriosus, interrupted aortic arch and other aortic arch anomalies, tetralogy of Fallot, double outlet right ventricle, and d-transposition of the great arteries. Of truncus arteriosus patients, 40% will have the 22q11.2 microdeletion, as will 50-60% of interrupted aortic arch (type B) patients, and 15% of tetralogy of Fallot patients.

Turner syndrome

Turner syndrome is a chromosomal syndrome with features of short stature, primary amenorrhea, webbed neck, barrel-shaped chest, congenital lymphedema, and cubitus valgus (the elbow deviates away from the body when extended). The chromosomal aberration is the presence of a single X sex chromosome leading to the 45, XO karyotype. Turner syndrome affects approximately 1 in 2,500 newborn girls worldwide, and is more common among pregnancies that lead to miscarriages and stillbirths.

Diagnosis is confirmed by a karyotype. The cardiac defects associated with Turner syndrome are coarctation of the aorta, aortic stenosis, bicuspid aortic valve (BAV), hypoplastic left heart syndrome, aortic dilation and hypertension. Approximately 11% have coarctation and 16% have BAV. Aortic coarctation and BAV are more frequent in patients with webbed necks (18).

Noonan syndrome

Noonan syndrome is single gene disorder affecting multiple organ systems. The estimated prevalence is 1 in 1000-2500. The major features are short stature, developmental delay, a characteristic facial appearance (hypertelorism, epicanthal folds, ptosis, and low-set ears), short webbed neck, chest deformity, cubitus valgus, peripheral lymphedema and cryptorchidism. Multiple gene mutations (all involving proteins in the RAS-MAPK pathway) have been identified as causing Noonan syndrome, with about half due to mutations of the PTPN11 gene.

Diagnosis is confirmed with widely available genetic testing. Several congenital heart defects are associated with Noonan syndrome, including pulmonary stenosis (dysplastic pulmonary valve), hypertrophic cardiomyopathy and secundum ASDs. The inheritance pattern is autosomal dominant.

Williams syndrome

Williams syndrome is another single gene disorder affecting multiple organ systems. Williams syndrome results from a defect in the ELN gene on chromosome 7 that codes for the protein elastin and can be confirmed with genetic testing. Although it is considered autosomal dominant, most cases are not inherited

Cognitive delay, distinctive facial features, unique personality traits, hypercalcemia, and CHD characterize the condition. Early case reports gave it the nickname “elfin facies syndrome” due to the distinctive facial features of broad forehead, periorbital fullness, flattened nasal bridge, upturned nose, long philtrum, wide mouth, full lips, and a pointed chin. Affected children have outgoing and engaging “cocktail” personalities. They have difficulty with visual-spatial tasks but perform well in tasks that involve spoken language and music. Some may have hyperacusis (acuteness of hearing with intolerance for normal sound levels).

Supravalvar aortic stenosis is commonly associated with Williams syndrome. Due to the ubiquitous nature of elastin, other forms of arterial stenosis (pulmonary, coronary and systemic) can also be seen, such as peripheral pulmonic stenosis.
Marfan syndrome

Marfan syndrome is caused by a defect in the fibrillin-1 gene (FBN1) on chromosome 15 that codes for the extracellular matrix protein fibrillin-1. It has autosomal dominant inheritance. The incidence is approximately 1 in 5,000.

Marfan syndrome is a connective-tissue disorder with a wide variability of phenotypic expression involving the musculoskeletal, ocular, dura, pulmonary and cardiovascular systems. Neonatal Marfan syndrome is the severest phenotype of this disease and has a poor prognosis. The main reason for death in the neonatal type is congestive heart failure from mitral regurgitation. This is in contrast to classic Marfan syndrome, in which death is more often from aortic root disease and dissection.

Individuals with Marfan syndrome are usually tall and slender, have arachnodactyly, and increased arm-span to height ratio. Other common features include scoliosis or kyphosis, pectus deformities, dural ectasia, spontaneous pneumothorax, myopia, ocular lens dislocation (ectopia lentis) and early cataracts or glaucoma.

Nearly all patients have some cardiovascular involvement, most commonly mitral valve prolapse and aortic root dilation. As the aortic root enlarges, these patients are at risk for aortic regurgitation, dissection, and rupture. Diagnosis is based on a set of established criteria focused on family history and physical findings involving more than one organ system.

Ehlers-Danlos syndrome

Ehlers-Danlos syndrome (EDS) is a group of connective-tissue disorders with variable presentation from mildly loose joints to life-threatening aneurysms. Multiple mutations in genes coding for collagen have been discovered as causing EDS. The incidence is similar to Marfan syndrome, i.e., approximately 1 in 5,000.

There are six types and the inheritance pattern varies by type (arthrochalasia, classic, dermatosparaxis, hypermobility, kyphoscoliosis, and vascular types). Most EDS patients have hypermobile joints. Infants have joint laxity that can delay the development of gross motor skills such as sitting, standing, and walking. The skin is often soft, highly elastic, with easy bruising, poor wound healing. EDS can be associated with mitral valve prolapse, aortic aneurysm and rupture.

CHARGE association

CHARGE association is an acronym for a group of congenital anomalies including coloboma, heart defects, choanal atresia, retardation of growth and development, genitourinary anomalies, and ear anomalies. Of those with CHD, conotruncal anomalies (tetralogy of Fallot, double-outlet right ventricle, truncus arteriosus) and aortic arch anomalies (vascular ring, interrupted aortic arch) are common. Other associated defects include PDAs, VSDs, and ASDs. Mutations in the CHD7 gene have been found in some cases.

VACTERL association

VACTERL is an acronym for vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities. In this syndrome, VSDs, ASDs and Tetralogy of Fallot are the most common heart defects. The etiology is unknown and there is no clear pattern of inheritance. Although diagnostic criteria vary, the incidence is estimated to be about 1 in 10,000 to 1 in 40,000 live-born infants (19).

Trisomy 13 (Patau’s) syndrome

Trisomy 13 syndrome’s major features are cleft lip and palate, holoprosencephaly, polydactyly, and cutis aplasia congenita (a localized scalp skin defect). CHD occurs in approximately 80% of cases, including PDAs, VSDs, ASDs, polyvalvular disease, coarctation of the aorta, conotruncal defects, and dextrocardia. The overall prognosis is poor, and rare long-term survivors are profoundly impaired.
Trisomy 18 (Edward’s) syndrome

Trisomy 18 syndrome is characterized by microcephaly, micrognathia, rocker-bottom feet and closed fists with overlapping fingers. Nearly all patients with Trisomy 18 syndrome have some form of CHD. The most common defect is a VSD. Other common defects are PDAs, polyvalvular disease, TOF, and DORV. As with Trisomy 13, the prognosis is poor, with high infant mortality within the first week. Survival into teen and adult ages has been reported but long-term survivors are profoundly impaired.

Alagille syndrome

These infants frequently present with acholic stools with jaundice due to a paucity of intrahepatic bile ducts. The associated heart defect is branch pulmonary artery stenosis. Mutations in the JAG1 gene cause Alagille syndrome and inheritance is autosomal dominant. Affected infants have a broad forehead, long straight nose, prominent chin, and small malformed ears.

Tuberous sclerosis complex (TSC)

TSC is characterized by benign tumors affecting the brain, skin, kidneys, and heart. The cardiac finding frequently encountered is rhabdomyoma. These are often multiple, variable in size and involve the ventricles. Large rhabdomyomas may obstruct the intracavitary space or cardiac valves, but more often they are small and not hemodynamically significant.

In the fetus TSC may be suspected if cardiac rhabdomyomas are seen. Infants may present with seizures (infantile spasms). With a careful examination of the skin and brain, it is possible to diagnose TSC in a very young infant. Facial angiofibromas, appear later. Mutations in the TSC1 or TSC2 gene can cause TSC and inheritance is autosomal dominant. The incidence is estimated to be 1 in 6,000.

Maternal systemic lupus erythematosus (SLE) and Sjögren’s syndrome

SLE and Sjögren’s syndrome are autoimmune diseases associated with anti-SSA/Ro and anti-SSB/La anti-nuclear autoantibodies. The congenital heart block associated with neonatal lupus is considered a form of passively acquired autoimmune disease in which maternal autoantibodies to these intracellular ribonucleoproteins cross the placenta and injure the previously normal fetal heart.

Complete heart block occurs in about 1-2% of babies born to these mothers and 10% have an associated cardiomyopathy at the initial diagnosis or develop it later. Cases may occur in infants of mothers who have these autoantibodies, but are not aware and do not have symptoms. About half of these mothers go on to develop SLE or Sjögren’s.

Fetal alcohol syndrome

Fetal alcohol syndrome develops in a fetus exposed to high levels of maternal alcohol consumption during pregnancy. Affected children have variable cognitive delays and abnormal facies (small eyes, smooth philtrum, thin upper lip and microcephaly). CHD occurs in 30-50%. The most common defects are VSDs, PDAs, ASDs, and tetralogy of Fallot.

Maternal diabetes mellitus

Maternal diabetes is a recognized teratogen affecting numerous organ systems including the heart. Studies estimate a relative risk of approximately 4 to 5 for fetal CHD in mothers having diabetes. Cardiac anomalies are the most common malformations with IDM, with VSDs and complex lesions such as transposition of the great vessels predominating. Woman most at risk for fetal CHD are those with poor peri-conceptional control, long-standing diabetes and vascular disease.

Ventricular hypertrophy with left ventricular outflow tract obstruction can also be seen.

Although most infants with this are asymptomatic, respiratory distress or signs of cardiac failure can occur. This cardiac hypertrophy likely
results from fetal hyperinsulinemia, leading to fat and glycogen deposition in the myocardium. Thus, it generally occurs in poorly-controlled pregnancies with resultant macrosomia. Symptoms improve over several weeks with supportive care, and echocardiographic changes resolve as well.

**Arrhythmias**

Rhythm disturbances are important causes of pediatric cardiac disease and can occur in children with either heart disease or an otherwise normal heart. Recognition of arrhythmias has increased because of the routine use of obstetrical ultrasonography and perinatal heart rate monitoring improving the prenatal diagnosis of congenital cardiac disease. Neonatal arrhythmias may be either benign or malignant, depending on their potential to cause death or morbidity. Some helpful general references are cited in the reference section (20-22).

**Ectopy**

Premature atrial beats (APBs) are a common arrhythmia that occurs when atrial tissue other than the sinoatrial node depolarizes prematurely. In the otherwise healthy infant, they rarely suggest an underlying abnormality and are unlikely to be symptomatic. They are frequently an incidental finding on cardiac monitoring, ECGs or Holters. APBs may trigger arrhythmias in patients predisposed to atrial tachyarrhythmias such as atrioventricular reentrant tachycardia and atrial flutter.

On the ECG, associated p-wave morphology may appear different from normal sinus and conduction may be blocked depending on the refractory period of the AV node. They are common in premature infants whose respiration is compromised by respiratory distress syndrome and on a ventilator support. They may be either conducted or blocked, the latter often confused for a primary bradycardia and can be recognized by discovering a blocked p-wave buried within the preceding T-wave (see Figure 1).

**Premature ventricular beats**

Premature ventricular beats (VPBs) are less common in neonates than APBs but are also infrequently associated with serious heart disease and are usually seen in an otherwise healthy infant. An echocardiogram may be helpful in infants with greater than 25-30% ectopy to rule out cardiomyopathy or structural heart disease.

**Bradyarrhythmias**

Bradycardia in the term newborn is defined as a heart rate <90 bpm; it increases to <110 bpm by the first month of age. The etiology of infant bradycardia ranges from suppression of the sinus node to complete atrioventricular (AV) block with various degrees of clinical presentation. Each component of the formation and propagation of the electrical impulse from atria to ventricles (sino-atrial node, atrial tissue, AV node, and His-Purkinje system) may be implicated in bradyarrhythmias.

While the cardiac conduction system is strongly influenced by the autonomic nervous system throughout life, sympathetic innervation dominates in infancy and bradycardia is frequently due to sympathetic withdrawal and increased parasympathetic tone.

**Atrioventricular block**

Careful study of the AV node has revealed that this structure is much more complex than previously thought with multiple conduction fibers. First degree AV block is characterized by a PR interval above the normal range for age. In neonates, this ranges from 0.14-0.16 ms although is strongly influenced by the underlying heart rate.

PR prolongation in association with normal heart rates is likely secondary to AV-nodal dysfunction whereas prolongation with bradycardia is more suggestive of increased parasympathetic tone. First degree AV block is rarely symptomatic; it usually only progresses to higher grade block in the presence of heart disease. Treatment is not necessary, though
when it is present the use of known AV blocking agents should be avoided.

Second degree AV block is divided into Mobitz I (Wenckebach) and Mobitz II. With typical Wenckebach there is gradual prolongation of the PR interval until non-conduction of a beat. Conversely in Mobitz II, there is no prolongation of the PR interval prior to the non-conducted beat. The greatest increment of PR prolongation in Wenckebach occurs during the first several beats, after which the change is minimal. This can lead to the incorrect diagnosis of Mobitz II because the non-conducted beat appears to come suddenly. Careful examination of the first conducted beat, however, will reveal shortening of the PR interval in Wenckebach and no change in Mobitz II and can be confirmed in classic cases to a shortening of the corresponding R-R interval prior to the dropped beat.

Complete heart block, or third degree, reflects complete interruption of electrical activity between the atria and ventricles. The most common etiology is neonatal lupus, accounting for 60-90% of congenital complete heart block; its presence is frequently the first indication of maternal disease. Among women with anti-Ro/SSA or anti La/SSB, roughly 1-2% of pregnancies will develop heart block, crossing the placenta to the fetus in the first trimester. That risk increases to 16% in subsequent pregnancies once a child is born with heart block.

The pathophysiology is likely immune mediated injury of the AV node, release of tumor necrosis factor causing fibrosis, and targeted inhibition of the cardiac calcium channels. Other causes of congenital complete heart block include tumors, myocarditis, and Long QT Syndrome (LQTS). Complex congenital heart disease, specifically L-looped ventricles, heterotaxy, and single ventricle physiology, account for 25-33% of cases.

The clinical presentation depends on the underlying ventricular heart rate, typically a narrow complex escape rhythm arising from the AV junction with rates less than 50 bpm more likely to be symptomatic. Treatment is typically dictated by whether a pacemaker is necessary or not. For congenital complete heart block in a structurally normal heart, a pacemaker is indicated in the presence of failure to thrive, decreased ventricular function, long pauses, or associated ventricular arrhythmias.

Remarkably, infants can do quite well with heart rates even in the 40s and careful observation may be the best initial course of action. Infants with structural heart disease or post-surgical block, on the other hand, should receive a pacemaker. Steroids have been used for complete heart block secondary to maternal autoantibodies including prenatally in-utero.

Tachyarrhythmias

Supraventricular tachycardia (SVT) is the most common tachyarrhythmia in children, occurring in as many as 1:1000, with most presenting within the first year of life. While this category encompasses a number of tachycardia mechanisms, the vast majority (90%) involve a reentrant circuit between the atria and ventricles (AV). These include AV reentrant tachycardia (AVRT), AV node reentrant tachycardia (AVNRT), and persistent junctional reciprocating tachycardia (PJRT). Children less than a year old are most likely to have SVT secondary to AVRT (85%) while the other mechanisms are more common later in childhood.

Atrioventricular reentrant tachycardia may be facilitated by a concealed or manifest accessory pathway. These strands of myocardium (accessory pathway) bridge the electrically insulated AV valve annuli and allow for anterograde or retrograde conduction independent of the AV node-His-Purkinje system. In young children, ventricular rates during tachycardia are typically 240-300 bpm and characterized by absent or retrograde p-waves (see Figure 2). Anterograde conduction results in ventricular preexcitation and the characteristic delta wave seen on a surface ECG (manifest conduction).

Ventricular preexcitation in the presence of palpitations or documented SVT describes the Wolff-Parkinson-White (WPW) syndrome which occurs with an incidence of 1.6:1000. A small subset of these accessory pathways have the ability to rapidly conduct atrial depolarizations to the ventricles during atrial fibrillation, making WPW a rare, and even rarer in newborn (but known), cause of sudden death in the young.

Atrioventricular nodal reentrant tachycardia is supported by a circuit that revolves around AV nodal
tissue. While its clinical presentation is similar to that of AVRT, it is very uncommon in the newborn.

PJRT is a rare reentrant tachycardia that is supported by retrograde conduction through a concealed accessory pathway with decremental conduction properties. It is implicated in less than 1% of SVT in children but usually presents during the first year of life. Criteria for diagnosis of PJRT are a narrow complex tachycardia, a long R-P interval, and inverted p-waves in leads II, III, and aVF.

Typical atrial flutter is a common arrhythmia in adults but comprises less than 1% of SVT in children with a structurally normal heart, the majority in infancy. Although a fetus may be symptomatic in-utero, the infant (if not diagnosed in-utero) will have a benign course; the flutter may spontaneously terminate or it can be converted with either DC cardioversion (0.5 j/kg) or by transesophageal overdrive pacing. Recurrence is rare. Anti-arrhythmic medications are of little value.

Atrial fibrillation is exceptionally rare in children most likely because the small atrial chamber size cannot adequately support the multiple reentrant waves that continuously circulate through the atrium causing disorganized activation and contraction. Two rare chromosomal abnormalities have been linked to fetal atrial fibrillation.

Multifocal atrial tachycardia (MAT), ectopic atrial tachycardia (EAT), and junctional ectopic tachycardia (JET) are arrhythmias characterized by disorders of impulse formation, i.e., abnormal automaticity in the newborn and infant.

MAT, also known as chaotic atrial tachycardia, is by far the most common in neonates. It is usually detected in an otherwise healthy newborn of infant who presents with a fast and irregular heart rate and it is characterized by p-waves of at least three morphologies, irregular p-p intervals with an isoelectric period between them, and a ventricular rate greater than 100 bpm. Unlike its presentation in adults, MAT can be seen in otherwise asymptomatic children. Treatment is frequently not required as the arrhythmia is typically self-limited unless there is underlying congenital heart disease.

JET occurring in the neonatal period presents as either a congenital form (rare) or in the post-operative period (most common). It originates from the AV node or His bundle and the heart rate may be extremely rapid, ranging from 150-240 bpm. In the post-operative period, therapy is geared toward lowering the ventricular rate such that atrial pacing can be performed to reestablish AV synchrony. It is typically transient and long term therapy is rarely required.

**Ventricular tachycardia**

The diagnosis of VT implies an arrhythmia that arises distal to the His bundle, typically within the ventricular myocardium. The differential diagnosis of wide QRS complex tachycardia in the young child includes several other forms of tachyarrhythmias other than ventricular tachycardia (VT) and is beyond the scope of this chapter as they rarely pertain to a wide QRS tachycardia in a newborn. However, certain ECG findings should be used to distinguish it from other tachycardias. First, the QRS duration must be longer than the normal duration for age.

Thus, it is important to recognize that QRS duration is an age related finding and >80 ms is considered prolonged in infants. Secondly, dissociation between atrial and ventricular beats may be observed but can be difficult to distinguish at the high rates typically seen in infants. P-waves can be seen buried in the QRS or the abnormal ST-T wave complex. A transesophageal electrogram recording can often helpful in differentiating the atrial from the ventricular electrogram.

Various descriptive terms are used to classify VT but are occasionally interchangeably and incorrectly used. Non-sustained VT describes greater than 3 consecutive ventricular beats that self-terminate before 30 sec and do not cause hemodynamic compromise. Sustained VT refers to an episode lasting longer than 30 sec (see Figure 3). In repetitive or recurrent VT, multiple episodes of non-sustained VT are separated by periods of sinus rhythm. Finally, incessant VT describes long periods of sustained VT typically requiring intervention to terminate.

A patient with repetitive/recurrent or incessant VT is not necessarily symptomatic; thus these terms only describe time course and onset pattern. Additionally, the morphology of VT is divided into monomorphic and polymorphic. In polymorphic VT, there is beat to beat variability in the QRS axis and
shape. This has clinical implications as polymorphic VT is more likely to degenerate into ventricular fibrillation.

The clinical presentation of VT varies and is dependent on the ventricular rate, and presence of concomitant heart disease. Infants can frequently tolerate higher heart rates although significant atrioventricular dissociation may compromise overall cardiac output. Asymptomatic patients are more likely to have non-sustained VT and/or slower ventricular rates (<150 bpm).

An important and most common form of VT in the newborn is accelerated idioventricular rhythm; in this arrhythmia, the wide QRS rhythm is approximately 125% of the sinus rate. As is seen with SVT, infants may manifest symptoms as irritability, decreased feeding, or pallor. Infants who present in congestive heart failure or complete cardiovascular collapse and shock are more likely to have had surgery for congenital heart disease or myocarditis after an infectious or inflammatory insult.

**Genetic disorders**

Advances in our understanding of molecular genetics have led to developments in the diagnosis and characterization of heritable cardiac arrhythmias. These disorders include channelopathies such as the Long QT syndrome (LQTS). In LQTS, multiple genes (with seven being primary) have been identified that can produce distinct manifestations of the disease. The majority of genes encode potassium channel subunits although sodium channels may also be affected. Inheritance patterns may be autosomal dominant or recessive and recent studies have suggested an incidence of 1:2000 live births.

These newborns can rarely present with life threatening ventricular arrhythmias (torsade de points) and even degrees of heart block (Figure 4). Diagnosis is based on measurements of the QT interval on a 12-lead ECG and corrected for the heart rate using Bazett’s formula. It is clear that LQTS mutations are incompletely penetrant and genetic testing is now recommended for first-degree relatives of genotype positive individuals.

Another channelopathy, the Brugada syndrome, is characterized by specific ST-segment elevations in the right precordial leads in the absence of cardiac ischemia or other structural heart disease. It is an autosomal dominant disorder with an incidence of up to 66 per 10,000 individuals. The risk is highest in males (8:1) and areas of Southeast Asia. Especially important for the infant, the ECG findings of Brugada syndrome, including life threatening ventricular arrhythmias, can be enhanced by fever. Thus the concomitant findings of fever (even induced by a vaccination) and VT should prompt the consideration of this genetic disorder.

**Conclusion**

Approximately 8 in 1,000 newborns have a congenital heart defect that can range from mild to severe and from asymptomatic to life-threatening. Identification of congenital heart disease is a vital component of the pediatric clinician’s responsibility in caring for the newborn in collaboration with experts in Pediatric cardiology. This discussion considers various aspects in this potentially complex task and provides a practical review of cyanotic heart defects, persistent pulmonary hypertension of the newborn, acyanotic defects, congestive heart failure as well as cardiogenic shock, associated congenital heart defects of the dysmorphic newborn, and cardiac arrhythmias. The newborn is a marvelous human being fueled by a remarkable organ—the newborn heart.

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**References**


Neonatal pulmonology

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Abstract

The lung provides alveolar capillary exchange surface of oxygen and carbon dioxide in order to meet the needs of aerobic cellular respiration. The embryonic lung buds originating from the foregut generate a tree like structure that develops into bronchi, bronchioles and alveoli. The lung alveolar epithelium consists of type I pneumocytes that exchange gases and type II pneumocytes that synthesize and secrete surfactant. Surfactant is comprised of lipids and proteins that reduce surface tension at the air-liquid interface and enhance host defense function. Congenital anomalies result from perturbations in lung and airway embryogenesis and may be associated with other birth defects. Both the level of the insult in the tracheobronchial tree and the gestational age of its occurrence correlate with the type of lesion and its histopathology.

Keywords: Pediatrics, neonatology, newborn, pulmonology

Introduction

The lung provides alveolar capillary exchange surface of oxygen and carbon dioxide in order to meet the needs of aerobic cellular respiration. The appropriate development and maintenance of lung functions are critical to the survival of newborn infants. Respiratory disorders account for most admissions to neonatal intensive care units. Respiratory distress in the newborn may be due to pulmonary disorders or to other conditions. Clinical findings include tachypnea, grunting, nasal flaring, retractions, cyanosis and apnea. Understanding lung development and function enables the treating team to provide suitable care for infants with respiratory distress.

Embryology

The lung consists of two entwined systems, the airways and the blood vessels that coordinate gas
exchange (1, 2). The epithelial components of the lung are derived from the endoderm, and the surrounding connective tissue from the mesoderm.

**Developmental stages**

During lung evolution there are five developmental stages:

*Embryonic stage: 4-7 weeks*

During embryonic development, at the 28th day (week 4), two primary lung buds appear at the ventral wall of the foregut that simultaneously separate into an anterior tube, becoming the trachea that connects to the lung bud and a dorsal tube, becoming the esophagus that connects to the stomach. The tracheal mesoderm differentiates into anterior open cartilage rings and posterior smooth muscle while the lung buds give rise to the two main bronchi, which extend into the surrounding mesenchyme and branch. Correspondingly at day 32 the heart that has 2 chambers and lakes containing hematopoietic cells appears in the peribronchial mesenchyme.

*Pseudoglandular stage: 8-16 weeks*

Following the embryonic phase the lung buds generate a tree like structure. The buds sprout at specific distances from the tip of the parent stalk and the tip bifurcates to produce new tubes. A clock mechanism mediated by fibroblast growth factor and its receptor sprout signaling plays a key role in timing the rate of bud extension and determines the inter-branch distance. The branching process includes the bud elongation, cessation of lengthening, expansion and bifurcation of the tip. The tubes are lined with cuboidal epithelia that resemble an exocrine gland, hence the stage’s name. Additionally epithelial cells differentiate with the appearance of ciliated cells, goblet and basal cells, and production of cartilage. At this stage thin-walled vascular channels appear and the pulmonary venous system establishes a central connection with the heart.

The intrapulmonary arterial tree develops and connects with the extrapulmonary artery arising from the aorta that develops at 10 weeks replacing a primitive bronchial artery that regressed. A network of thin-walled peripheral vessels develops and extends to the peripheral airway but outside the epithelial basement membrane. A communication between small muscular vessels and peripheral nonmuscular vessels develops.

*Canalicular stage: 16-25 weeks*

At this stage the respiratory tree is further expanded in diameter and length, accompanied by vascularization and angiogenesis along the airway. The terminal buds narrow to form the bronchioles and are then divided into respiratory bronchioles and alveolar ducts, and the airway epithelial cells differentiate into peripheral squamous cells and proximal cuboidal cells. The cuboidal cells form the type 1 and 2 pneumocytes. Between weeks 20 and 21 small blood vessels invade into the airway’s epithelium to create the air-blood barrier.

*Saccular stage: 24-35 weeks*

At this stage the small sacs develop into primary alveoli, there is extensive thinning of the interstitium, and the blood vessels become closely associated with the alveolar epithelium.

*Alveolar stage: from 36 Weeks*

Alveolarization begins in the near-term lung before birth, but primarilry occurs postnatally, during the first 2-3 years of life, and may continue at a slower rate beyond childhood. At this stage the increase in airway diameter and the formation of secondary septae that subdivide terminal sacculles into anatomic alveoli enables the maturation of the gas exchange mechanism (3).

**The epithelial cells**

Two epithelial cells line the respiratory membrane of the alveoli which are the gas exchange units. The lung alveolar epithelium consists of type I and type II
pneumocytes. Type I cells are large, flattened cells that cover more than 90% of the internal surface area of alveolus. They exchange oxygen and carbon dioxide between the airspace and the underlying microcapillaries and express transport proteins that maintain fluid homeostasis. Type II cells are cuboidal and located between type I cells. Type II cells contain characteristic lamellar bodies in their cytoplasm and their functions include synthesis and secretion of lung surfactant, fluid transport, and host defense. Animals studies have shown that type II cells injured by oxidant gases can also self-renew and trans-differentiate into type I cells (4).

Surfactant

Surfactant is comprised of lipids and proteins that reduce surface tension at the air-liquid interface and prevent end expiratory atelectasis. It is synthesized, packaged within lysosomally-derived organelles called lamellar bodies and secreted in the lung by alveolar type II epithelial cells. Surfactant forms a monolayer at the air-liquid interface in order to lower surface tension effectively. Surfactant is comprised mostly of lipids but about 10% of its weight is protein. Two structurally related hydrophilic proteins, surfactant proteins SP-A and SP-D are part of the collection family and encoded on human chromosome 10. SP-B and SP-C are hydrophobic and are encoded on separate genes on chromosomes 2 and 8 respectively. SP-B and SP-C are first synthesized as larger precursor proteins that are proteolytically processed to the mature forms of SP-B and SP-C found in the airspaces.

Pulmonary surfactant contains several classes of lipids, including phospholipids, triglycerides, cholesterol, and fatty acids. Phosphatidylcholine is the main phospholipid, whose foremost component is dipalmitoylphosphatidylcholine. The second most abundant phospholipid in surfactant is phosphatidylglycerol. Other minor phospholipids include phosphatidylethanolamine, sphingomyelin, phosphatidylinositol, phosphatidylserine and cardiolipin. The type II pneumocytes synthesize surfactant from fatty acids that are either supplied by the circulation in the form of free fatty acids or triacylglycerols within lipoproteins or internalized from alveoli after phospholipid hydrolysis. Alternatively, de novo synthesized fatty acids are formed from lactate as a precursor mostly in immature type II cells, and from glycogen in the late fetal period.

Surfactant phospholipid metabolism (5)

Lung surfactant is synthesized in the endoplasmic reticulum of the alveolar type II epithelial cell before it is transported and stored in the lamellar bodies. Lamellar bodies contain lysosomal enzymes and tightly packed lamellae composed of dipalmitoylphosphatidylcholine. Surfactant is secreted via exocytosis from type II cells by a process involving fusion of the lamellar bodies with the plasma membrane. After secretion from type II cells into the alveolar space, lamellar bodies undergo a structural and metabolic transformation. In the airspace, secreted lamellar bodies combines with SP-A, transforms into tubular myelin that at the air-fluid interface forms the surface-tension reducing film. Secreted surfactant is internalized by type II cells and can be incorporated back to lamellar bodies for recycling or degradation by alveolar macrophages.

The proteins SP-B and SP-C are associated with the surfactant lipids and regulate the integrity and composition of the surface lipid film to reduce interfacial surface tension. Both SP-B and SP-C processed in the Golgi are transported to lamellar bodies through multivesicular bodies via proteolytic processing. SP-A and SP-D are capable of inhibiting foreign pathogens and involved in innate immune responses in the lung. SP-A promotes the conversion of lamellar bodies into tubular myelin providing rapid formation of the surface film, mediates recycling of secreted surfactant components, acts in a negative feedback manner by inhibiting surfactant phospholipid secretion and interacts with diverse pathogens and immune effector cells facilitating their clearance. SP-D in addition to its host defense function regulates pulmonary surfactant homeostasis (6).

Congenital deficiency of SP-B gene is lethal in humans and results in disruption of normal processing of surfactant components and lamellar bodies. The absence of SP-B also blocks processing of SP-C, reduces surfactant function, and alters
phosphatidylglycerol degradation. Mutations in the SP-B gene are associated with fatal Respiratory Distress Syndrome (RDS) in neonates; SP-C mutations are linked to interstitial lung disease. Mutations in ATP-binding cassette transporter A3 (ABCA3) are associated with both phenotypes.

A secretion burst of surfactant occurs at birth with the first breath. Labor and hyperventilation are important physiologic triggers for surfactant secretion. Surfactant secretion consists of two steps in the type II cells: 1) transport of phospholipids from the endoplasmic reticulum to the lamellar bodies, and 2) translocation of phospholipids across the lamellar bodies' membrane at the cell surface. Surfactant components taken up by type II cells are recycled or degraded, while surfactant that is internalized by macrophages is largely degraded. The efficiency of recycling is age and species dependent.

Lung maturation and surfactant production are stimulated by glucocorticoids, thyroid hormones, estrogen, and other growth factors. Endogenous glucocorticoids directly affect fetal lung maturation via glucocorticoid receptors in the type II alveolar cells. Glucocorticoids also exert stimulatory effects on regulatory enzymes involved in phospholipid biosynthesis. Thyroid hormone accelerates lung maturation by increasing surfactant phosphatidylcholine biosynthesis. Estrogens up-regulate maturation of the fetal lung by increasing lyssolecithin acyltransferase activity. In contrast, androgens and insulin have an inhibitory effect on surfactant phospholipid synthesis.

Type II cell maturation is regulated by communication with fibroblasts which involves multiple paracrine factors, resulting in surfactant production. The timing of these events is accelerated by glucocorticoids and decelerated by androgens. The sex difference in circulating testosterone levels results in a delay in the surge of surfactant lipid synthesis among male fetuses. The delay in the surge of surfactant lipid is of no consequence for babies born at term, but is involved in the increased risk of RDS in males born prematurely (7). During both acute and chronic respiratory illness, surfactant levels can be reduced. In neonatal RDS, there is a lack of surfactant production and secretion that may be treated by surfactant replacement therapy. Inflammatory illness, such as pneumonia, is also associated with surfactant dysfunction that disrupts normal surfactant metabolism and increases mortality and morbidity from acute respiratory distress and failure (8).

### Congenital anomalies

Foregut separation requires coordinated cytoskeletal rearrangement and cell shape changes that enable the division of a single lumen tube into two separate organs. Abnormalities in these mechanisms may lead to defective separation processes resulting in birth defects.

Esophageal atresia with or without tracheoesophageal fistula is a common anomaly that is seldom associated with other birth defects, excepting the VACTERL association (vertebral defects, anal atresia, tracheoesophageal fistula with esophageal atresia, cardiac defects, renal and limb anomalies) (9). There are known mutations in genes encoding components of multiple signaling pathways that lead to the formation of esophageal atresia and TE fistula (10). Surgical repair with primary anastomosis and fistula closure is achieved in most cases, elongation of esophageal ends with serial dilations or using gastric interposition as esophageal substitution is used in large esophageal gaps (11).

### Tracheal atresia

Congenital high airway obstruction syndrome is the obstruction of the fetal upper airways; when complete, it is incompatible with life. Fetal ultrasonography findings include bilaterally enlarged hyperechoic lungs, dilated airways, and flattened or inverted diaphragm. Tracheal atresia results from deficient recanalization of the upper airways around the 10th week of gestation. The differential diagnosis includes laryngeal agenesis, subglottic stenosis or atresia, laryngeal webs or cysts, or external pressure from lymphatic malformation, cervical teratoma, and vascular ring (12).

### Tracheobronchomalacia

Congenital Tracheobronchomalacia is a disorder that results in the collapse of the trachea and bronchus...
during expiration due to abnormal cartilage development. The condition can be primary, secondary to other anomaly like tracheoesophageal fistula or due to degeneration of previously normal cartilage like in chronic lung disease or recurrent aspirations (13). Treatment is mostly conservative however some infants need high Positive End-Expiratory Pressure (PEEP) ventilation. Surgical repair includes aortopexy, internal stenting, external stenting, and reconstructive procedures (12).

**The lung**

Congenital lung lesions result from perturbations in lung and airway embryogenesis. Both the level of the insult in the tracheobronchial tree and the gestational age of its occurrence correlate with the type of lesion and its histopathology.

**Pulmonary agenesis**

Pulmonary agenesis is a rare anomaly consisting of unilateral complete absence of the lung, bronchus and vascular supply to the affected side. The pathogenesis is due to defective embryological development during the fourth week of fetal life and is commonly associated with developmental anomalies of the 1st and 2nd branchial arches. The left and right lungs are equally affected. Bilateral pulmonary agenesis rarely found in autopsies is incompatible with life. Right-sided agenesis has a worse prognosis because the greater displacement of the heart and mediastinum, and increased association with pulmonary artery slings. About half of the cases are associated with other congenital anomalies such as the VACTERL association (14) and tracheal stenosis (15).

**Cystic lung disease**

Congenital cystic diseases of the lung consist of cystic adenomatoid malformation, bronchogenic cyst, pulmonary sequestration, and congenital lobar emphysema (16).

**Congenital cystic adenomatoid malformations (CCAMs)**

CCAM present as cystic or solid lung masses formed by abnormal branching of the immature bronchioles and restricted to part of one lung. The pathological feature of CAMs is adenomatoid proliferation of the bronchioles that forms a cyst at the expense of alveoli. The new term is congenital pulmonary airway malformations since not all types are cystic.

There are five types: 0) which has solid lesion formed by bronchiole-like structures with cartilage and smooth muscle, also referred to as acinar dysplasia and is incompatible with life; 1) multiple large cysts that are lined with ciliated pseudostratified columnar epithelium. They may include elastic tissue beneath the epithelium, smooth muscle, and fibrovascular connective tissue, including cartilage; 2) small uniform sized cysts lined with cuboidal to columnar epithelium which have only a thin fibromuscular wall. This type is associated with other anomalies including renal, cardiac, skeletal, intestinal, extra-lobe sequestration; 3) large solid lesions, usually involving an entire lobe of the lung; 4) a single large cyst up to 10 cm in size which has an acinar-alveolar epithelial differentiation. At birth, the cysts that are filled with fluid, then fill with air as they communicate with the tracheobronchial tree and with each other, so that cysts may contain air or air-fluid levels. Treatment consists of resection of the involved tissue or lobectomy (17).

**Bronchiogenic cyst**

Bronchogenic cysts arise from abnormal budding of the tracheobronchial tree during airway development resulting in a fluid-filled blind-end pouch. Most cysts present in the mediastinum and about one third can occur in the lung parenchyma, usually within the lower lobes. The cysts may contain air, fluid, or both. Histopathology consists of cartilage, smooth muscle, and scattered submucous glands within the cyst wall. Clinical manifestations are related to various mass effects or secondary infection of the cyst (18). Complications include infection; compressive symptoms, malignant transformation; and the rare but
fatal air embolism. The appropriate treatment is surgery (19).

**Pulmonary sequestration**

Pulmonary sequestration is a mass of nonfunctioning lung parenchyma, which does not communicate with tracheo-bronchial tree and receives blood supply from a systemic artery. Sequestration is believed to be due to abnormal budding of the primitive foregut. Anatomically it can be classified as intra-lobar and extra-lobar. Intra-lobar sequestration lies within visceral pleura. Arterial supply is from abdominal aorta or thoracic aorta and venous drainage through pulmonary veins into left atrium. It communicates with adjacent lung parenchyma resulting with inadequate bronchial drainage and increased incidence of infection. Extra-lobar sequestration is surrounded by its own pleura, and is usually associated with other congenital anomalies such as diaphragmatic hernia, congenital heart disease, and CCAM.

It is believed that if the lung bud arises prior to the development of the pleura, it is invested with adjacent lung and becomes an intra-lobar lesion. If supernumerary lung development occurs after pleura formation, the bud will grow separately and acquire its own pleural covering, forming an extra lobar lesion. Recurrent infections result in bronchiecstasies, cystic areas, subsegmental atelectasis, mediastinal shift, and prominence of the ipsilateral hila. Differential diagnoses include CCAM, diaphragmatic hernia, terotoma, and accessory spleen. Treatment is surgical resection which usually results in good growth and lung function (20).

**Congenital lobar emphysema**

Congenital lobar emphysema is associated with changes in the bronchial cartilage and is most common on the left upper lobe. The pathophysiologic mechanism consists of disruptions of bronchopulmonary development due to abnormal interactions between embryonic endodermal and mesodermal components of the lung, resulting in progressive lobar hyperinflation. It is associated with congenital heart disease. Differential diagnosis includes CCAM, pulmonary hypoplasia, and pneumothorax. Treatment may be conservative or surgical by lobectomy of affected lung (21).

**Hypoplastic lung**

Lung hypoplasia is defective or incomplete development of lungs that are immature for gestational age. In most cases it is secondary to pathology outside the respiratory tract. Poor fetal lung growth may result from impairment in chest growth and fetal breathing as a result of skeletal dysplasia, dwarfism, oligohydramnios, and structural anomalies like congenital diaphragmatic hernia that restrict the capacity of the lung cavity.

**Potter syndrome**

Potter syndrome is a sequence of features associated with bilateral renal malformations including agenesis, hypoplasia or dysplasia resulting in severe renal failure. The mechanical sequence resulting from severe oligohydramnios include hypoplasia of the lungs, arthrogryposis and characteristic facial deformities including wide-set eyes, flat nose, receding chin and low-set ears deficient in cartilage. It is a common anomaly with male predominance occurring in about 1.3:1000 pregnancies including fetal deaths, still births and terminations of pregnancy (22).

**Congenital diaphragmatic hernia (CDH)**

Congenital Diaphragmatic Hernia is characterized by a discontinuity of the diaphragm, which allows the abdominal viscera to herniate into the chest during embryonic and fetal development. Visceral herniation into the thoracic cavity occurs between the 3rd and the 16th week of gestation during the critical period of lung development when the bronchi and pulmonary arteries are undergoing branching. Hence fetuses with CDH have lower lung volumes and lower weekly lung growth rates compared with healthy fetuses (23).
CDH is estimated to occur in approximately 1 in every 3500-5000 live births. When taking into account a pregnancy termination rate of 50-60% following the diagnosis of diaphragmatic hernia the real incidence is much higher. Risk factors for the development of CDH include male gender, maternal age past 40, caucasian ethnicity, smoking and alcohol use during pregnancy. Associated cardiac anomalies include: coarctation of the aorta, combined atrial and ventricular septal defects, hypoplastic left heart syndrome, Tetralogy of Fallot, double outlet right ventricle, atrioventricular canal defect and isolated atrial or ventricular septal defects (24).

The defect size is an important prognostic factor. The main reasons for mortality are pulmonary hypoplasia, and treatment-resistant pulmonary hypertension. Predictors of mortality include lung-to-head ratio, hepatic herniation and the presence of a major associated anomaly. There are three types of hernia: Bochdalek-posterolateral (70%), Morgagni-anterior (25-30%) and septum transversum-central (2-3%) (23).

Treatment includes assisted ventilation, vasopressors to increase blood pressure, treatment to decrease pulmonary hypertension with inhaled nitric oxide, sildenafil, prostacyclin and extracorporeal membrane oxygenation. Surgical repair of the defect in the diaphragm should be performed after physiological stabilization. Despite treatment about 10-15% do not reach surgery due to hemodynamic instability and survival remains about 70% (25).

Recently, intrauterine tracheal occlusion has been proposed to reverse pulmonary hypoplasia. The physiological basis is that obstruction of physiological fluid egression from the fetal lung to the amniotic cavity results in increased fetal airways pressure, promoting pulmonary proliferation and maturation of both lung architecture and pulmonary vasculature. The gestational age at balloon insertion ranges from 24 to 34 weeks and the balloon is removed at delivery by ex-utero intrapartum extraction (26).

**Pleural effusion**

Fluid accumulation in the pleural space is a rare event occurring during the neonatal period. Different types of congenital and acquired effusions have been described in the newborn. Chylothorax, hydrops fetalis, hemothorax, mediastinic extravasation of percutaneously inserted central venous catheter, parapneumonic effusion and congestive heart failure are the main causes. The volume of pleural liquid results from a balance of liquid in and out flow, occurring by Starling forces (28).

Strict control of the volume and composition of the pleural liquid is necessary to ensure efficient mechanical coupling between the lung and chest wall. Each pleural surface is composed of a mesothelial containing lymphatics, blood vessels, and nerves. The blood supply of the parietal pleura derives from the systemic circulation and it is drained by the systemic veins. The blood supply of the visceral pleura derives from the bronchial circulation and it is drained by the pulmonary veins. Liquid removal is carried out by an absorptive pressure gradient through the visceral pleura, by lymphatic drainage through the stomas of the parietal pleura, and by cellular mechanisms. Solute is actively transported via metabolically active mesothelial cells by vesicular transport of protein (29).

**Congenital eventration of the diaphragm**

Diaphragmatic eventration is a rare congenital defect. The impairment in the caudal movement of the diaphragm leads to poor lung expansion and decreased blood flow. The abdominal viscera are present in the thorax, but still confined below the diaphragm. Infants may suffer from respiratory distress, atelectasis, and recurrent pulmonary infections, however some are asymptomatic, hence the eventration may be an incidental finding in chest radiography. Treatment is surgical by plication of the diaphragm. Diaphragmatic paralysis, a more common entity, can be idiopathic or secondary to phrenic nerve trauma during delivery. Treatment is conservative, however when the respiratory symptoms persist plication of the diaphragm should be considered (27).

**Hydrothorax**

Congenital hydrothorax affects 1:10,000-15,000 still-born infants. In many cases the etiology is unclear and
the clinical course is unpredictable. Effusions especially if diagnosed in the second trimester and are small and unilateral may have spontaneous regression; however the effusion may become large and bilateral, resulting in hydrops fetalis by impaired venous return with congestive cardiac failure and pulmonary hypoplasia. The diagnosis of hydrothorax in the mid-trimester requires a comprehensive investigation including ultrasonography to study the fetal anatomy, fetal echocardiography to identify cardiac structural, karyotype, maternal serological assessment for virology screening especially parvo virus B19, maternal blood count and grouping investigation.

Intrauterine treatment modalities include fetal thoracentesis with thoracocamniotic shunting and pleurodesis with fetal intrapleural injection of OK-432. In the neonatal period, hydrothorax may require thoracentesis. The diagnosis of transudate is suggestive of heart failure while exudate is suggestive of chylothorax or hemothorax (29). Mortality in the neonatal period is related to pulmonary hypoplasia with respiratory dysfunction (30).

Congenital chylothorax is the most common cause of congenital pleural effusion during the neonatal period. It is defined as the accumulation of lymph in the pleural space. The estimated prevalence ranges from 1:8,600 to 1:10,000 live births. Chylothorax can be classified as traumatic or non-traumatic. Traumatic causes include thoracic surgery, thoracic duct damage following subclavian vein catheterisation, duct blockage due to central venous catheter-related venous thrombosis, thoracic duct damage following fracture or dislocation of the spine, and childbirth. During the pregnancy lymph vessel malformations or lymphatic dysplasia syndromes are an important cause of non-traumatic congenital chylothorax.

Congenital lymphatic dysplasia affecting the lung and the pleura leads to a blockage of both interstitial tissue and pleural space drainage. Congenital primary lymphatic dysplasia is associated with genes that have been demonstrated to play a role in the pathway regulating lymphangiogenesis which begins during embryonic week 6-7 in humans. In 2010, Connell et al. created a classification pathway founded on clinical phenotype, the age of onset of the lymphedema, the sites affected and the presence of associated features (31).

There are two neonatal forms: 1) Syndromic: including syndromes associated with lymphedema and or chromosomal abnormalities. In some of these conditions the lymphedema is not the primary problem but is an associated feature. Recovery from chylothorax and future prognosis are dependent on the underlying etiology (32) and 2) Widespread developmental abnormalities of the lymphatic system with systemic or visceral involvement associated with the onset of lymphatic dysfunction occurring prenatally can present with hydrops fetalis, pericardial and pleural effusions, chylous ascites, and pulmonary and intestinal lymphangiectasia (33).

Fetuses with congenital chylothorax can be treated by thoracocamniotic shunt placement that may result in resolution of fetal hydrops and prevention of pulmonary hypoplasia and intrauterine fetal death. When the diagnosis is made near or at term, delivery and postnatal drainage is usually preferred. Post natal treatment includes immediate ventilation, pleural fluid drainage, and total parenteral nutrition followed by medium chain triglyceride enriched formula. Somatostatin and its long acting synthetic analog Octreotide reduce accumulation of chyle (32).

**Genetic diffuse lung disease**

Genetic diffuse lung diseases are a heterogeneous group of rare disorders characterized by impaired gas exchange and diffuse infiltrates on imaging. Mutations in genes encoding surfactant synthesis and homeostasis represent an important subset of these diseases. It leads to the congenital form of pulmonary alveolar proteinosis (34).

**Alveolar capillary dysplasia**

Alveolar capillary dysplasia is a rare disorder of early lung development leading to defective angiogenesis and alveolar development. Histologically, it is characterized by inter-alveolar septal thickening, decreased terminal bronchial ramification and alveolar number, increased muscularization in small pulmonary arteries, misalignment of pulmonary veins
and decreased capillary number failing to make an appropriate contact with the alveolar basal membrane, leading to pulmonary hypertension. Associated malformations are described in more than half the patients. Pulmonary Interstitial glycogenosis consists of thickened interstitium with immature interstitial cells containing intracytoplasmic glycogen. Manifestations include respiratory failure and pulmonary hypertension, which improves with corticosteroid therapy (35).

The onset of respiration-transition from intra to extra-uterine atmosphere

The establishment of air breathing occurs concurrently with alterations in pressures and flows within the cardiovascular system. Before the onset of labor the fetal lung fluid in the airspaces starts to decrease, with further decrease during labor. The fetal lung fluid which is a filtrate of the interstitial fluid is secreted by the airway epithelium by the active transport of chloride. Cortisol, thyroid hormones, and catecholamines that increase during labor down-regulate the active chloride-mediated secretion of fetal lung fluid and activate the basal Na K ATPase pump of type II cells. Consequently sodium in fetal lung fluid enters the apical surfaces of type II cells and is pumped into the interstitium with water and other electrolytes following passively, thus removing fluid from the airways to the lung interstitium and then via the lymphatics into the vascular system.

The diminution in lung fluid results in decreased lung parenchymal tissue mass; hence, the gas volume of the airways and alveoli increases (36). The fetal high pulmonary vascular resistance results from suppression of nitric oxide and prostaglandin secretion by the endothelium due to the intra-uterine hypoxia. With birth and removal of the low resistance placenta, blood flow to the pulmonary circulation increases. Ventilation and oxygenation increase the nitric oxide and as a result a rapid fall in pulmonary vascular resistance. Shortly after birth, functional closure of the ductus arteriosus begins.

Following delivery, the pre-ductal saturation in healthy term infants gradually increases to about 90% at 5 minutes of age. The combination of cord clamping that prevents the influx of prostaglandins from the placenta that suppresses breathing, the tactile and cold stimuli and the changes in PCO2 and PO2 levels in the blood result in the onset of breathing. Cortisol is the major regulatory hormone for fetal maturation and neonatal adaption at birth. Cortisol levels progressively increase before labor and peak several hours after term delivery. Cortisol, in association with thyroid hormones, activates the sodium pump which clears fetal lung fluid at birth, and induces surfactant maturity (37).

By term, type II cells in the fetal lung contain much more surfactant than does the adult lung, and are prepared for release before and at delivery. The presumed mediators of this secretion are catecholamines that stimulate beta-receptors. Subsequently ventilation causes alveolar stretch and consequently deformations of type II cells resulting in further secretion signal. The secretory events concurrent with birth do not appreciably deplete surfactant stores in type II cells because surfactant synthesis and packaging into lamellar bodies continues and the surfactant that has been secreted also is recycled back into type II cells for further secretion as needed (38).

Acquired pulmonary conditions

Transient tachypnea of newborn (TTN) or retained fetal lung liquid syndrome results from delayed clearance of fetal lung fluid. The fluid begins to decrease in the alveolar spaces about 2 to 3 days before the onset of labor, when the pulmonary epithelium becomes an absorbing membrane. The chloride’s pump activity decreases fetal lung fluid and the sodium pump increases fluid movement from the airspaces to the interstitium. The interstitial fluid is subsequently absorbed by the pulmonary lymphatics and vasculature. About 40% of the fetal lung fluid is cleared before labor and the rest of the fluid clears in the first hour of life. Healthy newborns inflate their lungs at birth by generating negative pressure breaths, which pull the lung fluid from the airways into the distal airspaces.

Transient tachypnea of the newborn is most frequent in late preterm infants. This syndrome is thought to result from ineffective clearance of fetal
lung fluid due to inadequate sodium transport. Preterm infants with TTN may have low amounts of surfactant. Hence a continuum of infant morbidity between TTN and RDS is found and infants with TTN may develop surfactant deficiency and RDS (38). TTN is more common among infants born by cesarean section. Infants with TTN present with tachypnea and grunting. Diagnosis is by chest radiography that shows hyperinflation, increased interstitial markings, and fluid in the interlobar fissures. Treatment include oxygen supplementation, invasive and non-invasive ventilation (39).

**Respiratory distress syndrome**

Respiratory distress syndrome (RDS) is the clinical morbidity resulting from lung immaturity associated with surfactant deficiency in neonates. Surfactant reduces surface tension in the alveoli, stabilizes lung volume at low trans-pulmonary pressures, equalizes the pressures exerted on the different-sized alveoli and in turn increases the functional residual capacity of the lungs. Surfactant deficiency allows the larger alveoli to over-expand in order to compensate for the collapse of the small alveoli and increases the risk for pneumothorax (40). Diagnosis is by chest radiograph demonstrating reticulogranular pattern (ground-glass) representing open small alveoli surrounded by interstitial fluid and fluid-filled or collapsed alveoli and air bronchogram representing air-filled bronchi superimposed on the lung tissue.

**Surfactant therapy**

Surfactant therapy has demonstrated improvement in the clinical outcome of very preterm newborns. Surfactant therapy has been proven to reduce the need for ventilatory support and decrease the risk of pneumothorax, death and the combined outcome of death and morbidity from bronchopulmonary dysplasia (BPD). Surfactant is administered as an intratracheal bolus via endotracheal tube in two time frames: 1) Prophylactic strategy for surfactant administration immediately after birth and 2) Rescue or selective strategy for administration once the infant had evidence of RDS. A Cochrane analysis favored first stabilization on CPAP and then surfactant therapy (41).

There are three groups of surfactant: natural surfactants containing proteins, synthetic surfactants without proteins and synthetic surfactants with peptides or proteins. Natural surfactant preparations are isolated from animal minced lungs or lavages by extraction with organic solvents. They contain phospholipids (>80%) and the hydrophobic surfactant proteins (SP), SP-B and SP-C, but not the hydrophilic SP-A and SP-D, which are removed during the extraction process.

Natural preparations resulted in an improved outcome of preterm infants with RDS, fewer pneumothoraces and a reduction in mortality. To date, natural surfactants are the most widely used in neonatal units. Surfactant preparations demonstrate a variety of anti-inflammatory and immunomodulatory properties.

Chorioamnionitis may initiate an inflammatory cascade resulting in increased vulnerability of the premature lung for postnatal perturbations like oxygen toxicity, mechanical ventilation, patent ductus arteriosus and infections. The inflammatory process may lead to a secondary inactivation of surfactant and the development of BPD. Both natural and synthetic surfactant preparations decreased the release of pro-inflammatory cytokines. Surfactant preparations have been shown to affect the immune response of granulocytes, monocytes, alveolar macrophages, lymphocytes, natural killer cells and lymphokine-activated killer cells and to improve the remodeling processes following lung injury (42). To avoid lung injury infants stabilized on CPAP or non-invasive ventilation can be supplemented with surfactant via small diameter tube e.g., arterial catheter or suction or gastric catheter that is introduced through the vocal cords by direct visualization with a laryngoscope (43).

**Ventilation strategies**

Advances in neonatal care have led to increasing survival of very immature neonates, but the improvements in survival have increased the incidence of chronic lung disease in survivors. Mechanical ventilation is lifesaving in critically ill neonates; however it may contribute to lung injury.
New ventilation strategies may improve clinical outcomes. Ventilatory strategies to prevent the chronic lung disease bronchopulmonary dysplasia (BPD) are based on reducing the magnitude and duration of mechanical ventilatory support to the minimum possible necessary for achieving adequate gas exchange. This is achieved by redefining the blood gases goals or refining the methods of mechanical ventilation or using alternative techniques. By targeting a higher PCO2, lower oxygen goals and shorter inspiration time, less ventilatory support is needed. A fast ventilation rate with a lower tidal volume is preferred to a slower ventilator rate with a larger tidal volume to reduce volutrauma. Numerous strategies that improve ventilatory outcome are:

Synchronized intermittent mechanical ventilation: Mechanical breaths are synchronized with the onset of spontaneous inspiration. The positive pressure breath is in synchrony with the end of spontaneous inspiration or when inflation is completed. Respiratory signals used for synchronization include abdominal wall motion, esophageal pressure, thoracic impedance, airway pressure and gas flow.

Patient triggered ventilation is a mode of ventilation where every adequate spontaneous inspiratory effort is assisted with a mechanical breath. It provides back-up ventilation in the absence of spontaneous breathing effort or when the inspiratory effort is insufficient to trigger a mechanical breath.

Pressure support ventilation is a mode where flow cycling is used to assist every adequate spontaneous inspiratory effort and terminate the mechanical breath as the spontaneous inspiration ends or inflation is completed.

Volume targeted ventilation is a modality aimed at reducing high inflation pressure by adjusting the peak pressure or duration of the mechanical breath to maintain tidal volume (44).

High-frequency ventilation (HFV) is a form of mechanical ventilation that uses small tidal volumes and extremely rapid ventilator rates. HF oscillation (HFO) and HF jet ventilation (HFJV) or HF flow interruption (HFFI) are the techniques employed (45).

Continuous tracheal gas insufflation: nasal continuous positive airway pressure (nCPAP) and heated, humidified high-flow nasal cannula (HHHFN) are used in the NICU as a mode of non-invasive respiratory support (46).

Non-invasive Intermittent pulmonary Ventilation (NIPPV): Synchronization techniques enable delivery of nasal synchronized ventilation. In comparison to nasal continuous positive airway pressure NIPPV reduces chest wall distortion in preterm infants, reduces breathing effort and improves ventilation.

Prevention of RDS

In order to reduce the risk of respiratory distress syndrome (RDS) in newborns, antenatal glucocorticoids have been administered to mothers at risk of premature delivery. The effect of glucocorticoids on the fetal lung is induction of surfactant synthesis and modulating lung development by thinning of the alveolar wall and increasing potential lung gas volume. Glucocorticoids also increase the effectiveness of postnatal surfactant therapy. However, pre-natal exposure to glucocorticoids has been linked to cardiovascular, metabolic, and neuroendocrine disorders later in adulthood and multiple courses of antenatal glucocorticoids were associated with increased risk of low birth weight, a smaller head circumference, neonatal sepsis and prolonged adrenal suppression (7). The current recommendations are that women at risk of preterm delivery prior to 34 weeks gestational age should be treated with antenatal steroids. Betamethasone and dexamethasone are both considered effective in preventing neonatal RDS (47).

Air leak syndrome

Air leak syndrome results from the collection of air that leaked from the tracheobronchial tree to various body spaces including pulmonary interstitial emphysema (PIE), pneumothorax, pneumomediastinum, pneumopericardium, pneumoperitoneum, subcutaneous emphysema, and systemic air embolism. The most common cause of air leak is assisted mechanical ventilation with increased incidence in premature infants, neonates with hypoplastic lung, meconium aspiration and pneumonia.
**Pulmonary interstitial emphysema (PIE)**

PIE occurs when air leak into the pulmonary interstitium or the lymphatic and venous circulation. PIE may also be due to rupture at the junction of the bronchiole and alveolar duct. Predisposing factors include prematurity, RDS, meconium aspiration and pneumonia. The diagnosis of PIE is made by chest radiography that shows oval or spherical cystic air-containing spaces either in localized or diffuse distribution. PIE is usually managed conservatively, with gentle ventilation. Unilateral PIE may be treated by selective intubation of the uninvolved lung.

**Pneumopericardium**

Pneumopericardium is the collection of air in the pericardial space. It may cause abrupt onset of hemodynamic deterioration due to cardiac tamponade and be life threatening. It occurs mostly in mechanically ventilated preterm infants suffering from RDS with other air leak phenomena such as PIE and pneumothorax. The diagnosis is by chest radiograph that shows a gas shadow surrounding the heart. Management is mostly conservative and pericardial drainage is only applied in selected symptomatic infants.

**Pneumothorax**

Pneumothorax, the presence of gas in the pleural cavity between the visceral and parietal pleura is the most common air leak syndrome. Small pneumothorax may be asymptomatic but some may enlarge with subsequent deterioration of arterial blood gases and increased oxygen or ventilator requirement. Tension pneumothorax occurs when the air collection interferes with ventilation and circulation resulting in hypotension, bradycardia, barrel-shaped chest, and acute abdominal distension. Diagnosis is made by chest radiography but in the case of emergency the use of a chest transillumination may help to establish a preliminary diagnosis. In asymptomatic infants with small pneumothorax conservative treatment can be offered. In full-term neonates with small uncomplicated pneumothorax supplementation with 100% oxygen may improve the resolution of pneumothorax by nitrogen washout. Large pneumothorax and pneumothorax accompanied by clinical deterioration should be drained by chest tube insertion.

**Pneumomediastinum**

Pneumomediastinum is air leak into the mediastinal space. The diagnosis is made on a chest radiograph that shows hyperlucent areas around the heart border and between the sternum and the heart border. Management is conservative.

**Pneumoperitoneum**

Pneumoperitoneum occurs when extrapulmonary air gets into the peritoneal cavity. It may results from ruptured viscus which necessitate immediate surgical intervention. Treatment of pneumoperitoneum of intrathoracic origin is usually conservative.

**Subcutaneous emphysema**

Subcutaneous emphysema is air leak into the subcutaneous tissue. Diagnosis is done by palpation of crepitations in the face, neck, axillary, or supraclavicular regions. Management is mainly conservative.

**Systemic air embolism**

Systemic air embolism is when the air rupturing from the alveoli enters directly into the pulmonary capillaries and to the heart resulting in circulatory collapse. There is no specific treatment and when a large amount of air gets into the circulation the condition is fatal (48).

**Pulmonary hemorrhage**

Pulmonary hemorrhage in the newborn may vary from a focal, self-limited disorder to massive, lethal hemorrhage. Pulmonary hemorrhage usually occurs
between the second and fourth days of life in infants being treated with mechanical ventilation. Risk factors include prematurity, intrauterine growth restriction, respiratory problems, patent ductus arteriosus, bleeding problems, ventilator usage, surfactant treatment and overwhelming sepsis and endotoxin production. The incidence of pulmonary hemorrhage varies between units ranging between 2.2-27.6% (49). However, it was found in about half of premature infants who died in the neonatal period and suffered from RDS (50). Hemorrhage results from damage to the vascular bed of the lung. Increased pulmonary blood flow can be caused by surfactant therapy that improves lung function and patent ductus arteriosus with left-to-right shunt, but both result in high pressure injuries to the vascular bed.

Pulmonary hemorrhage is associated with increased incidence of intraventricular hemorrhage, probably due to alterations in the cerebral blood flow, coagulation disturbances and hypoxia. Diagnosis is made clinically by suctioning of blood tinged fluid from the upper airway. There is no effective emergent management for it except for supportive measures: positive-pressure ventilation, restoring blood volume, correcting hypotension, hypoxemia, acidosis and coagulation disorders.

**Pulmonary hypertension**

Persistent pulmonary hypertension of the newborn (PPHN) is a condition of persistently elevated pulmonary vascular resistance, with right-to-left shunting of blood across the foramen ovale, ductus arteriosus, or both, causing significant hypoxemia. PPHN may be primary or associated with pulmonary morbidity. In the fetus, the placenta serves as the organ for gas exchange. Concurrently, the pulmonary vessels are constricted and the pulmonary and systemic arterial pressures nearly equal, hence 90% to 95% of the cardiac output by-pass the fetal lungs.

At birth, the pulmonary artery pressure decreases to half the systemic artery pressure, and pulmonary blood flow increases almost tenfold, due to increased arterial pH and oxygen tension. The physical pulling open of capillaries accompanies lung inflation. The decline in pulmonary vascular resistance is greatest in the first 24 hours after birth and continues to fall over the first two postnatal weeks. Infants suffering with maladaptation fail to decrease the pulmonary vascular resistance despite normal pulmonary arterial number and muscularization.

Chronic in-utero hypoxia may cause an increase in medial muscle thickness and PPHN. Decreased number of pulmonary arteries, as seen in pulmonary hypoplasia, congenital diaphragmatic hernia and the oligohydramnios sequence is accompanied by a thickened alveolar septum and alveolar capillary dysplasia. Either intra-uterine perturbations like maternal diabetes, illicit drug use and the use of nonsteroidal anti-inflammatory drugs or perinatal morbidities like perinatal asphyxia and meconium stained amniotic fluid predispose the infant to PPHN. Additionally infants born with RDS, TTN, pulmonary hypoplasia, diaphragmatic hernia and sepsis or pneumonia have increased rates of PPHN. Radiographic findings may reflect the underlying illness. Diagnosis is done by echocardiography showing right-to-left shunting across the foramen ovale and or ductus arteriosus, deviation of the atrial septum from right-to-left, right atrial enlargement, and tricuspid regurgitation.

Treatment is by correction of the underlying condition, maintaining systemic blood pressure and selectively lowering pulmonary vascular resistance. Systemic blood pressure is maintained by adequate fluids supplementation and inotropic treatment such as dopamine. Pulmonary vascular resistance is lowered by of oxygen supplementation, inhaled nitric oxide (iNO) and prostacycline. iNO increases cyclic guanosine monophosphate (cGMP) production and activates a cascade causing calcium efflux with resultant vascular smooth muscle relaxation.

For infants with resistant pulmonary hypertension extra-corporal membrane oxygenation (ECMO) provides cardiorespiratory support until the vasculature recovers. This is especially done in infants suffering from congenital diaphragmatic hernia who often fail to response to iNO. Survival in PPHN varies with the underlying disorder. Increased rate of neurodevelopmental handicaps is probably the result of underlying condition such as birth asphyxia and systemic hypotension (51).
Meconium aspiration

Inhalation of meconium causes respiratory distress due to its biophysical properties, including high tenacity and the potent inhibition of surfactant function. It has a toxic effect to the pulmonary epithelium causing a haemorrhagic alveolitis (7). Meconium stained amniotic fluid occurs in about 13% of live births and of these infants, 4% to 5% develop meconium aspiration syndrome. Meconium contains substances that are chemotactic to neutrophils and activate complement.

Once inhaled, migration of meconium down the tracheobronchial tree initially causes obstruction of airways of progressively smaller diameter with “ball-valve” obstruction, with high resistance to airflow in expiration, resulting in gas trapping. The consequence of airway obstruction with meconium atelectasis may cause further deterioration due to hemorrhagic alveolitis and surfactant deficiency. Meconium aspiration occurs in utero or during labor. The volume of fetal lung fluid is regulated by the resistance to lung liquid efflux. The transpulmonary pressure is usually 1-2mm Hg above the amniotic sac pressure due to the elastic recoil of the chest wall. Lung fluid efflux is prevented by high resistance of the upper airways which prevents the lung fluid loss and maintains fetal lung expansion. During fetal breathing movements the larynx dilates, resistance to the fluid efflux decreases allowing fluid efflux (52).

Passing meconium in utero may be a sign of fetal stress that led to relaxation of the anal sphincter. The hypoxia and acidosis associated with fetal stress can lead to gasping in utero, resulting in transpulmonary pressure below the amniotic sac and asporation of the meconium stained amniotic fluid. Pathological findings from cases of severe meconium aspiration show alterations in the pulmonary vasculature, including remodeling and thickening of the muscular walls, suggesting chronic in utero stress. Infants born with severe meconium aspiration syndrome may suffer from resistant pulmonary hypertension. Due to airway obstruction and subsequent development of a one way valve phenomenon there is an increased incidence of air leak syndrome.

Diagnosis is made by the evidence of meconium in tracheal aspirate and chest radiography which demonstrates areas of patchy atelectasis due to airway obstruction, and areas of over-inflation due to air trapping. During delivery, in the presence of meconium-stained fluid, suctioning of the mouth and trachea should be done if the infant is not vigorous to prevent upper airway obstruction by meconium; otherwise no intervention should be undertaken. Treatment of meconium aspiration syndrome includes mechanical ventilation, antibiotics, iNO, prostacyclines and ECMO in the case of failure of the other treatment modalities (39).

Pneumonia

Pneumonia may develop in the antenatal, perinatal, or postnatal period, and the cause varies according to when the infection develops. Pneumonia may be associated with bacteremia, meningitis, abscesses and other infection in other body sites. Intrauterine infection by Rubella, herpes simplex virus, cytomegalovirus, adenovirus, Toxoplasma gondii, varicella zoster and Human immunodeficiency virus (HIV) is associated with congenital pneumonia. Perinatally acquired infection is mostly bacterial including group B Streptococcus (GBS), Escherichia coli, Klebsiella, Listeria monocytogenes and Chlamydia trachomatis; postnatal infection is mostly associated with various pathogens including bacterial, viral and fungal (39). Mycoplasma hominis and Ureaplasma species are associated with premature labor, and chorioamnionitis, causing the exposed neonate to develop pneumonia, bacteremia, meningitis, abscesses, and chronic lung disease (53).

Underlying pathology like immotile cilia (54), cystic fibrosis (55) may be rarely associated with pneumonia in the neonatal period. Neonatal pneumonias are often difficult to diagnose since clinical manifestations and laboratory findings are often nonspecific. Additionally radiological evidence of pneumonia may result from non-infectious causes such as RDS, TTN and meconium aspiration. Detection of microorganism by cultures from blood, cerebrospinal fluid and urine has a limited efficacy. Culture and Gram stain of an endotracheal aspirate obtained by aseptic technique as soon as possible after intubation may be diagnostic if taken in the first few hours of life. Serologic and genetic analysis tests are
also used to detect specific organisms. Treatment includes antibiotics and supportive care according to the infant’s condition (56).

Respiratory syncytial virus (RSV) bronchiolitis

Premature infants are at risk for RSV bronchiolitis. RSV is an ssRNA virus and a member of the Paramyxoviridae genera. Treatments for infants hospitalized with RSV are primarily supportive and aimed at maintaining adequate oxygenation and ventilatory support. Palivizumab, a humanized monoclonal antibody with neutralizing activity against the F protein of RSV given on a monthly basis throughout the RSV season has significant benefit in protecting against RSV hospitalization in premature infants with underlying prematurity, chronic lung disease of infancy and congenital heart disease (57).

Apnea of prematurity

Apnea is the cessation of breathing for more than 20 seconds and may be accompanied by bradycardia and desaturation. It may be central, obstructive or mixed. Central apnea is the cessation of inspiratory efforts; obstructive apnea is the absence of airflow associated with respiratory movements against a closed larynx or pharynx. In preterm infants, mixed apnea is the most frequent. Periodic breathing is an oscillatory pattern of breathing that is characterized by ventilatory cycles of 10-15 seconds with pauses of 5-10 seconds and can be associated with desaturations. Premature infants have central and peripheral mechanisms which control breathing, which are immature so that breathing is both un-sustained and punctuated by frequent respiratory pauses. This respiratory pattern is suitable for fetal life but can be harmful to the premature infant for which breathing is a prerequisite for life.

Apnea of prematurity occurs in infants born before 34 weeks gestational age and usually resolves by term. Apneic episodes can be hazardous if associated with intermittent hypoxemia. Chronic intermittent hypoxia increases free radical production and is associated with adverse neurodevelopmental outcome, retinopathy of prematurity and feeding difficulties. Respiratory rhythm is generated in the brain stem by endogenously bursting interneurons that project to premotor inspiratory neurons carrying inspiratory drive throughout the ventral respiratory column, and then to the diaphragm, external intercostal muscles and upper airway muscles. Active expiration is controlled by the retrotrapezoid nucleus/parafacial respiratory group (RTN/pFRG) (58).

Premature infants with the lower baseline saturations have a higher number of hypoxic episodes. They often have inadequate end expiratory lung volumes due to excessive chest wall compliance leading to distal airway closure. To compensate for the immature control of breathing preterm infants have a higher respiratory rate then full term infants. Continuous measurements of oxygen saturation are needed for detection of hypoxemia events and for maintaining a safe oxygen saturation target range. Apnea of prematurity is a diagnosis of exclusion. Other reasons for apnea include: sepsis due to up-regulation of inflammatory cytokines that inhibit respiration; central nervous system pathology such as intraventricular hemorrhage and ischemic stroke; metabolic imbalance such as hypoglycemia and electrolyte imbalance.

Treatment is indicated to prevent hypoxia. Supplemented oxygen, CPAP, invasive and non-invasive ventilation is used according to clinical indications. Medical treatment is by methylxanthynes mainly by caffeine. Its primary mechanism of action is thought to be blockade of inhibitory adenosine A1 receptors with resultant excitation of respiratory neural output. Caffeine treatment has a beneficial effect in decreasing the rate of BPD and improving neurodevelopmental outcome (59). Doxapram a central stimulant that activates medullary respiratory neurons may be used in the case of caffeine failure (60).

Bronchopulmonary dysplasia (BPD)

Bronchopulmonary dysplasia (BPD) was first described in 1967 in premature infants with respiratory distress syndrome (RDS) who developed chronic lung disease after being treated with intermittent positive pressure ventilation and oxygen
supplementation. Following the infants it was found that clinically significant respiratory symptoms early in life may have lifelong consequences. Today, newborns consistently survive at gestational ages of 23 to 26 weeks and new mechanisms of lung injury have emerged, and the clinical and pathological characteristics of pulmonary involvement have changed profoundly. Hence, bronchopulmonary is defined as an old and new disease evaluated at different time frames (61).

Current definition of bronchopulmonary dysplasia is according to gestational age. Old BPD: Infants born above 32 weeks gestation that were oxygen dependent for at least 28 postnatal days; and new BPD: infants born below 32 weeks gestation that were oxygen dependent at 36 weeks corrected age. Infants with old BPD are re-evaluated at the 56 day of life and given similar score as infants with new BPD at 36 weeks: Mild — FIO2-0.21, Moderate — FIO2-0.22-0.29, Severe — FIO2 ≥ 0.30 or continuous positive airway pressure or mechanical ventilation required (62).

Old BPD: The infants with old BPD were mostly infants who suffered from severe respiratory failure, received aggressive ventilation, and had a prolonged exposure to high inspired oxygen concentrations. Chest radiography demonstrated severe morphologic changes including emphysema, atelectasis and fibrosis. Histopathology from such infants demonstrated marked epithelial squamous metaplasia and smooth muscle hypertrophy in the airways and in the pulmonary vasculature. The survivors suffered from severe respiratory failure with airway obstruction, pulmonary hypertension, and cor pulmonale (61).

New BPD: The new BPD is mostly a developmental disorder. The introduction of antenatal corticosteroids, new methods of gentle and non-invasive ventilation and surfactant replacement therapy allowed the survival of infants born during the canalicular and saccular stages of lung development before alveolarization begins. Even with gentle ventilation oxygen toxicity, volutrauma and barotrauma are hazardous to the immature lung. Additional factors including inflammatory processes due to ante or post-natal infections, persistent ductus arteriosus (PDA), difficulty to provide enough nutrients and genetic susceptibility may aggravate the lung damage.

The main histopathological finding is a decrease in alveolar septation and impaired vascular development associated with lung edema, mild inflammatory response, and decrease in surface area for gas exchange. The pulmonary vasculature remodeling includes medial hypertrophy and distal muscularization of small peripheral arteries that can lead to pulmonary hypertension. The disrupted microvascular development decrease VEGF expression by the endothelium of the capillaries and lead to further decrease in alveolization (63).

Treatment of BPD is mainly a preventive strategy. Delivery room care should avoid aggressive ventilation during resuscitation. Early surfactant treatment, methylxanthines to promote extubation and the use CPAP or non-invasive ventilation modalities are the main modalities to prevent lung injury. The golden hour concept is to allow optimal post-resuscitation care in order to stabilize ventilation, thermoregulation, blood glucose level, fluids homeostasis and sepsis management (64).

The aim of active nutritional management is to support a rate of growth that approximates the intrauterine rate of growth and meets the estimated fluid, protein, and energy needed. Since excessive fluid intake in first days of life increase the risk of BPD fluid restriction is indicated to prevent lung edema. Parenteral nutrition is used until full enteral nutrition is achieved. Enriched formulas and supplementation of breast milk with human milk fortifier, multi-vitamins and iron supplementations are given to promote growth and prevent nutritional deficiencies and osteopenia of prematurity (65).

Diuretics are commonly used in BPD to increase reabsorption of fluid from the lung. Capillary leak from inflammation, infection, ventilator-induced lung injury, or left to right shunting through a patent ductus arteriosus (PDA) may increase pulmonary edema and lead to decreased lung compliance. The two most common diuretics used in BPD are loop diuretics and thiazides. Systemic and inhaled steroids are used to reduce the inflammatory response, decrease airway edema, stabilize capillary leakage and decrease lung fibrosis. Previous reports of poor neurological outcome associated with ante and postnatal steroids
led to the reservation of the treatment with steroids to the more complicated cases (66).

Infants with BPD have pulmonary sequelae during childhood and adolescence. Respiratory syncytial virus (RSV) is one of the most clinically important viruses infecting infants with BPD resulting in severe pulmonary deterioration. A humanized monoclonal antibody directed against the fusion (F) protein given routinely on a monthly basis to premature infants prevents most of these cases (67).

Children with BPD exhibit lower average IQ than infants born in corresponding gestational age. Additionally they face academic difficulties, delayed speech and language development, visual-motor integration impairments, and behavior problems (68).

Conclusion

Normal lung branching in coordination with pulmonary vascular development provides a surface area for adequate gas exchange. Maturation of the lung and associated vasculature allows the transition to air breathing at birth. Congenital malformations may result from primary developmental defect of the lung or secondary to anomalies in other organs. Premature infants suffering from respiratory distress due to immaturity of the lung may suffer from chronic lung disease associated with mechanical ventilation, inflammatory response and genetic predisposition. Integrated approaches to therapy that reflect the basic pathology and treatment options have the promise for better prognosis.

References


Neonatal pulmonology


Neonatal nephrology

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Abstract

This discussion is a review of neonatal nephrology geared toward the practitioner in the newborn nursery. First, basic embryology and physiology of the newborn kidney are explained. Then there is a discussion of the more common problems encountered in the neonatal period including hydronephrosis, abdominal mass, and failure to thrive of renal origin. Infection and electrolyte imbalance are also quite common in the newborn period and this summary considers their etiology and management. Finally, information is given regarding several congenital anatomic problems with which the practitioner should be familiar.

Keywords: Pediatrics, neonatology, newborn, nephrology

Introduction

Kidneys are vital organs with a complex morphogenesis. Functional development of kidneys continues until 2 years of life after birth. Developmental abnormalities of the kidneys account for almost 50% of cases of end stage renal disease (ESRD) in the United States. The following is a brief review on development, physiologic changes and some common neonatal renal pathology.

Renal development

Mammalian kidneys follow a complex evolutionary process. In humans there are three stages in renal development. Pronephros and mesonephros are rudimentary kidneys that start rostrally and progress to metanephros caudally. The rudimentary kidneys disappear towards the end of the first trimester. Induction of the metanephros starts at 5 weeks of gestation and this involves ureteric bud invagination of the metanephric mesenchyme. Several important genes including PAX2, WT-1 and signaling pathway including Glial derived neurotrophic factors (GDNF)
are involved in the initial cross talk between the ureteric bud and metanephric mesenchyme. Kidneys formed initially are in the pelvic region and ascend up to their abdominal location by about 10 weeks of gestation. Around the same time urine generation is initiated as well.

Nephrogenesis continues until 34 to 36 weeks of gestation. Babies born prematurely might continue to form new nephrons but different factors including IUGR, NICU mortality and morbidity might affect the ultimate total. The number of functioning nephrons (nephron endowment) varies significantly and follows a bell shaped curve in the normal population. The range for nephron endowment varies between 300,000 to 1 million in each kidney. There are many studies linking a reduced nephron endowment early in life with hypertension (1) and vulnerability to secondary renal insults in adulthood (2).

**Physiology of the neonatal kidney**

Fetal urine formation increases from 2 ml/hour at 20 weeks of gestation progressively up to 26 ml/hr by the end of 34 weeks contributing to the amniotic fluid (3). Babies with decreased amniotic fluid secondary to renal agenesis, exposure to angiotensin blockers or with bilateral renal obstruction will have the Potter (oligohydramnios) sequence. If the oligohydramnios is severe babies can be stillborn with characteristic facial features including flattened nose, prominent bilateral epicanthal folds and low set ears with wide pinnae. Most of these babies suffer from severe lung hypoplasia which contributes to mortality. There are skeletal malformations including prominent bilateral club feet and bowing of legs.

After birth multiple changes occur in renal physiology. Rapid increase in glomerular filtration rate (GFR) occurs with increase in mean arterial pressure and decreased renal vascular resistance. But when compared to adults GFR within the first week of life is only 40 ml/min/1.73m2 and reaches adult equivalent (120 ml/min/1.73m2) at 2 years of age. Serum creatinine which is a measure of GFR is elevated in the first days of life as it mainly reflects maternal creatinine levels and reaches newborn value of 0.4 ± 0.02 mg/dl at 2 weeks of life. The Schwartz formula is used in calculation of GFR from serum creatinine in children <18 years of age and for newborns the following applies: GFR (ml/min/1.73 m2) = K x Height in cm/Plasma creatinine. K = 0.45 (Newborn with normal weight)

Renal blood flow gradually increases from fetal life (2 to 4% of cardiac output) to ultimate adult value of 20 to 25% of cardiac output. Irrespective of decreased renal blood flow GFR is maintained with the help of marked vasoconstriction of the efferent arterioles. Angiotensin II, endothelin I and the sympathetic nervous system play a main role in this physiologic effect. A greater sensitivity to angiotensin converting enzyme inhibitors with a drop in GFR is elicited in the newborn secondary to the rapid decrease in angiotensin.

Total body water in the newborns account for 75 to 80% of their body weight with almost 40% making up the extracellular space. Within a few days after birth 10 to 15% of body weight is lost (physiological weight loss) and contributes to the increased urine output irrespective of low GFR. As the ability for newborn kidneys to excrete water and sodium is limited the fluid requirement on day 1 of life will be 60 ml/kg/day. Progressively fluid requirements increase to about 150 ml/kg/day in a term neonate at about a week of life.

After the physiologic diuresis it is essential to provide adequate fluid to the newborn as urine concentrating capacity is very limited. Causative mechanisms include short loops of Henle, decreased urinary medullary urea concentration and reduced number of aquaporin channels in the distal tubules. The maximum urine concentration ability is 600 mosm/kg in the first week of life and reaches adult concentration ability of 1100 mosm/kg by about a year of age.

Newborns are also in a constant state of salt wasting as documented by the elevated fractional excretion of sodium (FeNa). FeNa <1% indicates a salt avid kidney and usually takes a few weeks of life before this level is achieved. Salt wasting is more prominent in premature babies with FeNa as high as 5%. Reasons for salt wasting include decreased sodium reabsorption in the proximal and distal convoluted tubules secondary to an alteration in sodium potassium ATPase (4). Aldosterone resistance is another mechanism behind increased sodium loss and decreased potassium excretion seen
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in the newborn (5). If on parenteral nutrition it is important to add sodium at 2 to 3 meq/kg/day and potassium 1 to 2 meq/kg/day to the regimen after 48 hours of life for maintenance.

Neonatal hydronephrosis

Fetal hydronephrosis is the most common detected congenital anomaly (60%) and seen in 0.5 to 1.5% of all prenatal ultrasounds. Most of the hydronephrosis is physiologic, transient and improves with time (6). The Society of fetal Urology (SFU) has developed a grading system (SFU grade 0 to 4) with higher grades (3 and 4) more likely to be pathologic. In case of mild prenatal hydronephrosis it would be appropriate to repeat renal ultrasound at about a week to 10 days of life. Postnatal ultrasounds done in the first week of life can be falsely negative secondary to low GFR and renal plasma flow. Persistent or worsening hydronephrosis will warrant a voiding cystourethrogram (VCUG) to rule out reflux.

Vesico ureteral reflux (VUR) is classified into Grades 1 to 5. Higher grade reflux (3 to 5) has an increased risk for recurrent urinary tract infection and renal scarring. No clear consensus exists on antibiotic prophylaxis for reflux but current practice is to initiate daily low dose antibiotic treatment for higher grade reflux (3 to 5). Surgical intervention including deflux or ureteral reimplantation may be needed for higher grade reflux if there is recurrent infection.

With persistence of hydronephrosis in the absence of reflux, the other possible etiology is obstructive uropathy, one of the most common causes of ESRD in children. Obstruction can occur anywhere in the urinary tract but uretero pelvic junction obstruction (UPJO) is the most common abnormality. The most useful diagnostic method to evaluate for obstruction is a nuclear medicine scan. Most UPJ obstruction improves with time but surgical intervention is indicated in the setting of worsening obstruction and renal function.

Posterior urethral valves are a life threatening urinary tract obstruction in male infants. Most of the cases are detected prenatally. Ultrasound shows severe bilateral hydronephrosis with cortical thinning, significant bladder dilatation and a ‘key hole’ sign consistent with posterior urethral dilatation.

Intrauterine procedures like vesico amniotic shunt have been performed at 18 to 20 weeks of gestation to prevent oligohydramnios and subsequent lung hypoplasia. Clinical results have been variable and the degree of renal dysplasia determines the prognosis. Postnatally management includes immediate placement of a Foley catheter to relieve obstruction and ideally surgical fulguration of the valves done in the first 24 to 48 hours of life. Most babies with significant obstruction irrespective of intra uterine intervention will progress to end stage renal disease requiring renal replacement therapy.

Another significant cause of urinary tract obstruction especially in the female infant is ureterocele. Ureterocele is cystic balloon-like dilatation of the ureter and can be intravesicular or extravescicular leading to obstruction of urine flow. The condition can be detected with an ultrasound and VCUG showing a filling defect in the bladder. Almost 95% of ureteroceles are associated with a duplicated collecting system and VUR. Very rarely ureterocele can present as a firm non tender prolapsing mass from the vagina (7). Surgical decompression of the ureterocele if done promptly will prevent a decline in renal function.

Various renal malformations are associated with lower spinal cord anomalies. These could be structural such as presence of a horseshoe kidney with VACTERL association. More commonly functional obstruction of the bladder outlet with obstructive uropathy can be present. Any infant with a lower spinal cord mass like meningocele, myelomeningocele should have a screening ultrasound. Later in life a combination of gait anomalies and constipation will also be a clue to consider spinal cord anomalies and obstructive uropathy.

Abdominal mass in the newborn

Neonatal abdominal masses encompass a variety of pathology in various organ systems. Most of the lesions are benign but the physician should be vigilant for malignant lesions such as Wilms’ tumor or neuroblastoma. Almost 55 to 60% of all abdominal masses are secondary to renal involvement (8,9). Most of these lesions are detected prenatally by
ultrasound. Postnatally a thorough history, physical examination urinalysis and appropriate imaging techniques will be of help in the diagnosis of abdominal masses.

Multicystic kidney disease (MCKD) is one of the most common causes of unilateral renal mass. In cases not detected prenatally the usual presenting feature is a flank mass noted on routine physical examination in an asymptomatic newborn. Ultrasound will reveal a dysplastic kidney with multiple hypoechoic non communicating cysts. Most cases of MCKD will involute over a period of 2 years. Surgical intervention may be indicated in the setting of persistent multi cystic kidney, recurrent UTI, hypertension or if the cysts continue to show increase in size on follow up ultrasounds. Almost two thirds of patients with multicystic kidney disease will have abnormalities on the contralateral kidney, the most common being VUR.

In contrast to MCKD, polycystic kidney disease involves both kidneys. Affected infants usually have an autosomal recessive inheritance and will progress to renal failure requiring renal replacement therapy. As the mutated protein fibrocystin is present in both the kidneys and biliary duct, most of these children have liver involvement and may present with hepatic cysts and sometimes severe congenital hepatic fibrosis. Ultrasound will show enlarged kidneys with multiple small cysts in the collecting ducts. Nuclear medicine scan will reveal tracer uptake and drainage in contrast to MCKD which is totally non-functional.

UPJO can present as an abdominal mass if not detected prenatally. Some of these obstructive lesions can go unnoticed until adolescence when they can present with significant flank pain. The usual clinical scenario is flank pain after an episode of binge drinking as the obstructed pelvis is unable to allow the passage of the excess urine that is produced.

As newborn babies are prone to dehydration and have polycythemia, renal vein thrombosis could present rarely as an abdominal mass. Symptoms may be minimal but consider renal vein thrombosis in the setting of microscopic or macroscopic hematuria and thrombocytopenia. A duplex renal ultrasound which evaluates renal blood flow will be helpful in diagnosis. Treatment includes correction of underlying cause and systemic heparinization may also be indicated to preserve renal function.

Solid lesions in the kidney are rare and a solid abdominal mass is more likely to be a neuroblastoma originating from the adrenal gland. A benign solid mass involving the kidney will be mesoblastic nephroma otherwise called renal hamartoma. Malignant lesions of the kidney like neonatal Wilm’s tumor are rare and treatment usually involves surgical removal of the kidney and extensive radiation and chemotherapy. Other clinical findings associated with Wilm’s tumor include aniridia, hemihypertrophy, hematuria and hypertension.

**Failure to thrive**

There is no clear cut definition for failure to thrive (FTT). It is a clinical diagnosis based on anthropometric measurements. Weight percentile is the most preferred measurement and weight gain less than 5% on a standard growth curve on consecutive measurements defines FTT (10). In the United States the incidence is about 5 to 10% of outpatient visits. In infants the most common cause is nutritional. A precise history of caloric intake will aid with the diagnosis in most cases. Breast fed babies not receiving adequate calories will benefit from formula supplementation. If babies are bottle fed, improper formula preparation could cause inadequate caloric intake. If babies are failing to thrive in spite of adequate intake, focus should be on conditions that can interfere with caloric absorption or cause excessive caloric expenditure.

Kidneys play a main role in acid base balance. Daily acid production is about 1 to 2 meq/kg/day. Kidneys rid the body of excessive acid and also help in preserving bicarbonate to maintain a neutral pH, essential for several enzymatic reactions and growth. There are two main mechanisms by which kidneys handle acid base balance. The proximal convoluted tubules play a main role in reabsorbing almost 85% of the bicarbonate that is filtered across the glomeruli (11). Distal tubules play a main role in acid secretion by secreting hydrogen ions which are excreted as ammonium. A defect in either mechanism will cause renal tubular acidosis. Biochemically this is characterized by hypokalemic, hyperchloremic non anion gap metabolic acidosis. Typical clinical
presentation includes FTT, polyuria, constipation and some infants can present with severe dehydration.

Though most cases of RTA in adults is sporadic, in children a thorough surveillance for systemic conditions is necessary. Distal RTA (Type 1) is usually seen in association with obstructive uropathies. Urinary calcium excretion is increased and patients are at increased risk of stones and nephrocalcinosis. The increased calcium excretion is attributed to calcium leaching from the bones in the presence of acidosis.

Proximal RTA (Type 2) characterized by bicarbonate wasting can be sporadic or can be secondary to inborn errors of metabolism. Conditions including cystinosis, tyrosenemia, hereditary fructose intolerance, galactosemia, Wilson’s disease, Lowe syndrome and glycogen storage disorder can present with proximal RTA. Usually in these systemic conditions a more generalized loss of proximal tubular function characterized by aminoaciduria, glycosuria, phosphaturia and bicarbonate loss causing Fanconi syndrome. These children in addition to failure to thrive are at risk for hypophosphatemic rickets.

Cystinosis is an autosomal recessive lysosomal storage disorder characterized by accumulation of amino acid cystine in the cells. Nephropathic cystinosis, associated with Fanconi syndrome presents initially with failure to thrive, rickets, polyuria, polydipsia and constipation. As cystine crystals start accumulating systemically, corneal involvement will manifest with photophobia. Cystine crystals can be detected by slit lamp exam and can help establish the diagnosis along with genetic studies. Early diagnosis is important as therapy with cysteamine can prevent renal failure. Untreated patients are likely to reach end stage renal disease by 10 years of age.

If there is a clinical suspicion of RTA, begin with a measurement of urine pH. Urine pH levels < 5.5 in the setting of acidosis will rule out distal RTA as a cause. As distal RTA is defective acid secretion, patients will not be able to lower their urine pH below 5.5. But as proximal RTA is a bicarbonate threshold defect in the presence of a working distal tubule they will be able to lower urine pH to <5.5. Measurement of urine electrolytes, sodium, potassium and chloride will be helpful to calculate urine gap: Urine Na + Urine K – Urine Cl.

As ammonium is excreted usually as ammonium chloride one can indirectly measure ammonium and hence hydrogen ion secretion from urinary chloride concentration. In proximal RTA, with increased distal ammonium secretion urine gap will be negative. In distal RTA with decreased ammonium secretion the gap will be positive. Measurement of urine electrolytes to distinguish between RTA is valid only in the child not having extra renal bicarbonate loss (diarrhea) and before starting parenteral fluids. Other useful clues for differentiation will be elevated urinary calcium to creatinine ratio (Normal <0.8 in the first 7 months of life) in distal RTA and evidence of nephrocalcinosis on renal ultrasound. Proximal RTA as a part of Fanconi syndrome will have presence of glucose, protein on urine dipstick along with increased phosphorus loss (tubular reabsorption of phosphorus <85%)

Treatment of RTA will include identifying and treating the underlying cause. Biochemical abnormality can be corrected with potassium citrate or bicitra. The acidosis is much harder to correct in proximal RTA and might require bicarbonate supplementation up to 6 to 12 meq/kg/day. Bicarbonate therapy from 1 to 4 meq/kg/day is required for distal RTA.

Infants with chronic kidney disease (CKD) have difficulty gaining weight, attributable to several factors. Most of these babies have a tendency to salt diuresis secondary to tubular damage and present with significant polyuria. Caloric requirement for an infant with CKD is much higher than an infant with normal kidney function and most babies require G tube feeds overnight to provide adequate calories for growth. Anemia, metabolic acidosis and resistance to growth hormone all contribute to inadequate weight gain. Most infants with cystic kidney diseases also have difficulty concentrating urine and usually present with polyuria and FTT.

**Urinary tract infection in the newborn**

Urinary tract infection (UTI) is a leading cause of bacteremia and sepsis in infants and young children. Population based studies have shown the incidence of UTI to be between 0.1 to 2% of all term infants (12).
Incidence is much higher in the preterm infants. During the first year of life UTI is more common in boys than girls and the incidence reverses after a year of age. UTI should be considered in the differential diagnosis in any infant presenting with fever. In neonates presentation can be nonspecific and might include fussiness, poor feeding, vomiting, and diarrhea with or without fever.

The gold standard for diagnosing UTI is urine culture. In children who are not toilet trained an effective way of collecting the specimen will be by suprapubic tap or catheterization. Any number of bacteria growing in a suprapubic tap, a catheter specimen >10,000 CFU/ml or clean catch specimens in children who are toilet trained with counts >100,000CFU/ml is pathologic. Bagged specimens in infants are almost always contaminated and a positive culture result is of no significance. Urine dipstick is a quicker method of assessing for UTI as cultures can take up to 48 hours. Presence of pyuria, positive leukocyte esterase and nitrites will be helpful in diagnosing a UTI. In infants though, dipstick can be unreliable. As they are frequent voiders, urine bacteria do not stay for adequate time in the bladder to convert nitrates to nitrites. Also the urine is so dilute that frequently dipstick results can be falsely negative.

UTI associated with fevers indicate possible kidney involvement (pyelonephritis). There are no clinical criteria that can differentiate acute pyelonephritis from lower urinary tract infection. Pyelonephritis in infancy places the child at risk for renal scarring. Elevated white cell counts, inflammatory markers (CRP, procalcitonin) and positive blood and urine cultures indicate upper urinary tract involvement. The gold standard for diagnosing acute pyelonephritis is a nuclear medicine (MAG3) renal scan during early presentation. A renal scan may not be possible in the acute setting and a negative scan after treatment with antibiotics may not rule out acute pyelonephritis.

UTI in any infant warrants investigation with renal ultrasound to rule out any anatomical anomalies (posterior urethral valve, ureterocele, UPJO) that can predispose to UTI. Though there are no clear cut guidelines on how to proceed further, there are two kinds of approaches that have been widely practiced. A “top down” approach will consist of a renal scan (DMSA), two to three months after the febrile episode or a MAG3 scan during acute presentation. If there is evidence of renal scarring, further investigation including a VCUG is recommended. A “bottom up” approach is a VCUG after initial few days of antibiotic therapy to rule out reflux. AAP has developed guidelines for screening diagnostic techniques for first episode of febrile UTI from 2 to 24 months of age, recommending a renal ultrasound and if normal, not to proceed with further imaging until a second episode of febrile UTI. These guidelines do not apply to infants less than 2 months of life.

Treatment with parenteral antibiotics is indicated in acute pyelonephritis. Treatment up to 14 days is appropriate for urosepsis and from 7 to 10 days for a lower UTI. Once fever resolves and inflammatory markers are normalizing, oral antibiotics can be administered. It is common practice to document a sterile urine culture before switching to oral antibiotics though there are no clear cut guidelines. In the presence of reflux diagnosed after a febrile UTI there is no clear consensus on antibiotic prophylaxis. A few trials done of late do not support protective effect of antibiotics on preventing recurrent UTI (13). A randomized study (RIVUR) for vesicoureteral reflux has finished recruiting subjects with results expected in the next few years. This might provide more information on the utility of antibiotic prophylaxis. Current practice is to administer low dose antibiotic prophylaxis with high grade reflux (3 to 5).

### Electrolyte imbalances in the newborn

Newborn babies are at risk for dehydration secondary to limited urine concentrating ability and inability to preserve sodium. Association of lactation failure with severe hypernatremic dehydration is well known (14). Some of the predisposing factors include breast feeding problems (technique, maternal inverted nipple, cracked nipple, mastitis). Presenting symptoms usually include lethargy, decreased oral intake, decreased wet diapers and jaundice. Retrospective analysis has shown that neonates at risk for hypernatremic dehydration have a higher weight...
loss (>15%) within the first week of life. This underscores the importance of early clinic visits after hospital discharge to diagnose or prevent this life threatening complication.

Another rare cause for hypernatremia is diabetes insipidus. Though a predisposing cause is noted in most patients (intracranial defects, meningitis, and intra ventricular hemorrhage) very rare case reports of neonatal neurogenic diabetes insipidus have been reported in healthy infants (15). Anti diuretic hormone (ADH) which is produced by the supra optic and paraventricular nucleus of hypothalamus acts on renal collecting ducts to mobilize aquaporin channels for water reabsorption. Defective ADH secretion causes central or neurogenic diabetes insipidus. Resistance to the action of ADH at the site of collecting ducts is seen in nephrogenic diabetes insipidus. The baby presents with signs of dehydration while continuing to make significant amounts of urine.

In any neonate presenting with hypernatremia measuring urine output will give clues to the diagnosis. Normally, in the setting of dehydration, urine osmolality and specific gravity will be elevated. Even in dehydrated neonates with limited urine concentrating ability, urine osmolality > up to 600 mosm/kg can occur. In complete central diabetes insipidus urine osmolality will be < 300 mosm/kg. Urine specific gravity by dipstick will be usually < 1.005 in DI. A water deprivation test, with subsequent administration of DDAVP will help differentiate between central and nephrogenic DI. If central DI is suspected imaging studies of the brain to rule out any space occupying lesion is essential.

Gradual correction of hypernatremia with normal saline over a period of 48 to 72 hours is of paramount importance. But in the setting of extreme hypernatremia (sodium > 190 meq/L) initial fluid resuscitation with normal saline can lower sodium rapidly and can be potentially lethal. In such rare instances initial resuscitation fluid should be hypertonic (a mixture of 3% NS and NS to provide sodium content about 20 meq less than the serum sodium levels). Maintenance fluid will be normal saline (16). Checking sodium levels after initiation of treatment is essential to ensure that their rate of decrease every two to three hours is < 0.5 meq/L. Rapid correction of hypernatremia can cause acute cerebral edema and death.

Screening renal ultrasound in other organ anomalies

Association between renal anomalies and ear anomalies is well known. It is customary to get screening ultrasounds for any ear anomaly such as ear tags, ear pits or any malformation of the ears. A recent retrospective study showed that there is a slight increase in renal anomalies in association with ear anomalies (17). But the yield for a screening ultrasound will be better if it is done for ear anomalies associated with dysmorphic features, family history of renal disease, deafness or maternal gestational diabetes mellitus. As certain genes like PAX and BMP (bone morphogenic protein) plays an early role in both renal and ocular development, syndromes or anomalies involving both organs have been described as well (18). Some of the common syndromes associated with renal abnormality are discussed below.

CHARGE association/syndrome

The CHARGE association occurs sporadically. The association consists of coloboma of iris or retina, heart defects, atresia choanae, retarded growth and development, genital and ear anomalies. Screening ultrasound can show a wide variety of renal anomalies from hydronephrosis to renal agenesis.

Renal coloboma syndrome

Mutations in PAX2 genes (early transcription factor) presents with bilateral optic nerve colobomas and renal hypoplasia. There is increased incidence of VUR in the hypoplastic kidneys.

Townes-Brocks syndrome

This is an autosomal dominant condition with varying phenotype caused by mutation in an early
transcription factor namely SALL1 gene. This gene is essential for the developing ears, limb buds and kidneys. Clinical features include bilateral ear anomalies and hand malformations. They can present with imperforate anus and rectovaginal or rectourethral fistula. Renal anomalies range from hypoplasia to obstructive uropathy.

**Branchio-oto-renal (BOR) syndrome**

This is an autosomal dominant disorder which is caused by a mutation in early transcription factors involved in organogenesis. The genes involved include Eya1/PAX/6 transcription factors which play a role in ureteric bud formation in the kidney and ear formation. Clinical features include branchial cyst or fistula, ear anomalies including microtia, cupped ears, preauricular pits and varying degree of conductive or sensorineural hearing loss. Renal anomalies usually include small hypoplastic kidneys or rarely agenesis.

**Aniridia and renal anomalies**

Aniridia is a severe anomaly of the eye which presents with absence of iris. Mutation in PAX6 gene is involved in most of the cases. A large deletion involving the nearby WT1 gene along with PAX6 gene puts the patient at risk for Wilm’s tumor. This comes under WAGR syndrome (Wilm’s tumor, aniridia, genital anomaly and mental retardation syndrome). Screening for WT1 mutation and a screening ultrasound will be appropriate in patients diagnosed with aniridia.

**Beckwith –Wiedemann syndrome (BWS)**

This is an overgrowth disorder with predisposition to tumor development (19). BWS is a disorder of genetic imprinting on chromosome 11p15 and presents with a varying phenotype. Classic presentation will be presence of abdominal wall defect like omphalocele, macrosomia, macroglossia, visceromegaly and hypoglycemia in the newborn. As the child grows hemi hyperplasia could be the only presenting sign. Presence of hemi hyperplasia and nephromegaly are known risk factors for tumor formation. A variety of other renal anomalies including nephritogenic rests, renal medullary dysplasia and cysts may be present. If there is a clinical suspicion for BWS, a screening abdominal ultrasound must be obtained. Referral to genetics will also help in diagnosis. Once diagnosed, screening abdominal ultrasounds are advised 4 to 6 months until the child turns 8 years of age. Screening for alpha fetoprotein (AFP) to diagnose patients at risk for hepatoblastoma every 4 to 6 months until the age of 4 years is also recommended.

**Conclusion**

This discussion summarizes some of the morphologic changes of the developing kidney. A brief overview of the importance of kidneys in maintaining fluid, electrolytes and acid base balance is provided. Common neonatal issues including urinary tract infection, neonatal hydronephrosis and the current available guidelines for their management are discussed.

**References**


Neonatal hematology

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Abstract
A number of hematologic problems may arise in the newborn and during infancy because hematopoiesis and hemostasis are not fully mature until six months of age. Concepts of normal hematopoietic development are reviewed. Conditions that are discussed include anemia, thrombocytopenia, neutropenia, and coagulation disorders. Consultation with experts in hematology is recommended for complex situations.

Keywords: Pediatrics, neonatology, hematology

Introduction
Hematopoiesis and hemostasis in the newborn is not fully mature. Adult levels of most procoagulant and anticoagulant proteins are reached by age six months, some do not reach adult levels till adolescence (1). Immaturity of hematopoietic system makes a newborn vulnerable to hematologic disorders such as anemia, neutropenia and thrombocytopenia. Anemia, thrombocytopenia, neutropenia and bleeding triggered by passage through birth canal are some of the reasons for hematology consult in the newborn period.

Normal development of hematopoiesis
Hematopoiesis is a complex process of cell renewal as red blood cells (RBC), white blood cells (WBC) and platelets senesce and regenerate. The hematopoietic germ cell originates from mesodermal germ cell layer (1, 2). Hematopoiesis begins early in embryonic life and gradually moves to aorto-gonado-mesonephron (AGM), to liver and then to bone marrow. Tightly regulated by specific cell growth factors each cell line undergoes changes specific to its developmental age. These changes impact the clinical manifestation,
laboratory diagnosis and management of hematologic disorders in the newborn period.

Erythrocytes

Embryonic hematopoiesis starts in the yolk sac and moves from the ventral aspect of the aorta to liver and then to the bone marrow as the fetus matures. Microenvironment in each location affects the RBC size and other characteristics. Erythropoietin (EPO) is produced by liver in early fetal life with transition to kidneys occurring postnatally. EPO concentration decreases at birth and reaches a nadir at 4-6 weeks of life. This is followed by a gradual increase to adult levels by 10-12 weeks of life. Hemoglobin is a tetrameric molecule consisting of two pairs of polypeptide chains.

Changes in hemoglobin structure and transition from embryonic (ζε₂), fetal HbF (α₂γ₂) to adult hemoglobin HbA (α₂β₂) occur to accommodate for oxygen needs of developing fetus. Gamma chain synthesis starts early and peaks mid gestation. Beta chain synthesis starts in 6th week of life with a subsequent steady increase throughout fetal life.

Platelets

Megakaryopoiesis is the process of platelet production. Similar to erythropoiesis the site of production of platelets changes during embryonic and fetal life with bone marrow being the major site of production at birth. Megakaryocyte nucleus has the unique ability to undergo endomitosis and increase nuclear ploidy and DNA without undergoing cell division. The number of platelets produced by a megakaryocyte is directly proportional to its nuclear ploidy. Although platelet number reaches near adult values in early fetal life the megakaryocytes at birth are smaller with lower nuclear ploidy, <8N, and produce fewer platelets.

White blood cells

Macrophages are the early white blood cells produced in yolk sac and liver. Neutrophils become primary WBC once bone marrow hematopoiesis starts around 10-11 weeks of gestation. Hemoglobin and WBC at birth are higher and red cells are larger in size but platelet count is normal (see Table 1).

<table>
<thead>
<tr>
<th>Table 1. Normal blood count values in newborn period</th>
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<tbody>
<tr>
<td><strong>Red Blood Cells</strong></td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Hemoglobin GM/dl Mean(-2SD)</td>
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<tr>
<td>Hematocrit % Mean (-2SD)</td>
</tr>
<tr>
<td>MCV fL Mean (-2SD)</td>
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<tr>
<td>MCHC G/dl RBC Mean(-2SD)</td>
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<tr>
<td>Reticulocyte Count %</td>
</tr>
<tr>
<td>White Blood Cell X 10³/CC₃ Mean (Range)</td>
</tr>
<tr>
<td>Platelet Count X 10³/CC₃</td>
</tr>
</tbody>
</table>

Hemostatic disorders

Hemostasis is a complex process that involves endothelium, subendothelium, platelets and a number of proteins. A delicate balance between procoagulant factors (F I-XIII), natural anticoagulants protein C, S and antithrombin (AT), fibrinolytic system, plasminogen, plasmin and inhibitors of fibrinolytic system keeps the blood in the fluid state. Platelet disorders and procoagulant protein deficiencies are major causes of bleeding in the newborn period and are discussed below.

Coagulation disorders

Coagulation factors (F I-XIII) do not cross the placenta; hence the newborn has to synthesize all the factors de-novo. Levels of FV,VIII, fibrinogen and von Willebrand factors at birth are normal whereas Factor XII, XI, X, IX, VII, II, protein C and S and AT
are present at 30-50% of adult levels (2,3). The relevance of developmental hemostasis to hemorrhagic disorders in newborn is well described; low levels of vitamin K dependent factors (F II, VII, IX, X, proteins C and S) and immaturity of liver results in decreased levels of all clotting proteins.

Biochemical differences account for the characteristics of fetal fibrinogen that polymerizes slower than adult fibrinogen(2). Despite these qualitative and quantitative differences, most newborns are healthy with no increased tendencies towards either bleeding or clotting. The neonatal module and diagnostic algorithm of the free downloadable app called “coags uncomplicated TM” may be helpful in determining age related normal values in the newborn (4).

Bleeding disorders in the newborn period pose unique challenges in diagnosis and management. Bleeding is often iatrogenic and factors such as the mode of delivery, circumcision, injections, heel sticks impact bleeding manifestations. Hemophilia A (FVIII deficiency) and B (FIX deficiency) are the most common congenital bleeding disorders although bleeding can also occur with other factor deficiencies (Fibrinogen, FVII, II, V, XI, X, XIII)5. The Rare Coagulation Disorder resource room of the National Hemophilia Foundation provides information about these rare deficiencies (5).

Hemophilia and other clotting factor deficiencies

While hemophilia A can be diagnosed at birth, diagnosis of hemophilia B (FIX deficiency) can be challenging due to low levels of FIX, hence a repeat testing at 6 months of age is recommended. Regarding sites of bleeding in babies with hemophilia, data from 633 babies, ages 0-2 years registered in the United States, Centers for Disease Control and Prevention’s (CDC) Universal Data Collection (UDC) showed that 44% of babies with hemophilia had a bleeding episode by one month of age; the most common site of bleeding was circumcision followed by intracranial hemorrhage (ICH). ICH associated with delivery was seen in 22/633 (3.4%) of newborns (7, 8).

Treatment of congenital factor deficiencies include replacement therapy with recombinant factor concentrates (FVIII, IX, VII and XIII) or pathogen safe plasma derived concentrates (FVIII, IX, von Willebrand Factor/FVII concentrate, fibrinogen, FXIII) (9). Fresh Frozen plasma is used in situations where no concentrate is available; the use of cryoprecipitate (contains FVIII, fibrinogen, FXIII and fibronectin) is not recommended when recombinant or virally inactivated plasma derived products are available. Clinical trials are underway on the use of long acting FVIII and IX concentrates.

Vitamin K deficiency

Vitamin K deficiency cause low levels of vitamin K dependent FII, VII, IX and X. Failure to give prophylactic dose of vitamin K at birth coupled with limited placental transfer and low levels in breast milk. Early Vitamin K deficiency bleeding (VKDB) occurs within 24 hours of birth and is due to maternal ingestion of medications that affect storage; “Classic” VKDB is seen between days 2-7 of life and late VKDB occurs between 7 days and 6 months with 50% of infants presenting with ICH (10). Both classic and late VKDB can be prevented by prophylactic administration of vitamin K at birth.

Neonatal thrombosis

Neonates are at highest risk for developing thrombosis including venous thromboembolism (VTE), central sinus-venous thrombosis (CSVT) and arterial ischemic stroke (AIS). Acquired thrombophilic states such as central venous access devices (CVAD), dehydration, sepsis, DIC, congenital heart disease, total parenteral nutrition and transplacental passage of maternal antiphospholipid antibodies etc., are the most common cause of thrombosis11. Low levels of naturally occurring anticoagulants such as protein C, S and antithrombin (AT) rarely cause thrombosis as they may be counterbalanced by low levels of procoagulant factors. Rarely homozygous protein C and S deficiency (levels less than 5%) can manifest as purpura fulminans; heterozygous deficiencies of protein C, S and AT on the other hand, are more difficult to diagnose as the levels overlap with the age
related values. There are little data to support routine thrombophilia workup in neonates; except in neonates with non-catheter related VTE/stroke (CSVT/AIS) or those participating in clinical trials (2, 11).

One should consider the impact of developmental hemostasis on anticoagulant management. Higher doses of heparin are required by neonates due to low levels of AT. In adults, the anticoagulant effect of unfractionated heparin is usually monitored using the activated partial thromboplastin time (aPTT). In the neonates the aPTT is prolonged and does not correlate with anti Xa levels, hence anti Xa levels are utilized for monitoring unfractionated and low molecular weight heparin (1, 2, 11).

**Laboratory diagnosis of neonatal hemostatic disorders**

Small sample volumes coupled with varying age related reference values makes laboratory diagnosis of neonatal hemostatic disorders particularly challenging. Besides obtaining a pediatric hematology consult, the clinical phenotype and family history should be taken into account (2). Screening tests should be carefully interpreted. Whenever possible, any plasma remaining after tests should be frozen. Carefully collected cord blood sample free of contamination by maternal blood can be used for determining factor levels. Figure 1 below presents an algorithm to approach neonatal bleeding.

![Figure 1. Approach to bleeding newborn.](image)

**Thrombocytopenia**

Thrombocytopenia in the newborn is the most common hematologic condition seen in newborn period. Prevalence of thrombocytopenia in this age group may be as high as 1-5% (ref). In sick newborns in neonatal intensive care units this number is as high as 25-35% (ref). Platelet count reaches 150X103/L at the end of first trimester and continues to rise in the later part of pregnancy.

Normal Platelet count at birth irrespective of gestational age is >150X109/L. However, more recent studies show that platelet count in healthy newborns is as low as 104X109/L in newborn gestational age <32 weeks and 123X109/L in newborn gestational age >30 weeks. Neonatal megakaryocytes are smaller and have lower ploidy. As a result newborn is more prone to thrombocytopenia. Newborn platelets are also hyporeactive. In spite of lower platelet count and hyporeactivity newborns are
generally hypercoagulable. Clinical classification severity of thrombocytopenia in the newborn is

1. Mild 50-100x10^9/L
2. Moderate 20-50 x10^9/L
3. Severe <20 x10^9/L

**Causes and pathogenesis of thrombocytopenia**

The mechanism is either increased destruction or decreased production of platelets. In sick or premature infants both increased destruction complicated by decreased production might be at play. The list of causes of thrombocytopenia is long. Newborn’s clinical condition and age at the onset help with developing a pertinent approach to a patient with thrombocytopenia. For example the babies with immune thrombocytopenia in the absence of serious bleed with the exception of bruises, purpura and petechiae appear and act normal. Occasionally history of thrombocytopenia in the mother or previous pregnancies is the sole reason for obtaining CBC in this patient population. Causes of thrombocytopenia in otherwise well appearing babies are listed in Table 2.

**Table 2. Causes of thrombocytopenia in well newborn**

<table>
<thead>
<tr>
<th>Cause</th>
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<tbody>
<tr>
<td>1. Immune thrombocytopenia</td>
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<tr>
<td>- Alloimmune</td>
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<tr>
<td>- Autoimmune</td>
</tr>
<tr>
<td>2. Congenital thrombocytopenia</td>
</tr>
<tr>
<td>- Congenital amegakaryocytic thrombocytopenia (CAMT)</td>
</tr>
<tr>
<td>- Thrombocytopenia Absent radii syndrome (TAR)</td>
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<tr>
<td>3. Kasabach-Merritt Syndrome</td>
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<tr>
<td>4. May Haeglin MYH 9 syndromes</td>
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<tr>
<td>5. Familial Thrombocytopenia</td>
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</tbody>
</table>

Thrombocytopenia in sick newborns is noted on CBC done for evaluation of underlying disease. Bruises, petechiae and purpura are seldom the only reason for ordering a CBC. Important causes of thrombocytopenia are listed in Table 3. Please note that babies with Kasabach- Meritt syndrome and congenital thrombocytopenia sometimes are sick enough to appear on both lists. Antibody mediated destruction causes thrombocytopenia. Newborn with immune thrombocytopenia are generally healthy and present with bruises, petechiae, oozing after heel sticks or cephalhematoma (see Table 3).

**Table 3. Causes of thrombocytopenia in sick newborn**

<table>
<thead>
<tr>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Perinatal Asphyxia</td>
</tr>
<tr>
<td>2. Infant of diabetic Mother</td>
</tr>
<tr>
<td>3. Intrauterine growth Retardation</td>
</tr>
<tr>
<td>4. Neonatal Sepsis both perinatal as well as late onset</td>
</tr>
<tr>
<td>5. DIC</td>
</tr>
<tr>
<td>6. Congenital Infections (CMV, Rubella, HIV, Toxoplasma)</td>
</tr>
<tr>
<td>7. Renal Vein Thrombosis</td>
</tr>
<tr>
<td>8. Kasabach-Meritt Syndrome</td>
</tr>
<tr>
<td>9. Bone marrow replacement (congenital leukemia, disseminated neuroblastoma)</td>
</tr>
<tr>
<td>10. Inherited Thrombocytopenia (congenital amegakaryocytic thrombocytopenia CAMT, Thrombocytopenia absent radii (TAR)</td>
</tr>
<tr>
<td>11. Wiscott Aldrich Syndrome (WAS)</td>
</tr>
<tr>
<td>12. Metabolic Disorders (proprionic and methylmalonic acidemia)</td>
</tr>
<tr>
<td>13. Medications</td>
</tr>
</tbody>
</table>

**Autoimmune thrombocytopenia**

Autoimmune thrombocytopenia is due to passive transfer of IGG antibodies across placenta. The mother usually has thrombocytopenia or history of treated immune thrombocytopenic purpura. Other autoimmune conditions in the mother such as SLE or inflammatory bowel disease could also cause thrombocytopenia in the newborn and often neonatal thrombocytopenia is the first sign of disease in the mother. The onset usually is within first 72 hours of life but could be delayed by several days. Affected babies usually are healthy. Thrombocytopenia is mild in 90%, moderate 10% and severe in 4% of the babies born to the mothers with ITP.

Babies with mild to moderate thrombocytopenia are usually normal except for bruises or petechiae. Occasionally excessive oozing after a heel stick might be the first sign. The condition is self-limiting and resolves in 3-6 weeks. Babies with severe thrombocytopenia are treated with a course of
intravenous immunoglobulins (IVIG). Babies who are refractory to IVIG may be treated with prednisone. Platelet transfusion is reserved for babies with serious bleeds and is usually not very effective.

Drug induced immune thrombocytopenia in the mother secondary to quinidine, penicillin, digoxin, heparin or anti-epileptic could cause thrombocytopenia in the newborn. It usually resolves as soon as the offending agent is withdrawn. Babies with bleeding or platelet count < 20 x10^9/L may be treated with a course of IVIG.

**Neonatal alloimmune thrombocytopenia (NAIT)**

Alloimmune thrombocytopenia occurs when the baby inherits platelet antigen that the mother lacks. The mother develops IGG antibodies that cross the placenta and cause fetal and neonatal thrombocytopenia. Thrombocytopenia may develop as early as 20 weeks of gestation. Therefore this condition is also called fetal and neonatal thrombocytopenia (FNAIT). Platelet antigens are designated as Human Platelet Antigen (HPA). About 98% of Caucasians express HPA-1a.

HPA-1a incompatibility is responsible for 80-90% cases of NAIT in the Caucasian population (14). HPA-1b is the next most common antigen implicated. HPA-4 incompatibility is the most common cause of NAIT in Asian population.

The mothers have normal platelet count. History of thrombocytopenia may be absent and first pregnancy could be affected. Maternal aunts may have history of affected pregnancies. There is a very high recurrence with subsequent pregnancies. Although most babies have skin bleeding intracerebral bleeding is seen in 14-20% patients. Intracerebral bleed could occur, prior to delivery or as late as 96 hours of delivery (15). Ultrasound of the head to evaluate for intracranial bleed should be done at birth.

Babies with presence of bleeding should be treated with platelet transfusion. The mother’s washed irradiated platelets are the treatment of choice. However maternal platelets are not always immediately available. HPA-1a negative and HPA-5b negative platelets, the next best option, is expensive and also often not available. In emergency situations random platelets can be used. However the survival of random donor platelets is short. To prevent intracranial bleed prophylactic platelet transfusion is indicated for term newborn with platelet count < 30x10^9/L and preterm newborn with platelet count < 50 x10^9/L for first 96 hours of life.

Because of high risk of recurrence and intracerebral bleeds subsequent pregnancy should be managed at a center for high risk pregnancies. Infusion of IVIG 400mg/kg/d for 3-4 days or 1G/kg is effective but takes a few days for response. Steroids are usually not indicated for treatment of babies with NAIT. The risk of recurrence and severity of thrombocytopenia is high. Intracranial bleed may occur prenatally. For these reasons the subsequent pregnancies in mothers with history of NAIT should be managed at centers for high risk pregnancies.

**Disseminated intravascular coagulation (DIC)**

DIC in term newborn is usually secondary to a serious underlying problem such as sepsis, perinatal asphyxia or respiratory distress syndrome. Bleeding and oozing from phlebotomy sites, umbilical cord, petechiae, purpura or hematoma are usual presentations. Gastrointestinal or intracranial bleed may occur in serious cases. Thrombosis due to DIC presents as cyanosis or organ failure.

Laboratory diagnosis of DIC in newborn period is complex. Elevated PT, APTT, D-dimer with low platelet count and fibrinogen are the hallmark of DIC. PT and aPTT in this age group are normally elevated. Platelet count <100x10^9/L, fibrinogen <150mg/dl, PT >15.3 seconds and APTT >59.8 seconds are considered abnormal and could be used for diagnosis of DIC in this age group. D-dimer may be slightly elevated in the newborn and should be interpreted with caution. Vitamin K deficiency is an important differential diagnosis. Platelet count and fibrinogen levels are normal in vitamin K deficiency.

Treatment of DIC consists of treatment of underlying disease and supportive care. Patients with bleeding symptoms may be treated with platelet concentrate or FFP. To correct hypofibrinogenemia Cryoprecipitate may be used in bleeding newborn.
**Congenital thrombocytopenia**

Thrombocytopenia and absent radii syndrome because of obvious deformity is diagnosed in the newborn period. The deformities involving upper extremities may vary from bilateral radial aplasia, radial club hand, hypoplastic carpal bones or phalanges, clinodactyly, syndactyly, hypoplasia of the humerus or ulna. Inheritance is autosomal recessive. Other associated abnormalities include, micrognathia, cleft palate, rib abnormality and cardiac defects. About 50% patients have thrombocytopenia in first week of life. Thrombocytopenia improves with age reaching levels as high as >100x10⁹/L (16). Treatment consists of supportive care to avoid bleeding and platelet transfusion.

Inheritance of congenital amegakaryocytic thrombocytopenia (CAMT) is variable (17) and occasionally present in newborn period with platelet count <50 x 10⁹/L. Thrombocytopenia gets worse over time. Patients with CAMT are at high risk for aplastic anemia or leukemia. Diagnosis is often not established in newborn period. Newborn with thrombocytopenia should be monitored until a stable normal level is reached. Failure to achieve normal count would prompt further evaluation.

Newborns with MYH9 mutation and giant platelet syndrome usually have minimal bleeding symptoms. Some patients with these mutations develop renal failure, cataract or deafness during 2nd or 3rd decade of life.

**Inherited platelet function disorders**

Delta-storage pool defect the most common inherited platelet function disorder seldom causes bleeding in newborn period. Disorders of platelet glycoprotein Ib Bernard-Soulier disease and Glycoprotein IIb/IIIa Glanzmann thrombasthenia due to abnormalities are rare. Glanzmann thrombasthenia the more severe of the two usually presents later in infancy as the baby becomes mobile. Muco-cutaneous bleeding is common.

**Kasabach-Meritt syndrome**

Kasabach-Meritt syndrome (KMS) a combination of hemangioma, thrombocytopenia and coagulopathy sometimes present in newborn period. Depending on the location, size and degree of coagulopathy and thrombocytopenia the baby may be mildly to severe ill. The baby may present with pallor, jaundice, petechiae, purpura, enlarged abdomen, and tachycardia with large irregular or multiple hemangioma. In addition to thrombocytopenia PT and aPTT may be prolonged and fibrinogen is low. Schistocytes are often reported on peripheral smear. A newborn presenting with thrombocytopenia and coagulopathy without obvious hemangioma requires further evaluation with abdominal ultrasound. Depending on the location further evaluation with flow Doppler, CT and or MRI may be indicated.

The management consists of corticosteroids to reduce the size of hemangioma and supportive care. Platelet transfusions, fibrinogen concentrate, FFP are used to stabilize an actively bleeding patient. The antiplatelet agents, aspirin, ticlopidine and antifibrinolytic agents are used to stabilize a patient with fulminant KMS. Occasionally surgical intervention to reduce the size of tumor is necessary. Vincristine, cyclophosphamide and propranolol have been used to reduce the size. Because of risk of spastic diplegia alfa interferon is rarely used.

**Anemia**

Anemia is a common hematologic problem in the neonatal population. Neonatal anemia is defined as a hemoglobin or hematocrit level less than 2 standard deviations below normal for postnatal age. Since erythropoiesis evolves throughout fetal life, these laboratory parameters will change based on the gestational age of an infant. Normal ranges are summarized in Table 1. The etiology of neonatal anemia can be divided into three main categories: blood loss, decreased production, or increased destruction of erythrocytes (see Table 4).
Table 4. Causes of anemia in the newborn period

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Loss</td>
<td>Prenatal</td>
</tr>
<tr>
<td></td>
<td>• Fetoplacental, fetomaternal hemorrhage</td>
</tr>
<tr>
<td></td>
<td>• Twin-twin transfusion</td>
</tr>
<tr>
<td></td>
<td>During Delivery</td>
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<tr>
<td></td>
<td>• Hematoma</td>
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<tr>
<td></td>
<td>• Obstetric complications</td>
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<td></td>
<td>• Placenta previa</td>
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<td></td>
<td>• Abruptio placenta</td>
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<td></td>
<td>• Placental incision during cesarean section</td>
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<tr>
<td></td>
<td>Internal bleeding</td>
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<td></td>
<td>• Intraventricular hemorrhage</td>
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<tr>
<td></td>
<td>• Subdural/cephalohematoma</td>
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<tr>
<td></td>
<td>Iatrogenic</td>
</tr>
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<td></td>
<td>• Phlebotomy losses</td>
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<tr>
<td>Decreased Erythrocyte Production</td>
<td>Physiologic nadir</td>
</tr>
<tr>
<td></td>
<td>Anemia of prematurity</td>
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<tr>
<td></td>
<td>Infection</td>
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<tr>
<td></td>
<td>• Sepsis</td>
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<td></td>
<td>• TORCH infections/HIV/Parvovirus</td>
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<tr>
<td></td>
<td>Bone marrow disorders</td>
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<tr>
<td></td>
<td>• Diamond-Blackfan anemia</td>
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<tr>
<td></td>
<td>• Fanconi Anemia</td>
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<tr>
<td></td>
<td>• Congenital leukemia</td>
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<tr>
<td></td>
<td>Nutritional Deficiencies</td>
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<tr>
<td></td>
<td>• Iron/B12/Folate deficiency</td>
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<tr>
<td>Increased Erythrocyte Destruction</td>
<td>Infection</td>
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<tr>
<td></td>
<td>• Sepsis/DIC</td>
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<tr>
<td></td>
<td>• TORCH infections</td>
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<tr>
<td></td>
<td>Immune hemolytic anemia</td>
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<td></td>
<td>• ABO incompatibility</td>
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<td></td>
<td>• Rh disease</td>
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<td></td>
<td>RBC membrane disorders</td>
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<tr>
<td></td>
<td>• Hereditary Spherocytosis (HS)</td>
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<tr>
<td></td>
<td>• Hereditary Elliptocytosis (HE)</td>
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<td></td>
<td>RBC enzyme disorders</td>
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<td></td>
<td>• Glucose-6-phosphate dehydrogenase deficiency (G6PD)</td>
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<td></td>
<td>• Pyruvate kinase deficiency (PK)</td>
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<td></td>
<td>• Glycolytic pathway abnormalities</td>
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<td></td>
<td>Hemoglobin disorders</td>
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<td></td>
<td>• α/β Thalassemia</td>
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<td></td>
<td>• Sickle cell</td>
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<td></td>
<td>• Hemoglobin E disease</td>
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</tbody>
</table>

**Physiologic anemia of newborns**

The most common cause of anemia in newborns is a physiologic response following delivery into an oxygen rich environment. An infant’s first breath of oxygen-rich air results in a significant increase in hemoglobin oxygen saturation and down-regulation of erythropoiesis. Decreased neonatal EPO levels lead to a physiologic nadir of hemoglobin concentration in full term infants at approximately 6-12 weeks of age with a hemoglobin concentration of 9.5-11 g/dL (18). The physiologic nadir is more profound in premature
infants with hemoglobin concentrations of 7-9 g/dL at approximately 4-6 weeks (19).

Anemia of prematurity is mainly a result of severely decreased erythropoietin levels, though it may be exacerbated by vitamin deficiencies related to severe prematurity, including decreased levels of iron, folate, B12, B6, and vitamin E. Studies on the use of EPO administration in preterm infants have shown mixed results, with most showing an improvement in hemoglobin levels but not necessarily significantly decreasing PRBC exposure. Correction of nutritional deficiencies with combinations of iron, folate, and B12 along with erythropoietin have shown some benefit, though these interventions need further validation with randomized controlled trials (20, 21).

**Blood loss**

Blood loss is a readily identifiable cause of anemia in neonates, due to fetal blood loss, obstetric complications, or hemorrhage due to birth trauma. Iatrogenic anemia from frequent blood draws is a common complication in premature infants (22).

**Decreased production**

Decreased RBC production can result from the physiologic mechanisms noted above or from disorders of erythrocyte production. Congenital bone marrow failure syndromes, including Fanconi anemia and Diamond Blackfan anemia, may present in newborns as isolated anemia with reticulocytopenia or with pancytopenia at more advanced stages. These children often have associated congenital anomalies which may increase suspicion of an underlying bone marrow failure syndrome. Acquired causes of decreased erythrocyte production include TORCH infections and other congenital infections (including HIV and parvovirus). Similarly, acquired nutritional deficiencies such as iron, copper, folate, vitamin A, vitamin B12, vitamin B6, vitamin C, and vitamin E have all been associated with reduced RBC production (23).

**Increased destruction**

Increased destruction of newborn erythrocytes can result from a variety of mechanisms and lead to severe anemia in certain infants. The lifespan of a RBC in newborns is significantly reduced (~70 days) compared to adult RBCs (~120 days), predisposing newborns to anemia. Bacterial or viral sepsis is a common cause of increased RBC destruction and clinically significant anemia in extremely ill newborns. Additional causes of RBC destruction are reviewed below.

**Immune-mediated destruction**

Immune-mediated RBC destruction results from maternal antibody production following exposure to foreign antigens on fetal erythrocytes. Maternal IgG then crosses the placenta, binds fetal erythrocytes leading to removal by the reticuloendothelial system and anemia in the newborn. Rh incompatibility can involve multiple antigens, though the D antigen is the most significant. Second pregnancies with an Rh+ infant of an Rh- mother are at risk of a severe anemia and hyperbilirubinemia as a result of maternal IgG response. ABO incompatibility (type A or B baby born to a type O mother) is more common in newborns, though this typically results in only a mild anemia and hyperbilirubinemia as these are IgM antibodies which do not cross the placenta. There are reports of newborns with significant hemolytic anemia caused by naturally occurring maternal anti-B or A IgG (24).

**Erythrocyte membrane defects**

Erythrocytes membrane defects included disorders of the RBC membrane and cytoskeleton which result in removal of the abnormally shaped RBCs from circulation. Hereditary spherocytosis (HS) is a relatively common RBC membrane disorder resulting most often from defects in spectrin attachments to the RBC membrane. This autosomal dominant disorder results in spherocytic, fragile RBCs that are at risk for lysis. HS should be considered in newborns with an unconjugated hyperbilirubinemia without evidence of
immune-mediated hemolysis. A family history of HS is often known; though up to 30% of cases can be spontaneous new mutation (25).

Osmotic fragility testing as well as mutational analysis is available to confirm the diagnosis of HS. Hereditary elliptocytosis (HE) is also related to defects in structural proteins within the RBC, leading to characteristic elliptical or oval shaped RBCs which are readily hemolyzed by the reticulo-endothelial system. HE is typically inherited in an autosomal dominant manner and family history is often positive. Hereditary Pyropoikilocytosis (HPP) is an autosomal recessive severe form of HE in which infants may have severe hemolysis requiring transfusion but slowly resolves into more typical HE with time (26).

Erythrocyte enzyme deficiencies

Defects in RBC enzymes and metabolic pathways can lead to significant RBC damage and subsequent anemia in newborns. Glucose-6-phosphate dehydrogenase (G6PD) deficiency results in accumulation of toxic metabolites within the RBC, leading to hemolysis. This is an x-linked recessive disorder with a hemolytic crisis typically brought on by exposures to oxidative stress (foods including fava beans, infection, etc.). While food exposures are typically not an issue in the newborn period, G6PD deficiency should be suspected in any infant with evidence of non-immune hemolytic anemia with Heinz bodies (degraded hemoglobin deposits) present on peripheral smear.

Pyruvate kinase (PK) deficiency may also present during the newborn period. This autosomal recessive disorder leads to decreased ATP production within a RBC and may result in significant hemolysis and hyperbilirubinemia. Both G6PD and PK deficiency can be diagnosed based on serum enzyme levels, though these may be falsely elevated in children who were recently transfused and levels may need to be repeated to accurately to diagnose these conditions.

Hemoglobinopathies

Defects in hemoglobin production are an uncommon cause of anemia in the newborn period. Newborn erythrocytes contain mainly hemoglobin F (α2γ2). Defects in the production of globin chains, alpha thalassemia in particular, can lead to formation of unstable hemoglobins and increased hemolysis. Significant hemolysis is only seen with a three gene deletion in alpha-thalassemia, however. Four gene deletions in alpha thalassemia typically results in hydrops fetalis. Beta thalassemia is not typically an issue in the newborn period as beta globin production does not peak until 3 months of life. Newborns are protected from significant hematologic effect of other hemoglobinopathies such as sickle cell disease by elevated levels of hemoglobin F through the first 6 months of life.

Determining the etiology of anemia in newborns

The cause of newborn anemia can be determined through a thorough history (h/o sepsis, TORCH infections, family history of RBC disorder), physical examination (organomegaly, congenital anomalies), and laboratory studies including CBC with examination of peripheral smear, reticulocyte count, bilirubin levels, enzyme levels, and electrophoresis). In addition, the newborn screen will detect a number of underlying hemoglobinopathies. Primary care providers may receive information on newborn screen findings in asymptomatic newborns. These findings and recommendations for referral to a hematologist are summarized in Table 5.

Prevention of anemia in newborns

Preventative approaches include limiting unnecessary blood draws in neonates as well as improved nutritional supplementation for high risk populations. As noted above, the physiologic anemia seen in premature infants may be improved with nutritional supplementation and the use of EPO (20). The American Academy of Pediatrics recommends preterm infants receive 2-4 mg elemental iron/kg per day. Additional recommendations from the AAP can be found in the Pediatric Nutrition Handbook (28).
Table 5. Newborn screening for hemoglobinopathies (27)

<table>
<thead>
<tr>
<th>NBS Result</th>
<th>Interpretation</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>FA</td>
<td>Normal</td>
<td>---</td>
</tr>
<tr>
<td>F only</td>
<td>Premature infant B thalassemia major</td>
<td>Confirmatory testing — if persistent F only, hematology referral</td>
</tr>
<tr>
<td>AF</td>
<td>Post-blood transfusion</td>
<td>Repeat 3-4 months post-transfusion</td>
</tr>
<tr>
<td>FS</td>
<td>Sickle Cell Disease (SCD, HbSS) Sickle β thalassemia Sickle/Hereditary persistence of fetal hemoglobin</td>
<td>Confirmatory testing, referral to hematologist</td>
</tr>
<tr>
<td>FSA</td>
<td>Sickle β thalassemia SCD with transfusion</td>
<td>Confirmatory testing, hematology referral</td>
</tr>
<tr>
<td>FAS</td>
<td>Sickle cell trait Sickle β thalassemia</td>
<td>Education and genetic counseling, repeat testing at age 6 months to r/o sickle β thalassemia</td>
</tr>
<tr>
<td>FSC</td>
<td>Hemoglobin SC disease</td>
<td>Confirmatory testing, hematology referral</td>
</tr>
<tr>
<td>FC</td>
<td>Hemoglobin C disease Hemoglobin C/β thalassemia</td>
<td>Confirmatory testing, hematology referral</td>
</tr>
<tr>
<td>FE</td>
<td>Hemoglobin E disease Hemoglobin E/β thalassemia</td>
<td>Confirmatory testing, hematology referral</td>
</tr>
<tr>
<td>FAE, FAC</td>
<td>Hemoglobin variant trait</td>
<td>Education and genetic counseling</td>
</tr>
<tr>
<td>FA Bart’s</td>
<td>Silent α thalassemia carrier α thalassemia HbH disease HbH Constant Spring disease</td>
<td>If Bart’s &lt;10%, education and genetic counseling If Bart’s &gt;10%, confirmatory testing for HbH disease, referral to hematology</td>
</tr>
</tbody>
</table>

Treatment of anemia in newborns

The physiologic nadir seen in full term infants does not require intervention in asymptomatic infants. Similarly, most infants with mild-moderate anemia from the variety of etiologies described above will not require intervention. Parents should be counseled on the signs and symptoms of anemia which would require further evaluation and possible treatment.

Judicious use of PRBC transfusions should be considered in certain populations. In general, stable infants without ongoing cardiac or respiratory disease do not require transfusion until hemoglobin levels fall below 7g/dL. Table 6 summarizes basic transfusion guidelines in newborns. For infants less than 6 months of age, PRBCs should be leukoreduced, irradiated, and CMV negative to decrease the potential for complications from transfusion.

Table 6. Newborn blood transfusion guidelines (29)

| 1. Acutely bleeding infant. |
| 2. Infants with severe cardiopulmonary disease [high frequency ventilation (HFV), nitric oxide (NO), fractional inspired oxygen (FiO2) >50%, mean airway pressure (MAP) >8 cm], transfuse for hematocrit <40%. |
| 3. Infants with moderate cardiopulmonary disease [MAP 6-8 cm, FiO2 >35%], transfuse for hematocrit <35. |
| 4. Infants with mild residual lung disease [mechanical ventilation with low settings, MAP <6 cm, nasal continuous positive airway pressure (NCPAP) with FiO2 <35%, diuretic therapy, bronchodilator therapy, significant apnea or bradycardia >10 episodes in 24 hours or >2 episodes requiring bag-mask ventilation], transfuse for hematocrit <30%. |
| 5. Infants with congenital heart disease, transfuse for hematocrit <40%. |
| 6. In stable growing infants, transfuse for hematocrit <23% if reticulocyte count <5%. Consider transfusion for hematocrit <30% if patient with increased severity of apnea, bradycardia, desaturations (ABD), sustained tachycardia (>180 bpm), sustained tachypnea (>80), poor weight gain (<10 g/day in prior 4-day period with adequate calorie intake), pre-operative, post-operative. |
In summary, anemia is a commonly encountered abnormality in neonates. Diagnostic evaluation should include a thorough family history, laboratory studies including a CBC and reticulocyte count, and review of the peripheral smear. In general, stable infants with mild-moderate anemia do not require PRBC transfusion or other intervention, though additional workup, monitoring parameters, and need for transfusions should be tailored to an individual patient’s case. Referral to a pediatric hematologist is prudent for cases of persistent anemia in a newborn without a clear etiology or when an underlying hematologic disorder has been identified.

Neutrophil disorders

Macrophages are the early white blood cells produced in the yolk sac and liver during embryogenesis. Neutrophils become the primary WBC once bone marrow hematopoiesis starts around 10 – 11 weeks of embryonic development. Neutrophil disorders may be either due to a decrease in the number of neutrophils (quantitative disorders) or due to abnormal function resulting in ineffective bacterial killing (qualitative disorders). In the newborn period, the quantitative disorders are common and the qualitative disorders are very rare.

Neutropenia

Neutropenia is usually defined as absolute neutrophil count (ANC) less than 1500 in infants and children. ANC is calculated as % neutrophils + bands/100 x WBC. In the neonate however, the definition of neutropenia is not simple. Theoretically, neutropenia should be defined as an absolute neutrophil count (ANC) less than 2 standard deviation below the mean value for age. Others have defined it as neutrophil count below the 5th percentile for a specified age group. Using these concepts, Christensen and others established the following values: for neonates born at >36 weeks gestation, ANC <2700; for neonates born at 28 to 36 weeks gestation, ANC <1000; for neonates born at <28 weeks gestation, ANC <1300. Using the 2 standard deviation concept for all neonates, regardless of gestational age, neutropenia is defined as ANC less than 6000 at birth and 5000 in first week of life (see Table 7).

By the end of the neonatal period, normal ANC has decreased to that of infants and children. ANC and WBC are lower in Africans30. Decrease in ANC below normal range increases the risk of infection. The risk of infection correlates with severity (see Table 8) and duration of neutropenia.

### Table 7. Normal neutrophil count in neonates

<table>
<thead>
<tr>
<th>Age</th>
<th>Neutrophil Count/mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
</tr>
<tr>
<td>At birth</td>
<td>11,000</td>
</tr>
<tr>
<td>At 1 week</td>
<td>5,500</td>
</tr>
<tr>
<td>&gt; 1 week</td>
<td>4,400</td>
</tr>
</tbody>
</table>

### Table 8. Clinical classification of neutropenia

<table>
<thead>
<tr>
<th>Neutrophil count/mm³</th>
<th>Clinical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,500</td>
<td>Normal</td>
</tr>
<tr>
<td>1,000 - &lt;1,500</td>
<td>No significant infection risk</td>
</tr>
<tr>
<td>500 - &lt;1,000</td>
<td>Some increased infection risk</td>
</tr>
<tr>
<td>&lt; 500</td>
<td>Significant infection risk</td>
</tr>
</tbody>
</table>

A neonate with neutropenia may present with no specific signs or symptoms at birth, but may become very sick very quickly requiring aggressive clinical interventions. In this age group, the presence of neutropenia may be an indication of some intrauterine event, leading to decreased production or
increased destruction of neutrophils. It may also be as a result of neutropenia syndromes, collectively referred to as congenital neutropenias. Table 9 gives an abridged list of causes of neutropenia in the neonate.

**Table 9. Causes of neutropenia in the neonate**

1. **Deceased Production**
   - Maternal Hypertension
   - Neonates with Rh Hemolytic Anemia
   - Viral Infections
   - Donor of Twin-twin Transfusion

2. **Congenital Neutropenias**
   - Kostman Syndrome
   - Reticular Dysgenesis
   - Shwachman Syndrome
   - Cartilage-Hair Dysplasia
   - Cyclic Neutropenias

3. **Increased Neutrophil Destruction**
   - Bacteria and Fungal Sepsis
   - Necrotizing Enterocolitis
   - Allo-immune
   - Auto-immune
   - Drugs (beta-lactam antibiotics, Acyclovir)

**Neutropenia associated with maternal hypertension**

This is a very common phenomenon and it has been well described in neonates. It is short-lived and lasts no more than 1 week. It is much worse in preterm babies than in term babies.

**Rh hemolytic disease**

Neonates with Rh hemolytic anemia tend to have neutropenia as well. The severity of the neutropenia correlates well with the severity of the hemolysis. This is probably as a result of decreased production of neutrophil progenitors in the bone marrow which is synthesizing more erythroid precursors.

**Viral Infection**

A neonate with intrauterine viral infection may have neutropenia. The viral infections associated with this phenomenon include Epstein-Barr virus, cytomegalovirus, HIV, and hepatitis virus. The mechanism is selective suppression of neutrophil progenitors.

**Congenital neutropenia syndromes**

Several disorders have been described that associate neutropenia with specific syndromes. Table 10 lists some of these syndromes and their modes of inheritance.

**Severe congenital neutropenia**

This is a group of disorders that manifest as Neutropenia in the newborn period and beyond. There are several of these conditions that have been described, making them heterogenous.

In this group of conditions, the absolute neutrophil count (ANC) may be very low and assessment of the bone marrow will reveal myeloid maturation arrest. Several specific genes have been described (31).

**Kostmann syndrome**

Kostmann syndrome falls under severe congenital neutropenias. Until the exact genetic mechanism was discovered, all of these conditions were referred to as Kostmann syndrome. Dale (31) described several mutations that code for variants of this disease.

**Reticular dysgenesis**

This is a genetic condition inherited in an autosomal recessive fashion. There are several mutant alleles, homozygosity or compound heterozygosity of which will lead to the disease. Neonates present with leukopenia, neutropenia and very low Gamma-gammaglobulin levels (agammaglobulinemia or hypogammaglobulinemia).
Table 10. Neutropenia syndromes and mode of inheritance

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Mode of Inheritance</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe congenital neutropenia</td>
<td>Autosomal dominant</td>
<td>Neutropenia: Risk for MDS and AML</td>
</tr>
<tr>
<td>Kostmann’s syndrome</td>
<td>Autosomal recessive</td>
<td>Neutropenia and lymphopenia</td>
</tr>
<tr>
<td>Reticular dysgenesis</td>
<td>Autosomal recessive with multiple</td>
<td>Neutropenia, leukopenia</td>
</tr>
<tr>
<td></td>
<td>mutant alleles</td>
<td></td>
</tr>
<tr>
<td>Schwachman-Diamond syndrome</td>
<td>Autosomal recessive</td>
<td>Neutropenia, exocrine pancreatic insufficiency, bone marrow failure</td>
</tr>
<tr>
<td>Cartilage-hair dysplasia</td>
<td>Autosomal recessive</td>
<td>Neutropenia, short-limb dwarfism</td>
</tr>
<tr>
<td>Cyclic neutropenia</td>
<td>Autosomal dominant</td>
<td>Cyclic neutropenia</td>
</tr>
</tbody>
</table>

**Shwachman-Diamond syndrome**

This condition is also inherited in an Autosomal Recessive manner. It is characterized by severe neutropenia and pancreatic exocrine insufficiency. A number of these infants exhibit pancytopenia, indicating bone marrow failure.

**Cartilage-hair dysplasia**

This condition is associated with short-limb dwarfism and neutropenia. It is inherited as an autosomal recessive condition; thus is a condition seen frequently in communities that practice consanguinous marriages.

**Cyclic neutropenia**

Individuals with this condition have episodes of recurrent neutropenia that last for up to 7 days every 3 to 4 weeks. During the period of neutropenia, the individuals are susceptible to infections. It is very rare and is inherited in an autosomal dominant pattern.

**Neutropenia due to Increased Destruction**

Unlike in older children and adults, neonates with significant sepsis, particularly bacterial and fungal, often present with neutropenia. Neonates have fewer neutrophil progenitors and a diminished precursor storage pool and, as a result, neutrophils are easily depleted in stress situations.

**Necrotizing enterocolitis (NEC)**

This condition occurs when the lining of the intestinal wall dies with subsequent tissue loss. It is a disease of premature babies or sick mature babies. Although the cause for this disorder is largely unknown, it is speculated that a decrease in blood flow to the bowel keeps it from producing mucus that protects the gastrointestinal tract. It is believed that bacteria in the intestine may also contribute to the disease process. The neutropenia seen in this condition is thought to be as a result of egress of neutrophils into the intestine and peritoneum.

**Alloimmune neonatal neutropenia**

This occurs as a result of maternal-infant neutrophil antigen incompatible. In this condition, the baby has neutrophil antigens (inherited from father) which the mother does not have causing mother to be sensitized into producing neutrophil-specific antibodies against the babies neutrophils. It is estimated that about 3% of all live births have this condition, sometimes sub-clinically. The consequences of neutropenia in this case are typically mild.

**Neonatal autoimmune neutropenia**

In this condition, maternal anti-neutrophil antibodies are passively transferred to the baby in utero, causing destruction of neutrophils. Unlike in Alloimmune neutropenia where mothers have normal platelets, in this condition both mother and baby have neutropenia. This condition is also different from...
autoimmune neutropenia of infancy or childhood where in infant is making antibodies directed against its own neutrophils. The majority if babies with this condition are asymptomatic (31).

**Drugs**

One of the most common causes of neutropenia in the newborn is drug-induced neutropenia. Several mechanisms have been postulated for this phenomenon. In some cases, it is autoimmune when the drug induces the production of auto-antibodies against neutrophils. Other mechanisms include the drug directly damaging myeloid precursors. Removal of the offending drug resolves the problem.

**Evaluation of neonates with neutrophil abnormality**

Evaluation of a neonate with neutropenia should include detailed history including history of maternal infections and exposures, associated symptoms, exposure to medication, and family history. Thorough physical examination including genital and perianal examination for presence of early signs of infection is important. Patients with severe neutropenia are unable to form pus or abscess. A CBC will usually reflect the health of the bone marrow. If it is associated with anemia and or thrombocytopenia, it may indicate a generalized bone marrow failure. WBC differential can also provide very useful information about the nature of the defect.

Calculating immature to total neutrophil (I/T) ratio is of great help. IT ratio is calculated by adding bands + metamyelocytes + myelocytes divided by mature segmented neutrophils + bands + metamyelocytes + myelocytes. An elevated IT ratio (>0.3) with neutropenia may indicate utilization or increased destruction of neutrophils. IT ratio that is low or normal in a neutropenic baby may indicate bone marrow failure. In a neutrophilic infant however, normal or low IT may indicate a transient benign condition.

**Treatment of neutropenia**

The approach to the clinical management of neutropenia depends on the severity, the cause and the duration. If the neonates are critically ill, sepsis must be assumed and appropriate antibiotics instituted. In this group, reverse isolation procedures must be considered necessary.

RhG-CSF 5 micrograms/kg/d SQ daily may be given either prophylactically or during periods of febrile illness. Patients with Kostmann syndrome and severe congenital neutropenia require high doses of rhG-CSF. The dose is titrated to keep the ANC >1000. Similarly cyclic neutropenia is also treated with prophylactic rhG-CSF. Some patients with chronic Benign Neutropenia or Autoimmune Neutropenia may also need this treatment.

**Neutrophilia**

In the newborn neutrophilia is even more difficult to define precisely than neutropenia. This is probably because of the variability in WBC count in this group. When defined as 2 standard deviations above the mean, 2–3% of all normal neonates will have Neutrophilia. The most recent published report on this subject defined neutrophilia as absolute neutrophil count (ANC) >13,000 (32). However, “leukemoid” reaction has also been defined as ANC>10 standard deviations from the mean.

When neutrophilia occurs in newborns, it may be as a result of one or more four mechanisms: 1) Increased Production, 2) Accelerated Release from the Bone Marrow, 3) Neutrophil demarginalization, and 4) Diminished egress of Neutrophils from the blood into tissues. Table 11 below outlines causes of neutrophilia.

Increased production of neutrophils can occur in neonates with Sepsis and those with TORCH infections (toxoplasmosis, rubella, CMV and herpes). Increased production is the cause of Neutrophilia and Leukocytosis seen in Down syndrome. Accelerated release results in the presence of immature granulocytes in the peripheral circulation. It is therefore not unusual to find Myelocytes and Metamyelocytes in blood smears. We see accelerated release in babies treated with corticosteroids and
catecholamines. Sepsis may also stimulate accelerated release.

Neutrophils exist in two pools outside the bone marrow, the circulating pool and the marginal pool. The release of neutrophils from the marginal pool occurs in several clinical settings. It occurs as a result of the stress of delivery, as well as crying of the baby. Babies transfused with packed RBC will demarginalize their neutrophils. Treatment with catecholamines as well as Sepsis with antibiotics demarginalizes neutrophils. Neutrophils will normally egress into tissues from the blood. There are some clinical conditions that will diminish this process. The most clinically significant of these conditions is Adhesion Molecule defect which leads to marked neutrophilia and delayed separation of the umbilical cord. Treatment with steroids can also diminish egress of neutrophils (32).

**Table 11. Causes of neutrophilia**

<table>
<thead>
<tr>
<th>1. Increased Production</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Sepsis</td>
</tr>
<tr>
<td>- TORCH Infection</td>
</tr>
<tr>
<td>- Down Syndrome</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Accelerated Release from Bone Marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Treatment with Steroids</td>
</tr>
<tr>
<td>- Treatment with Catecholamines</td>
</tr>
<tr>
<td>- Sepsis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. Neutrophil demarginalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Crying</td>
</tr>
<tr>
<td>- Sepsis</td>
</tr>
<tr>
<td>- Treatment with Catecholamines</td>
</tr>
<tr>
<td>- Stress of delivery</td>
</tr>
<tr>
<td>- Packed Red Blood Cell Transfusion</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. Diminished Egress of Neutrophils into tissues</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Adhesion Molecule defect</td>
</tr>
<tr>
<td>- Treatment with steroids</td>
</tr>
</tbody>
</table>

### Management of neutrophilia

This should be focused on the primary cause of the condition. Other associated complications, such as hyperviscosity and electrolyte imbalance, seen in older children are very rare, but should be addressed.

### Conclusion

Hematology disorders of the newborn are varied and complex. A detailed history, physical examination, and supportive laboratory data are essential in identifying the underlying cause. Management issues are considered in this discussion. Consultation with specialists in hematology are needed for complex situations.

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Neonatal hematology


Neonatology and gastrointestinal issues

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Abstract

This discussion reviews gastroenterological problems that are most likely to be seen in a normal newborn nursery under the care of a general pediatrician. Conditions are divided into congenital and acquired. Congenital conditions that are considered are tracheoesophageal fistula, intestinal atresia, intestinal malrotation, and imperforate anus. Acquired conditions are gastroesophageal reflux, constipation, food allergy and failure to thrive.

Keywords: Pediatrics, neonatology, gastroenterology

Introduction

Tracheoesophageal fistula (TEF) is a congenital anomaly in which a fistulous tract connects the trachea with the esophagus. This condition is associated with esophageal atresia (EA). TEF is rare occurring in 2.86 out of 10,000 births (1). The initial presentation of TEF in the newborn period is dependent on the severity of the malformation. Symptoms include feeding intolerance, respiratory difficulty, recurrent pneumonia, and abdominal distention (2). The gastrointestinal tract forms during the fourth week of fetal development. The esophagus develops from the foregut as does part of the respiratory tract. The trachea and the esophagus separate with the formation of a tracheosophageal septum. TEF develops due to incomplete division between the trachea and esophagus.

There are five common types of TEF (see Figure 1). The most common is type C which consists of a distal TEF and esophageal atresia proximal to the fistula. Type C occurs in 84 % of cases (3). Type B is the least common occurring in only 1% of cases. With the exception of type “H”, TEF is always associated with EA. EA should be considered prenatally if polyhydramnios is found. If the atretic portion of the esophagus is located distal to the TEF, significant...
gastric distention is a presenting sign in the newborn. In addition, the fistula will allow either swallowed or gastric contents to pass into the respiratory tract leading to pneumonia. TEF is typically detected early, but with type “H” TEF, diagnosis may be delayed because of the lack of association with EA. Figure 1 delineates the types of TEF.

![Image of types of tracheo-esophageal fistulae]

Figure 1. Types of tracheo-esophageal fistulae.

There are several genetic anomalies and syndromes associated with TEF, especially Down syndrome. VACTERL (vertebral defects, anal atresia, TEF with EA, cardiac defects, renal and limb anomalies) is found in up to 10% of TEF/EA cases (4, 5).

**Diagnosis**

TEF/EA should be suspected in the newborn when there is difficulty passing a nasogastric tube. A chest x-ray will reveal a coiled nasogastric tube in the esophagus. An esophagram should be obtained to confirm the presence of EA. The “H” type TEF may pose a diagnostic challenge. A nasogastric tube is placed in the stomach and pulled back in the cephalad direction while infusing contrast material in order to identify the fistulous tract. A more definitive approach involves performing a bronchoscopy and esophagoscopy simultaneously. Methylene blue is infused into the trachea. Confirmation of a TEF is made if the methylene blue is subsequently found in the lumen of the esophagus.

**Treatment**

Surgical ligation of the fistula is the primary approach and may be performed using thoracoscopy. If there is a significant distance between the two atretic ends of the esophagus, a staged repair and possibly gastric transposition may be required (6). Gastroesophageal reflux disease (GERD) is a common problem for patients with TEF/EA occurring in up to 95% of cases. Although medical therapy may be successful in managing symptoms of GERD, up to 59% of TEF/EA patients may require a Nissen fundoplication (7).

**Intestinal Atresia**

Intestinal atresia (IA) is a rare congenital anomaly that most commonly affects the jejunum and ileum. IA occurs in 2.66 per 10,000 births (8). Duodenal atresia may be linked with chromosomal abnormalities and has a clear association with Down syndrome.
There are four types of IA, with type 3 being the most common, and type 1 the least (see figure 2) (9). Type 1, or “windsock” deformity is caused by an isolated luminal obstruction within the bowel. Type 2 is associated with a gap between two bowel segments connected by a fibrous band. Type 3A is similar to type 2, but without the fibrous band leading to two disconnected blind ends of bowel. Type 3B, also known as “Christmas tree” or “apple peel” deformity, consists of atresia at the level of the proximal small intestine with absence of mid-intestine and a coiled like appearance of the remaining small intestine. Type 4 consists of multiple areas of atresia scattered throughout the small intestine.

The pathogenesis of IA may include interruption of blood supply to the bowel during intrauterine development; intruterine volvulus and possible genetic factors given that there are familial cases of IA (10). Presentation of IA in newborns consists of feeding intolerance, abdominal distention and bilious emesis, all of which can lead to severe dehydration. Figure 2 delineates the different types of intestinal atresia.

**Diagnosis**

Imaging studies may reveal polyhydramnios on prenatal ultrasound, and a “double bubble” sign found on abdominal x-ray in newborns with duodenal atresia. A contrast study should be performed in order to confirm the diagnosis. Additional studies may be indicated to evaluate for systemic anomalies if a chromosomal disorder is suspected.

**Treatment**

Surgical resection and repair of the atretic bowel is the definitive treatment. The patient should be stabilized with nasogastric decompression prior to surgery along with correction of any electrolyte abnormalities. Delayed reanastomosis may be necessary depending on the location and extent of IA. Patients should be monitored for post-operative complications including sepsis and stricture formation.

**Intestinal Malrotation**

Intestinal malrotation (IM) is a congenital anomaly in which the normal rotation of the intestine fails to occur in utero. This process typically begins by the fifth week of gestation. The mid-gut loop will herniate into the base of the umbilical cord. The superior mesenteric artery acts as the axis separating the mid-gut pre and post-arterial segments. This loop of bowel eventually rotates a total of 270 degrees counterclockwise with eventual fixation of the bowel to the retroperitoneum. IM occurs when the bowel fails to fully rotate by 90 degrees. This can lead to the formation of Ladds bands due to the malpositioned cecum. These bands can cross over the duodenum and lead to intestinal obstruction. In addition, patients with IM are at risk for developing intestinal volvulus. IM occurs in up to 2.86 per 10,000 births (11). The incidence of volvulus in symptomatic malrotation is 42% reaching 50% outside of the newborn period (12). Bilious emesis and abdominal distention are the most common signs of IM with volvulus (13). Newborns may mistakenly be diagnosed with sepsis due to their ill appearance. It is critical to identify patients with IM with suspected volvulus as quickly as possible in order to reduce morbidity and mortality. These infants require immediate evaluation by surgery.
Diagnosis

An upper gastrointestinal contrast series is very accurate in detecting IM. A misplaced duodenum right of the Ligament of Treitz is very suggestive. A barium enema may provide supportive evidence as well revealing a misplaced cecum.

Treatment

Surgical management consists of division of the Ladd’s bands, widening the mesenteric vascular pedicle and placing the bowel in a position of non-rotation in which the small intestine and colon are repositioned to the right and left side of the abdomen respectively. In cases of volvulus, viable bowel is assessed and surgical resection may be necessary. If viability of bowel is uncertain, it may be prudent to delay resection and return for surgical exploration 24 to 48 hours later. Although the risk of future volvulus is significantly reduced post-operatively, it is still possible and should be considered if future concerns develop.

Imperforate anus

Imperforate anus refers to a spectrum of anorectal malformations. The prevalence of imperforate anus is 4.8 per 10,000 births (14). In some cases, there is a familial pattern suggesting an underlying genetic cause (15). Associated defects include urologic, cardiac and spinal cord abnormalities, including sacral agenesis. There is also a clear association between Down syndrome and anorectal malformation (16).

There are various types of imperforate anus. The most benign form is perineal fistula in which the rectum opens into a narrow orifice anterior to the center of the sphincter complex. In rectal atresia, the anus and anal sphincter are normal; however, the distal rectum is atretic. This particular form has a very favorable prognosis. Imperforate anus without fistula occurs when the rectum ends blindly (see Figure 3). The sphincter complex is usually preserved.

Anorectal malformations that involve the urogenital tract are associated with urologic defects. Vestibular fistula is the most common form of imperforate anus in females. This occurs when the rectum opens into the vestibule of the female genitalia. Rectourethral fistula is the most common defect found in males in which the rectum opens into the posterior urethra. In recto-bladderneck fistula, the rectum empties into the bladder. Cloaca is the most severe form of imperforate anus. The rectum, vagina and urethra are fused into one common structure.

Diagnosis

A thorough physical exam that includes a digital rectal exam should identify the majority of patients with imperforate anus. Once suspected, an abdominal ultrasound should be ordered to assess for associated urologic defects. In addition, an echocardiogram and sacral ultrasound should be obtained to rule out cardiac and spinal cord defects. Figure 3 depicts imperforate anus.

Treatment

An electrical stimulator is used in order to precisely define the location of the anal sphincter muscle. A posterior sagittal anorectoplasty is then performed in order to separate the rectum from the genitourinary tract. The goal is to place the rectum within the anal sphincter complex (17,18). Despite surgery, many patients will have problems with constipation and achieving fecal continence. Anorectal manometry can provide data pertaining to the anal sphincter resting...
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tone. Higher resting anal sphincter pressures were found to be good prognostic indicators for achieving continence (19).

It is important to involve the patient in a bowel management program that involves aggressive use of laxatives, enemas and toilet training (20). A system of antegrade enemas may be necessary in order to manage constipation and achieve fecal continence (21). Enema solution is infused directly into the cecum through a surgically placed cecostomy button. This approach should be considered in patients refractory to oral laxative and rectal enema treatment.

Gastroesophageal Reflux

Gastroesophageal reflux (GER) is a normal physiologic process in which gastric contents are expelled into the esophagus. Gastroesophageal reflux disease (GERD) occurs when there is GER in association with pain and/or mucosal injury. This condition is commonly caused by transient relaxation of the lower esophageal sphincter (TRLES). GER in infancy is very common occurring in up to 30% of infants at 3 months of age. It typically resolves by 18 to 24 months of age. If symptoms of GERD are persistent beyond two years of age, patients should be referred to a pediatric gastroenterologist for further evaluation as this could suggest chronic GERD or another condition (22).

Diagnosis

There are many approaches when diagnosing and treating GERD. Most newborns with GERD are diagnosed based on clinical presentation alone. Rarely is additional testing necessary. Esophageal pH-impedance 24 hour testing is the gold standard for diagnosing and quantifying the degree of GERD. This test can be performed with or without acid suppressant therapy. It enables the clinician to accurately determine symptom correlation with GER (23). This diagnostic modality may be beneficial when attempting to correlate acute life-threatening events (ALTE) and GER. ALTE in the setting of GER may be secondary to retrograde aspiration, however, GER induced reflex hypoxemia is another recognized etiology (24). An upper gastrointestinal series is generally not helpful in diagnosing GERD. It is, however, useful when evaluating a patient for anatomic abnormalities such as stricture, tracheoesophageal fistula and malrotation.

A gastric emptying study may help in the diagnosis gastroparesis. The study is typically conducted over 120 minutes or longer in duration. It can be used to screen for retrograde aspiration and is a superior test for this indication compared to esophagography (25). Esophagogastroduodenoscopy (EGD) with biopsies has become less helpful in diagnosing GERD since many patients are already on acid suppressant therapy at the time of the EGD which may mask evidence of erosive esophagitis. Endoscopy can help in distinguishing GERD from other inflammatory conditions including eosinophilic esophagitis, an allergy mediated disease that leads to inflammatory changes in the esophagus.

Treatment

Simple feeding modification to treat uncomplicated GERD is usually the first intervention before starting medication. Adding 1 tablespoon of infant rice cereal per 2 ounces of formula or breast milk may reduce the number of vomiting episodes, but does not appear to have an effect in reducing the number episodes of GER. There are anti-regurgitation formulas available that do not require the addition of infant rice cereal as a thickening agent. Prone position has been shown to reduce the number of episodes of GER; however, given the association with SIDS, infants should be placed in the supine position when asleep. An empiric trial on a hypoallergenic formula may be appropriate, especially if there are signs of milk/soy protein allergy (26).

Histamine-2 (H2) antagonists have been used successfully for the treatment of mild esophagitis. They have traditionally been used as the first line agent in the “step-up” approach to treat GERD. Tachyphylaxis (development of tolerance) is associated with H2 antagonists, and therefore, dose adjustments should be made periodically, especially with weight gain. Proton pump inhibitor (PPI) therapy is the most effective form of acid suppressant therapy when treating moderate to severe esophagitis.
There is a lack of strong evidence to support the role of prokinetic therapy in the treatment of GERD alone; however, gastroparesis confirmed using scintigraphy (gastric emptying study) may warrant the use of prokinetic drugs. Unfortunately, severe side effects have been associated with the prokinetic agent Metoclopramide including dystonia and tardive dyskinesia. Erythromycin, an antibiotic with prokinetic properties affecting motilin receptors, may be an alternative to metoclopramide, but is associated with tachyphylaxis (27). Also, intravenous administration of erythromycin during the newborn period may be linked with the development of pyloric stenosis (28).

Those patients refractory to medical therapy and have a history of ALTE or failure to thrive may require surgical intervention. A Nissen fundoplication involves wrapping the gastric fundus around the base of the esophagus improving the function of the lower esophageal sphincter. Newer therapies directed towards TLESR have involved the use of gamma-aminobutyric acid (GABA) type B receptor agonists. Baclofen has been shown to reduce the number of TLESR and improve symptoms of GERD. Other GABA (B) agonists with fewer side effects and improved tolerability are currently being studied (29).

Constipation

The Rome III criteria for functional constipation in infants and toddlers includes at least two of the following present for at least one month duration of time (30):

- Two or fewer defecations per week
- At least one episode/week of incontinence after the acquisition of toileting skills
- History of excessive stool retention
- History of painful or hard bowel movements
- Presence of a large fecal mass in the rectum
- History of large diameter stools which may obstruct the toilet

This set of criteria may have limitations in its application in infancy, especially the newborn period. For instance, many parents misperceive symptoms of infant dyschezia for constipation. Infant dyschezia is a normal physiologic process in which the infant may have difficulty coordinating pelvic floor muscle relaxation and/or generating adequate intra-abdominal pressure. This can lead to irritability and straining lasting up to 20 minutes. Although tempting, rectal suppositories should be avoided as they may help to perpetuate this process. Over time, infant dyschezia usually resolves on its own (31).

The vast majority of constipation is functional, meaning no specific organic etiology is identified. However, a history of delayed passage of meconium, unusual appearance or configuration of the anus, or prominent sacral dimple requires testing to exclude an underlying medical disorder.

Anorectal malformation occurs in about 1:5,000 patients (32). Imperforate anus can present in isolation, or associated with urogenital and spinal cord abnormalities. In one form of imperforate anus, a perineal fistula is present creating a tract between the rectum and perineum, anterior to the anal sphincter muscle. A cloaca is the most severe form of imperforate anus found in girls. This occurs when the rectum, vagina and urethra are fused together with a common opening. Surgical intervention may include an anoplasty or posterior sagittal anorectoplasty.

Hirschsprung’s disease (HD) is due to congenital absence of ganglion cells starting in the rectum and potentially involving the entire colon. In rare cases, the small bowel is involved as well. Ganglion cells are required for relaxation of the bowel, and as a result, patients with HD have chronically constricted bowel which leads to an obstruction. A newborn afflicted with HD will typically present with absent or delayed passage of meconium followed by significant abdominal distention. A timely diagnosis is necessary to avoid significant morbidity and mortality.

Diagnosis

In patients with suspected anorectal malformation, an abdominal ultrasound is necessary in order to exclude involvement of the urogenital system. In addition, patients with a prominent sacral dimple should undergo a sacral ultrasound to exclude a spinal cord abnormality (i.e. myelomeningocele, tethered cord). A barium enema has limited value when diagnosing HD in the newborn period. If HD is suspected, a suction
or full thickness rectal biopsy should be performed. In addition to absence of ganglion cells, hypertrophic nerve fibers and elevated acetylcholinesterase activity are also found on biopsy (33).

Anorectal manometry to assess for a rectoanal inhibitory reflex may have additive value as part of the diagnostic work-up, but should not be used exclusively. Anorectal manometry consists of inserting a catheter with multiple sensors, including an inflatable balloon, into the rectum. Rectal distention produced by inflating the balloon should elicit a rectoanal inhibitory reflex (RAIR) in which the anal sphincter relaxes. Absence of a RAIR is concerning for Hirschsprung’s disease (34).

Additional studies to consider may include a sweat chloride to evaluate for cystic fibrosis and thyroid function studies to rule out hypothyroidism. Testing for both conditions may already have been performed as part of the newborn screen.

Treatment

If infant dyschezia is suspected, no intervention is required. Usually, parental reassurance after a thorough physical examination is all that is necessary. If true constipation is diagnosed, careful assessment for adequate formula intake, taking into consideration vomiting secondary to GER, should be confirmed. Prior to initiating laxative therapy, adding a small amount of highly osmotic juice (i.e. prune juice) to their diet is the first step in treatment of uncomplicated constipation.

Osmotic laxatives include lactulose, PEG 3350, milk of magnesia and magnesium citrate. Lactulose has been associated with flatulence and abdominal discomfort. Although rare, magnesium citrate and milk of magnesia have been associated with magnesium toxicity. PEG 3350 has an excellent safety profile which makes it an appealing drug for long term use. Stimulant laxatives include bisacodyl and senna. Stimulants can cause abdominal cramping and long term use is possibly associated with dependency.

Suppositories and rectal enemas have not been proven to be superior to oral therapy alone (35). Chronic use of suppositories and enemas should be avoided in infants. Constant rectal stimulation in an attempt to alleviate perceived constipation in this age group can be counterproductive leading to dependency and eventual worsening symptoms of constipation and straining.

Food protein allergy

Infants with food protein allergy mount an immunologic response to the glycoprotein component of ingested food. The mechanism of food allergy is classified as either IgE or non-IgE mediated (T-cell response). Food protein induced proctocolitis is typically a non-IgE mediated allergy with onset by the first month of life (36). The prevalence of infant rectal bleeding secondary to cow’s milk protein allergy may range between 0.16% and 7.5%. There is a frequently cross-reactivity with soy protein (37).

Infants typically present with rectal bleeding. They are otherwise healthy without compromised growth and development. Food protein induced enterocolitis (FPIES) is a severe form of protein allergy, commonly associated with milk, but may also include non-dairy protein from solid food (37,38). In comparison to food protein induced proctocolitis, FPIES is associated with significant morbidity. Infants may present with hypoalbuminemia, severe diarrhea, failure to thrive and even shock. It is crucial that this condition is recognized so that the offending allergen is immediately removed from the infant’s diet. Most children outgrow these non-IgE mediated allergies by 2 years of age (39,40).

Diagnosis

In food protein induced proctocolitis, sigmoidoscopy may reveal erythema and/or lymphonodular hyperplasia. Histology may reveal an abundance of eosinophilic infiltrate. In FPIES, endoscopy of the small bowel may reveal substantial inflammation along with villus atrophy (41).

Radioallergosorbent testing is generally not helpful since these conditions are non-IgE mediated. There may be a role for atopy patch testing for non-IgE mediated allergic conditions. Oral food challenge (OFC), however, remains the gold standard for diagnosis. OFC should only be conducted in an
appropriate setting with the assistance of a pediatric allergist (42, 43). Fecal calprotectin, an inflammatory marker of the bowel, has been used to diagnose and follow infants with food protein proctocolitis (44). Hemoccult testing is less useful since infants may continue to have positive results weeks after starting a hypoallergenic diet.

**Treatment**

Infants diagnosed with cow’s milk protein proctocolitis should be refrained from further exposure to cow’s milk. Mother’s who are breast feeding should restrict their diet to exclude all dairy products. Infants that are formula fed should transition to a partially hydrolyzed formula. Transitioning to a soy based formula is not appropriate in the setting of food protein allergy since 25-60% of infants may also be sensitized to soy protein.

Infants that continue to demonstrate rectal bleeding despite transitioning to a partially hydrolyzed formula may benefit from an extensively hydrolyzed formula. The majority of infants with food protein induced proctocolitis outgrow this condition by 12 months of age (45). For patients with FPIES, carefully supervised OFC is necessary under the guidance of a pediatric allergist. Recent literature suggests that an OFC with soy be carried out between 6-8 months of age, and after 12 months of age for cow’s milk (46).

**Failure to Thrive**

There is no absolute consensus on the definition of failure to thrive (FTT). Some widely excepted parameters include infants with weight percentiles below 2%, weight for length ratio <10% or a decreased weight percentile below two or more percentile lines on the growth chart. These guidelines may not apply to patients that have other pre-existing conditions that may account for their abnormal growth parameters (i.e., genetic abnormality, prematurity). It is important to monitor growth velocity for weight, height and head circumference. Fomon et al. established expected gains in growth based on the age of the patient (see Table 1).

<table>
<thead>
<tr>
<th>Table 1. Growth parameters in the newborn</th>
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<tbody>
<tr>
<td><strong>Expected Growth Velocity</strong>25</td>
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<tr>
<td><strong>Age</strong></td>
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<tr>
<td>Preterm</td>
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<tr>
<td>0-3 months</td>
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<tr>
<td>3-6 months</td>
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<tr>
<td>6-12 months</td>
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</table>

**Diagnosis**

Infants that meet the criteria for failure to thrive should be evaluated for possibly underlying organic causes. Some conditions to consider include hypothyroidism, cystic fibrosis, congenital heart disease, genetic abnormality and metabolic disorder. A thorough history and physical exam may help guide the evaluation. Also, many states test for these conditions as part of the newborn screen.

By far, the most common cause of infant failure to thrive is inadequate caloric intake (47). Daily caloric intake may be difficult to determine when the infant’s mother is nursing. Weighing the infant before and after nursing or asking the mother to pump and bottle feed temporarily may help objectively measure the volume of breast milk given throughout the day (48). In severe cases, hospitalization may be required in order to monitor the infant’s feedings and more accurately measure nutritional intake. Enlisting the services of a social worker is necessary if there are psychosocial concerns (49).
**Treatment**

The average caloric intake for a preterm infant should be between 110-140 kcal/kg, and 108 kcal/kg for a term infant (50). If the desired calories are unattainable with standard breast milk or formula concentration (19-20 kcal/oz), fortifying breast milk or formula to 24 or 27 kcal/oz should be considered.

When insufficient caloric intake is found to be the cause of FTT, a nasogastric tube may be necessary in order to achieve adequate nutritional intake. Significant GER may lead to feeding refusal and loss of calories. Acid suppressant therapy may be indicated and in severe cases, a Nissen fundoplication may be considered.

Infant feeding disorder is commonly unrecognized. Dysfunctional infant feeding may start with an abnormal parent infant bond and lead to feeding refusal. In an attempt to promote weight gain, a rigid mechanistic forced feeding regimen may be implemented further worsening feeding refusal. Referral to psychology and an infant feeding therapist is necessary in order to end the cycle of pathologic feeding (51).

**References**


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Neonatal endocrinology

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Abstract

Normal hormone function is required for normal growth and development in the newborn period and throughout life. A variety of factors influence endocrine health including maternal factors, genetic influences, transcription factors, and enzymes. This discussion reviews major endocrine disorders in the newborn and infancy periods. Consultation with experts in pediatric endocrinology is recommended for newborns and infants with complex endocrine conditions.

Keywords: Pediatrics, neonatology, endocrinology

Introduction

Normal hormone function is essential for normal growth and development as well as normal metabolic function in newborns and infants. Early diagnosis and treatment of hormone dysfunction is therefore vital for the well-being of the newborn. A multitude of maternal factors, genetic influences, transcription factors, and enzymes influence the anatomic development of endocrine glands and their physiologic function. This review looks at a few of the main endocrine glands and endocrine disorders resulting from their dysfunction, and further discusses the recognition, causes, and management of some of the common hormone disorders seen in this age group.

Pituitary gland

The pituitary gland has a key role in regulation of normal growth and development. It is comprised of the adenohypophysis (anterior pituitary) and the neurohypophysis (posterior pituitary). The adenohypophysis is derived from stomodeal ectoderm (Rathke’s pouch) and is comprised of 3 lobes: pars anterior, intermediate and pars distalis. It constitutes...
about 80% of the pituitary gland and pars distalis houses the majority of the hormone producing cells of the anterior pituitary (1). The neurohypophysis is derived from neuroectoderm and is comprised of the hypophyseal stalk, posterior lobe (in fundibular stalk) and median eminence of the tuber cinereum. The pituitary gland of a newborn weighs about 100 mg and increases to about 600 mg in the adult (2).

Specific transcription factors are responsible for the development and differentiation of the pituitary gland and the hormone producing cells. Few of these include: HESX1, PROP1, POU1F1 and LHX3. Defects in one or more of these factors may lead to specific or multiple pituitary hormone deficiencies (3). The hormones produced by the anterior pituitary gland are under hypothalamic control and secondarily affect the function of multiple endocrine glands via a feed-back inhibition/stimulation system of physiologic regulation. The major hormones produced by the anterior pituitary gland include: growth hormone, thyroid stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), gonadotropins (FSH, LH), prolactin, and oxytocin. Concerns with growth and growth hormone are discussed in this section. The other hormone axes are covered under other sections.

**Growth in the neonatal period**

Normal function of the hypothalamo-pituitary-growth axis is essential for normal growth. Aside from disorders in this axis, genetic syndromes, osteochondrodysplasias, and several maternal factors may be responsible for abnormal growth in neonates and infants. Many disorders of growth presenting in this period which originate in utero due to maternal or placental factors may improve after birth. Intrinsic fetal defects however will likely become more obvious with time. Some of the common causes of growth disorders in this age group are listed in Table 1.

<table>
<thead>
<tr>
<th>Table 1. Common causes of growth disorders in newborns and infants</th>
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<tbody>
<tr>
<td><strong>Intrauterine growth retardation:</strong></td>
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<tr>
<td>• Primary fetal disorders:</td>
</tr>
<tr>
<td>• Osteochondrodysplasias</td>
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<tr>
<td>• Chromosomal disorders</td>
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<tr>
<td>• Syndromes with growth retardation:</td>
</tr>
<tr>
<td>• Russel Silver</td>
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<tr>
<td>• Prader Willi</td>
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<tr>
<td>• Noonan</td>
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<tr>
<td>• Others:</td>
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<tr>
<td>• Seckel Syndrome</td>
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<tr>
<td>• Progeria</td>
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<tr>
<td>• Cockayne Syndrome</td>
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<tr>
<td>• Bloom Syndrome</td>
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<tr>
<td>• Congenital infections</td>
</tr>
<tr>
<td>• Congenital disorders of the hypothalamic-pituitary-growth axis</td>
</tr>
<tr>
<td>• Primary maternal factors:</td>
</tr>
<tr>
<td>• Maternal malnutrition</td>
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<tr>
<td>• Anatomical abnormalities of the uterus limiting fetal growth</td>
</tr>
<tr>
<td>• Placental abnormalities limiting fetal nutrition</td>
</tr>
<tr>
<td>• Maternal Illness</td>
</tr>
<tr>
<td>• Diabetes mellitus</td>
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<tr>
<td>• Toxemia, hypertension</td>
</tr>
<tr>
<td>• Drugs:</td>
</tr>
<tr>
<td>• Tobacco</td>
</tr>
<tr>
<td>• Alcohol</td>
</tr>
<tr>
<td>• Illicit drug use</td>
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</tbody>
</table>
Maternal history with details of pregnancy is essential for the evaluation of growth concerns in the newborn period. History of pre-natal care, weight gain in pregnancy; maternal illnesses, endocrine conditions in the mother including diabetes, hypothyroidism and their level of management; medication and drug use in pregnancy are all important for growth evaluation in this time period. Evidence of intra-uterine growth retardation, hypoglycemia, seizures, or cardiovascular instability also may offer important insight in to the underlying etiology.

Physical examination with accurate weight and length measurements, gestational age, head circumference, skull shape, body proportions, congenital anomalies, and presence of mid-line defects, offers important diagnostic clues. Details of important history and physical features are listed in Table 2.

**Table 2. Work up for growth failure in neonates and infants**

**History:**
- Maternal history:
  - Poor prenatal care
  - Inadequate weight gain in pregnancy
- Maternal Illness:
  - Infections
  - Diabetes mellitus
  - Hypertension
  - Toxemia
  - Other underlying chronic illness
- Endocrine disorders in the mother
  - Diabetes mellitus
  - Hypothyroidism / Hyperthyroidism
- Medications and drug use in pregnancy
  - Alcohol
  - Tobacco
  - Illicit drug use
  - Chronic medications
- Symptomatic Clinical Presentation:
  - Hypoglycemia
  - Seizures
  - Cardiovascular instability

**Physical examination:**
- Length and weight for gestational age: below - 2SD
- Disproportionate growth:
  - Abnormal upper segment: lower segment ratios
  - Abnormal body proportions
  - Head: abnormal head circumference, microcephaly, macrocephaly, abnormal skull shape
  - Congenital anomalies:
  - Mid-line defects: micropenis, cleft palate, central incisor
  - Other anomalies suggestive of chromosomal abnormalities

Laboratory evaluation is based on the clinical presentation and suspicion. Neonates presenting with hypoglycemia need evaluation with a critical blood sample at the time of hypoglycemia when the plasma glucose is less than 50 mg/dl. Specific hormone evaluation in the critical sample is done for insulin, cortisol and growth hormone levels. Thyroid function tests, ketones and a comprehensive metabolic panel should be included. Further testing may include a karyotype, chromosomal microarray, and imaging including skeletal survey and MRI of the brain and pituitary gland. Diagnostic evaluation that may be needed in these neonates is summarized in Table 3.
Table 3. Laboratory investigations for growth disorders

**Lab Evaluation: Based on clinical presentation and suspicion:**
- General
  - Glucose
  - Comprehensive metabolic panel
- Endocrine
  - Free T4
  - TSH
  - Critical sample at time of hypoglycemia:
    - Serum glucose - lab confirmed at less than 50 mg/dl
    - Insulin
    - Cortisol
    - Growth hormone
    - Ketones - acetoacetate, beta hydroxybutyrate
    - Free fatty acids
    - Carnitine
    - Ammonia
    - IGFBP1
- Genetic
  - Karyotype
  - Chromosomal microarray
- Imaging
  - Skeletal survey
  - MRI of the brain and pituitary

**Management:** The management of the growth failure is based on the results of the evaluation. Supportive care and symptomatic treatment is undertaken as indicated. Hypoglycemia, seizures, and cardiovascular instability are managed as needed. Growth hormone deficiency and thyroid hormone deficiency are treated with growth hormone and thyroid hormone respectively.

**Thyroid disorders**

The thyroid gland develops from two sources namely the median anlage from the primitive pharyngeal floor and the paired lateral anlagen from the 4th pharyngobranchial pouch by day 16-17 in-utero. Fusion of the thyroid lobes and descent to the anterior neck occurs by day 50 (4). The development of the thyroid gland is dependent on transcription factors namely NKX2.1 (TTF-1), FOXE-1 (TTF-2), and PAX8 (5). Disruption in function of any of these factors may give rise to thyroid dysgenesis. The fetal thyroid gland is able to concentrate iodine by day 70 and can form thyroid hormone by 18-20 weeks. The maturation of the thyroid function is the net effect of the fetal hypothalamic-pituitary-thyroid (HPT) axis and the maternal-placental-fetal function (D).

Maternal thyroxine (T4) crosses the placenta throughout gestation and is the only source of thyroid hormone for the fetus during the 1st trimester. Preterm babies have an immature thyroid axis and consequently have lower serum T4 levels than in full term babies. The levels correlate directly with gestational age and birth weight. The HPT axis is under a negative feedback control. At birth, exposure to cold causes a TSH surge within about 30 minutes, which secondarily causes stimulation of T4 release. The TSH level then falls to < 20 mµ/ml after about 48 hours. Therefore, the newborn screen drawn before 48 hours may have false positives for an elevated TSH. The T4 levels are elevated for about one week and return to normal by about two weeks of age.

Newborn screen (NBS) for congenital hypothyroidism: Congenital hypothyroidism (CH) was one of the first conditions to be screened for on the NBS. It qualifies the prerequisites of being difficult to diagnose at birth, as newborns may be asymptomatic, and also the fact that very effective
and easy replacement therapy is available which can prevent severe neurodevelopmental consequences. Presently, NBS for hypothyroidism is offered in the United States, Canada, Europe and most developed countries. NBS programs screen for TSH, T4, or both (6).

In the USA, NBS is drawn before the baby is discharged home, preferably after 48 hours of birth, to avoid false positives. The NBS programs contact the pediatrician of record with abnormal results. Free T4 (FT4) and TSH should be repeated in all these babies. If hypothyroidism is confirmed, thyroid hormone is started immediately, preferably within the first 7-14 days of life. This is most commonly done in conjunction with an urgent consultation with a pediatric endocrinologist. It is important to remember that there may be some cases of hypothyroidism that may not be picked up on NBS. TSH only programs will not detect babies with central hypothyroidism as TSH will not be elevated. Therefore any baby with suspicion for hypothyroidism should have FT4 and TSH done even if the NBS had been normal. Some of the common thyroid function concerns in the newborns and infants include (4):

- Newborn screening and Congenital hypothyroidism
- Hypothyroxinemia in preterm babies
- Neonatal goiter and Neonatal thyrotoxicosis
- Babies born to mothers with thyroid disease

**Congenital hypothyroidism**

The incidence of congenital hypothyroidism (CH) is about 1: 3,000 - 4,000 newborns and there is a female preponderance with a female: male ratio of 2:1. Geographic and ethnic variations in incidence of CH are also known. CH may result commonly from anatomical defects in the thyroid gland (thyroid dysgenesis) or may be due to defects in thyroid hormone formation (dyshormonogenesis). Central hypothyroidism and transient hypothyroidism are relatively less common Table 4 (4).

**Clinical presentation:** The majority of newborns are asymptomatic because of the protective effects of the maternal thyroid hormone crossing the placenta. Anthropometric measurements including birth weight and length are generally normal. Within a few days of birth, undiagnosed hypothyroidism may become symptomatic with lethargy, feeding difficulties, constipation, prolonged jaundice, hoarse cry, macroglossia, umbilical hernia, enlarged head circumference and anterior fontanel, hypothermia, and dry skin. The posterior fontanel may be open at birth and there may be delayed skeletal maturation. Thyroid enlargement/goiter may be noted in dyshormonogenesis. Overall a higher incidence of other congenital anomalies is also noted in infants with congenital hypothyroidism. Therefore in countries with NBS in place, it is extremely rare to see babies with symptomatic congenital hypothyroidism; however, symptomatic infants due to hypothyroidism are not uncommon in developing countries where NBS is still not routine.

**Table 4. Common causes of congenital hypothyroidism and their incidence**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence</th>
</tr>
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<tbody>
<tr>
<td>Thyroid dysgenesis</td>
<td>1:4,000</td>
</tr>
<tr>
<td>Thyroid dyshormonogenesis</td>
<td>1:40,000</td>
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<tr>
<td>Central hypothyroidism</td>
<td>1:20,000</td>
</tr>
<tr>
<td>Transient hypothyroidism</td>
<td>1:10,000</td>
</tr>
</tbody>
</table>

**Laboratory testing:** Thyroid function tests including total or free thyroxine levels (tT4; FT4) and TSH are done for confirmation of thyroid function status in babies who have an abnormal NBS and in those with suspicion of thyroid dysfunction. It is important to remember that thyroid hormone levels be evaluated in context of age appropriate reference ranges. Thyroxine levels are relatively higher in the first few weeks of life. A low FT4 and an elevated TSH confirms the diagnosis of primary hypothyroidism. Central hypothyroidism is characterized by a low FT4 with an inappropriately normal or low TSH.

Sub-clinical or compensated hypothyroidism is significant for a normal FT4 and slightly elevated TSH. Thyroid gland imaging with a thyroid ultrasound and a radio-nucleotide uptake scan may be undertaken but not routinely recommended as it does not alter treatment options, but in fact may cause delay in initiation of treatment. However, imaging may be helpful in delineating an underlying etiology for congenital hypothyroidism.
**Treatment:** Thyroid hormone replacement is the treatment of congenital hypothyroidism. Thyroid hormone is initiated within 7-14 days at a dose of 10-15 mcg/kg/day, administered as single dose, preferably at least half hour before a feed. FT4 and TSH are followed every 2-4 weeks for about the first two months. The dose of thyroid hormone is titrated based on these levels. Then TFTs are repeated every 2-3 months over the first year and every 3-4 months till 3 years of life, after which they may be checked every 6 months as needed.

**Hypothyroxinemia in preterm babies**

Hypothyroxinemia in preterm babies is characterized by low T4 and normal TSH levels. There are no clear recommendations for treatment of this hypothyroxinemia (7). However, FT4 and TSH should be closely followed to exclude primary and central hypothyroidism, and concerns for possible hypopituitarism should be investigated if indicated.

**Neonatal goiter**

Thyroid gland enlargement/goiter may be noted as an incidental finding on a prenatal ultrasound or on routine physical exam of the newborn. Clinical features of euthyroidism, hypothyroidism, or hyperthyroidism may be noted in the presence of a goiter. Thyroid enlargement may also be associated with sensory-neural hearing deficits as in Pendred syndrome. FT4 and TSH should be done to evaluate the thyroid function status. Close monitoring and treatment for hypo or hyperthyroidism should be undertaken as indicated and discussed earlier.

**Neonatal Graves’ disease**

Graves’ disease in the neonate may develop due to the trans-placental transfer to the newborn of TSH-receptor-stimulating immunoglobulins (TSI) from a mother with active/inactive Graves’ disease. High levels of TSI measured in the mother during pregnancy may indicate a high risk of neonatal Graves.’ The coexistence of TSH receptor blocking antibodies (TRBA) may initially negate the effect of TSI but may cause late onset neonatal Graves’ disease. Careful monitoring for fetal tachycardia and fetal goiter may lead to early in-utero diagnosis. Anti-thyroid medications administered to the mother during pregnancy result in successful treatment of the fetus. Ongoing monitoring, interpretation of frequent thyroid function tests and necessary treatment is continued after birth under guidance of a pediatric endocrinologist. High risk perinatologists should monitor and treat these pregnancies. Clinical features in the newborn with Graves’ disease may include: irritability, jitteriness, flushing, tachycardia, hypertension, goiter, exophthalmos, icterus, hepatosplenomegaly, thrombocytopenia, and even heart failure. There is a high risk of morbidity and mortality in these patients. Thyroid function tests (FT4, TSH, and T3) are monitored closely and reflect the overall effect of: TSI, TRBA and anti-thyroid medications. The effect of the maternal TSI on the infant’s thyroid function may need to be followed for up to 5-6 months of age.

Management: The treatment options address symptomatic concerns as well as specific medications to decrease the amount or effect of thyroid hormone. Iodide (Lugol’s iodine) and anti-thyroid medications (propylthiouracil and methimazole) are used for inhibiting further thyroid hormone synthesis and/or secretion from the thyroid gland. Doses of these medications are carefully adjusted to achieve the desired effect. Glucocorticoids may be helpful as well. Supportive treatment needs may include sedatives, propranolol, and digoxin as indicated by the clinical scenario.

**Babies born to mothers with thyroid disease**

Maternal hypothyroidism: If there is history of maternal hypothyroidism, further details of the cause and status of the hypothyroidism during pregnancy need to be sought. The underlying cause of maternal hypothyroidism is important for evaluation in the baby. If the mother has congenital hypothyroidism due to dysgenesis or dyshormonogenesis, the risk of inheriting congenital hypothyroidism is about 5%. These patients will be picked up on NBS. The mother may have autoimmune thyroid disease with acquired
hypothyroidism (Hashimoto’s thyroiditis) or iatrogenic hypothyroidism secondary to treatment for Graves’ disease. TSH receptor antibodies (inhibitory antibodies for Hashimoto’s or stimulatory antibodies for Graves’ disease) may be transmitted via the placenta to the fetus, causing hypothyroidism and rarely hyperthyroidism in the newborn.

Although the risk of neonatal thyroid dysfunction is low, if the antibody titers are high or not known, thyroid function tests may be done to confirm the thyroid status. Serial measurements may need to be done in the baby for about 3-5 months. Appropriate treatment for hypothyroidism or neonatal hyperthyroidism will need to be instituted.

Maternal Graves’ disease: The mother with Graves’ disease has TSH receptor stimulatory antibodies (TSI) which can cross the placenta and cause stimulation of the fetal and the neonatal thyroid gland and may cause thyrotoxicosis. This scenario is complicated further by treatment of the mother’s Graves’ disease. If the mother is on anti-thyroid medications, they too will cross the placenta and suppress the fetal hyperthyroidism, until they are cleared from the newborn’s blood stream, generally by the end of the 1st week of life.

The mother may have coexistent TSH receptor inhibitory antibodies also and this may also complicate the neonate’s thyroid function status further. The mother who has a history of Graves’ disease which has been treated in the past with Radioactive Iodine (RAI) or thyroidectomy, and now has hypothyroidism, and is on thyroid hormone replacement is another scenario that needs to be monitored carefully. TSH receptor antibodies may persist for a long time in these mothers, and this may predispose their babies to neonatal thyrotoxicosis as well. Careful monitoring of thyroid function every 1-2 weeks in these neonates may be needed in the first few weeks of life.

**Adrenal gland**

The adrenal gland in the fetus is comprised of 3 zones:

- Inner fetal zone: produces DHEAS
- Transitional zone: produces glucocorticoids
- Outer definitive zone: produces mineralocorticoids and is the store for progenitor cells

Adrenocorticotropic hormone (ACTH) from the pituitary gland as well as corticotropin releasing hormone (CRH) and ACTH from the placenta are believed to control the adrenal function in the fetus. The fetal adrenal gland undergoes significant changes in size after birth. The fetal zone, which comprises 80% of the adrenal cortex at term, rapidly decreases in size after birth. Steroidogenic factor 1 (SF1) and DAX1 (dosage sensitive sex-reversal (DSS), adrenal hypoplasia congenita (AHC) critical region on the X-chromosome, gene 1) have been recognized as two of the several important transcription factors for the development and differentiation of both the adrenal glands and the gonads (8).

Mutations in SF1 and DAX1 are known to cause various defects resulting in adrenal failure and gonadal disorders. CRH from the hypothalamus stimulates ACTH secretion from the pituitary which in turn stimulates the adrenal hormone pathway. The HPA axis slowly matures over the first few months after birth. The diurnal rhythm of cortisol secretion is developed by 8-12 weeks of age. The cortisol production rate is about 8 mg/m2/day in term infants although there is variability among individuals (9).

**Adrenal failure**

Adrenal failure may be primary when the defect is at the level of the adrenal gland, secondary or tertiary (central) when the defect is at the level of the pituitary or hypothalamus respectively. Common causes of adrenal failure in this age group are listed in Table 5.

Clinical manifestations of adrenal insufficiency (AI): The clinical presentation of AI may be variable and depend on the severity of the adrenal insufficiency as well as on the particular adrenal hormones that are deficient. Nonspecific symptomatology of AI includes: nausea, vomiting, abdominal pain, lethargy, fatigue. Glucocorticoid deficiency may present with hypoglycemia; mineralocorticoid deficiency manifests as salt wasting with hyponatremia, hyperkalemia, metabolic acidosis, dehydration and weight loss; high ACTH/POMC may
result in hyperpigmentation (noticeable in scrotal sacs, linea nigra, and skin creases).

Table 5. Common causes of adrenal failure in neonates and infants

A. Primary Adrenal Failure
   a. Congenital adrenal hyperplasia (CAH)
   b. Lipoid CAH
   c. Adrenal hypoplasia congenita (AHC)
   d. Adrenoleukodystrophy (ALD)

B. Central Adrenal Failure
   a. ACTH deficiency
   b. ACTH resistance/Familial glucocorticoid resistance
   c. Iatrogenic
      i. High dose glucocorticoid therapy
      ii. Steroid therapy given to the mother
      iii. Maternal Cushing’s syndrome

Adrenal crisis is a severe presentation of acute adrenal insufficiency and babies may present in shock. Other associated clinical manifestations may be seen based on the underlying etiology. Ambiguous genitalia may be noted in female newborns with congenital adrenal hyperplasia (CAH) due to 21 hydroxylase deficiency.

Diagnostic evaluation: A high index of suspicion is entertained for patients at high risk for AI. The aim of the diagnostic workup is to: confirm the diagnosis of AI; to determine whether it is primary or central, and also to investigate for underlying etiology for the adrenal insufficiency.

Initial screening laboratory workup includes an electrolyte panel, cortisol and ACTH levels. If there is suspicion for CAH, precursors of the adrenal hormone pathway will need to be evaluated along with renin and aldosterone.

The ACTH stimulation test is diagnostic and is the main test used: confirm the diagnosis of AI; to differentiate between central and primary AI; and to diagnose CAH. There are 2 types of ACTH stimulation tests available: 1) Low dose (1mcg ACTH/m2) stimulation test is done for central AI and 2) High dose ACTH stimulation test (250 mg/m2) is done for confirming suspicions of primary AI as well as for the diagnosis of CAH. Cortisol levels and profiles of the adrenal hormone pathway precursors are evaluated as per protocol for this test.

Management: Neonates and infants with primary adrenal insufficiency require replacement hormone therapy with glucocorticoids and mineralocorticoids while babies with central AI require only glucocorticoid replacement. Hydrocortisone is the only glucocorticoid recommended for treatment of AI in this age group because of shorter duration of action and lower potency and therefore the expectation of less effect on causing growth suppression. It is also recommended that the tablets be used instead of a suspension formulation because of the risk of erratic dosing.

Normal physiologic hydrocortisone replacement is about 10-15mg/m2/day. Higher doses may be needed and further dose titrations are based on clinical and/or biochemical monitoring. In general, children with CAH may require higher doses of hydrocortisone than those with AI due to other causes. The glucocorticoid dose in CAH can be evaluated based levels of 17 hydroxyprogesterone, androstenedione, and testosterone. Infants with AI are unable to mount a cortisol stress response on exposure to physiologic or medical stress, and therefore require increased glucocorticoid dosing in these circumstances. Based on the severity of stress (mild, moderate, or severe), the families are directed to increase the hydrocortisone dosing to 2-5 times the normal physiologic requirement during times of stress. The families are also trained to administer intramuscular hydrocortisone injection if the child is unable to take or tolerate oral hydrocortisone, and then seek medical attention.

High stress dose steroid therapy is also indicated for surgical procedures and various dosing protocols exist for these situations usually incorporating an intravenous (IV) hydrocortisone dose before the procedure followed by IV bolus every 4-6 hours or IV infusion of hydrocortisone after the procedure. The dosing method selected depends on type and duration of surgery as well as convalescence expected.

In adrenal crisis, IV fluids with saline and dextrose is indicated for hydration, hypoglycemia, and also for addressing any electrolyte imbalances. Stress dose IV hydrocortisone therapy is also given. Mineralocorticoid replacement is needed in babies with primary AI and in those with salt wasting CAH.
This is done by giving fludrocortisone, usually 0.1-0.2 mg daily. Extra dosing of mineralocorticoid is not required during stress as the stress dose of hydrocortisone has sufficient mineralocorticoid activity as well. The dose of fludrocortisone can be monitored by plasma renin activity levels and clinical monitoring of hydration, salt craving, and serum sodium and potassium levels. Neonates and infants also require extra salt supplementation as their dietary intake (breast milk, formula) during this period does not have sufficient salt. This is usually achieved by giving extra salt (about 1 gram) daily, diluted in water and distributed in formula over the day.

Newborns with CAH are managed as described above for AI and salt wasting. If the neonate is high risk for CAH because of preliminary lab work, ambiguous genitalia or clinical suspicion with positive family history, ACTH stimulation testing or repeat lab work is required. Close monitoring is essential for clinical well-being as well as for hydration and electrolytes status. The baby may need empiric treatment until definitive results are obtained to either confirm or rule out CAH. In 21 hydroxylase deficiency CAH, female newborns may have varying degrees of genital ambiguity with virilization. Decisions about corrective surgical procedures are more complex and need a multidisciplinary approach for discussion with the family.

Reproductive system

Embryology, anatomy, and physiology: Sex determination is the process by which the primordial gonad develops into a testes or an ovary and sex differentiation is the process of development of the internal reproductive structures and the external genitalia. These processes are dependent on a series of events occurring in a specific sequence. Irrespective of genotype (46 XX or 46 XY), the human embryo prior to seven weeks gestational age possesses bipotential germ tissue with both Wolffian and Mullerian ducts (10,11). The presence of SRY (sex determining region of Y) results in the triggering of a cascade of events which results in male or female gonadal differentiation (12). Aside from SRY, transcription factors and hormones like testosterone, dihydrotestosterone, and mullerian inhibitory substance (MIS) are responsible for the differentiation of the internal and external genitalia.

Mini-puberty of infancy

In the normal physiological functioning after birth an activation of the hypothalamo-pituitary-gonadal (HPG) axis has been well recognized and this is referred to as the mini-puberty of infancy. FSH, LH and sex steroids (testosterone and estradiol) are low in the neonatal period. After the initial fall over the first 2 weeks of life, there follows a rise in the FSH and LH levels accompanied by a rise in testosterone in boys and estradiol in girls. This process lasts for a few months in males and up to about 2-3 years in females. Subsequently, the levels fall and there is a quiescence of the HPG axis till onset of puberty (13). This mini-puberty seems to be important for later pubertal development and also the absence of specific hormonal changes in this time period may be seen in some disorders of sexual differentiation.

Disorders of sexual differentiation (DSD)

Disorders of sexual differentiation (DSD) refer to medical conditions wherein there are concerns with atypical chromosomal, gonadal or anatomic sex. The nomenclature and classification of disorders of sexual development is summarized in Table 6 (14).

<table>
<thead>
<tr>
<th>Table 6. Nomenclature and classification of disorders of sexual development</th>
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<tr>
<td>46, XY DSD:</td>
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<tr>
<td>- Male pseudohermaphrodite</td>
</tr>
<tr>
<td>- Undervirilization/ Undermasculization of XY male</td>
</tr>
<tr>
<td>46, XX DSD:</td>
</tr>
<tr>
<td>- Female pseudohermaphrodite</td>
</tr>
<tr>
<td>- Over-virilization/ Underfeminization of an XX female</td>
</tr>
<tr>
<td>Ovo-testicular DSD: True hermaphrodite</td>
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<tr>
<td>46, XX testicular DSD:</td>
</tr>
<tr>
<td>- XX male</td>
</tr>
<tr>
<td>- XX sex reversal</td>
</tr>
<tr>
<td>46, XY complete gonadal dysgenesis: XY sex reversal</td>
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Most of these are complex disorders requiring a multidisciplinary approach for management. The team comprises of: primary pediatrician/neonatologist, endocrinologist, geneticist, psychologist, urologist, medical social worker in addition to full participation of parents and family. Further discussion for these complex disorders including sex assignment is beyond the scope of this chapter.

**Common newborn endocrinologic conditions**

The ensuing discussion will focus on some common newborn conditions in this regard including premature thelarche of infancy, undescended testes, hypospadias, and the approach to a newborn with ambiguous external genitalia.

**Premature thelarche of infancy.** Premature thelarche of infancy is a common condition in which isolated breast development occurs during the first two years of life without other associated pubertal changes. Thelarche may be unilateral or bilateral and may be asymmetrical. The breast tissue often regresses by 24 months of age. Counseling and reassurance usually suffices for managing this self-limiting condition. Failure of breast tissue regression by 24 months of age should warrant a referral to a pediatric endocrinologist for evaluation and possible work up as indicated, mainly to rule out precocious puberty.

**Undescended testes (cryptorchidism):** Cryptorchidism describes the failure of testes to descend completely into the scrotum. It is more common in preterm infants and may often be unilateral. It should be differentiated from retractile testes which can be manipulated down into the scrotum. Prader-Willi and Laurence- Moon- Biedl syndromes have a higher incidence of undescended testes. Hence, physical examination looking for features of these syndromes is important. Referral should be multidisciplinary to both a pediatric surgeon/urologist and a pediatric endocrinologist. Treatment consists of surgical procedures to bring the testes down into the scrotum, referred to as orchidopexy. Delayed management beyond one year of age may be associated with an increased risk of testicular malignancy.

**Hypospadias:** Hypospadias refers to the position of the urethral meatus on the ventral side of the penis. It ranges in severity from glanular to penile to perineal to penoscrotal to perineal locations. It is commonly associated with a chordee or a downward curvature of the penis. Though most cases are idiopathic, there may be rare association with an endocrine disorder. Referral to a pediatric surgeon is necessary and also should be considered to a pediatric endocrinologist if micropenis, cryptorchidism, or scrotal abnormalities are present. Neonatal circumcision should be delayed as the foreskin may be necessary for surgical repair.

**Ambiguous genitalia:** Ambiguous genitalia is a complex condition in newborns which may have significant long term implications. The approach to a baby with ambiguous genitalia incorporates details of history, physical examination and biochemical and radiologic investigations for an accurate diagnosis and consequent appropriate management. This is also one of the important medical conditions in pediatrics requiring a long-term multidisciplinary approach.

Most babies with ambiguous genitalia may not have a significant positive history. Pertinent positive points in history should include (15):

- History of parental consanguinity
- History of unexplained neonatal deaths in the family
- Maternal ingestion or exposure to drugs such as anabolic steroids
- Use of progestagen containing drugs which may be associated with a higher likelihood of producing a male offspring with genital anomalies
- Known positive family history of a disorder associated with ambiguous genitalia such as partial androgen insensitivity syndrome

Aside from general physical examination of a newborn, focus on presence of other congenital anomalies and a detailed examination of the external genitalia is important.

Careful inspection and genital palpation is the first step. Swellings may be visible in the inguinal region or labioscrotal folds. Gonads which are palpable externally are usually testes, as ovaries remain in the pelvis. Stretched phallic length should be compared to appropriate normal reference values.
The presence or absence of chordee should be noted, along with the number and location of the orifice(s) either on dorsal or ventral surface of the phallic structure. The degree of labioscrotal fusion is important for evaluation of the level of virilization which may indicate exposure to androgens.

Evaluation includes looking for presence of scrotal fusion, posterior fusion of labia majora, and for the presence of partial fusion of the hemiscrotum.

Various scoring systems such as the Prader staging system for evaluation the degree of virilization may be used for an accurate description of the ambiguous genitalia (16).

The aim of laboratory testing is to evaluate the hormonal function and genetic testing for a karyotype.

**Determination of hormonal levels**

- 17 OH progesterone, testosterone, serum gonadotropins (FSH, LH)
- Mullerian inhibiting substance (MIS), Inhibin B
- Human Chorionic Gonadotropin (HCG) stimulation test: if needed - to confirm the presence of testicular tissue
- Testosterone/ dihydrotestosterone (T/DHT) ratio – for 5 alpha reductase deficiency.

**Chromosome analysis**

- FISH for SRY (sex- determining region of the Y)
- Chromosomal analysis: for genetic sex: XX, XY or mosaic pattern.

**Radiologic investigations**

- Ultrasonography (USG): The USG should evaluate for the inguinal, perineal, renal, and adrenal regions. It is useful to evaluate for the presence of a uterus and intrabdominal gonads.
- Urogenital sinogram: to delineate the anatomy of the urethral and vaginal areas.

**Chromosomal disorders**

Some chromosomal disorders may cause atypical sexual development by affecting gonadal differentiation and include:

- Turner syndrome (XO).
- Klinefelter syndrome (XXY)
- Complete and incomplete forms of XX and XY gonadal dysgenesis and
- Individuals with both testicular and ovarian tissue (true hermaphroditism).

These disorders may rarely manifest features of hypogonadism in the neonatal period but more commonly in childhood with concerns about poor growth, testicular size or anatomy of the genitalia, or later with concerns about delayed puberty.

**Metabolic concerns**

The following section includes a discussion on some common metabolic abnormalities seen in neonates and infants.

**Hypoglycemia**

Hypoglycemia, relatively common in the neonatal period is defined as plasma glucose of <50 mg/dl (17). Hypoglycemia may be further categorized as i) transient or ii) persistent based on duration. Transient forms of hypoglycemia usually occur in premature and small for gestational age infants. It usually represents an inadequate physiologic response to a fall in blood glucose in these babies attributed to the immaturity of the gluconeogenic and ketogenic metabolic pathways. The persistent forms of hypoglycemia have diverse etiologies which include: disorders of gluconeogenesis, disorders of ketogenesis, glycogen storage diseases, hypopituitarism with growth hormone and cortisol deficiencies.

Persistent hyperinsulinism is the commonest cause for persistent neonatal hypoglycemia (17,18). This is caused by congenital defects of insulin regulation. Various genes encode proteins which are
integral to insulin production and mutations of these genes may be associated with hyperinsulinism. The common causes of neonatal hypoglycemia are listed in Table 7.

Symptoms of hypoglycemia may be classified as adrenergic which are due to increased release of adrenergic agents, or neuroglycopenic which are caused by a decrease in cerebral glucose and oxygen availability. Clinical features of neonatal hypoglycemia may be non-specific with features such as cyanosis, apnea, respiratory distress, poor feeding, nausea, vomiting, sweating, and hypothermia. Coma and convulsions may also occur.

It is important to make an accurate diagnosis to ensure appropriate treatment. The history details should include symptoms of hypoglycemia, feeding pattern around the time of hypoglycemia, more specifically the occurrence of these symptoms in relation to the timing of feeds as hypoglycemia due to hyperinsulinism or a glycogen storage disorder will present with the neonate wanting to feed more frequently.

In order to evaluate for SGA it is important to know the gestational age. Other historical data includes: medication use in the neonatal period such as beta blockers and oral hypoglycemic; tocolytics such as terbutaline which may be associated with hypoglycemia. Defects in gluconeogenesis, growth hormone deficiency, or adrenal insufficiency may be associated with hypoglycemia occurring after more than 8 hours of fasting.

On physical examination suspicious features include: macrosomia (infant of diabetic mother); hepatomegaly, which may be present in some glycogen storage diseases; jaundice, nystagmus, midline defects such as micropenis, and midline facial defects such as central incisor which may be associated with pituitary hormonal insufficiencies.

Laboratory evaluation: The critical diagnostic test is a blood sample obtained at the time of the hypoglycemic episode to evaluate for hormones and metabolites that are involved in maintaining normal blood glucose. This is detailed in Table 3. Further studies are based on results obtained. If there is documented hyperinsulinism, genetic testing is available to evaluate for an underlying defect. PET scan using 18 F fluoro- L-DOPA is also used to assess for genetic defects in insulin production.

Table 7. The common causes of neonatal hypoglycemia

- Transient neonatal hypoglycemia
  - Prematurity
  - Small for gestational age infants
  - Infant of a diabetic mother
  - Peripartum stress:
    - Birth asphyxia
    - Maternal toxemia and pre-eclampsia

- Persistent neonatal hypoglycemia
  - Hypopituitarism
  - Adrenal insufficiency
  - Inborn errors of metabolism (associated with glucose metabolism)
    - Glycogen storage diseases
    - Gluconeogenesis
    - Ketogenic
  - Congenital hyperinsulinism
    - ATP sensitive K channel hyperinsulinism
    - Glutamate dehydrogenase hyperinsulinism
    - Glucokinase hyperinsulinism
    - Short chain 3-hydroxyacyl CoA dehydrogenase

- Galactosemia
- Hereditary fructose intolerance
- Fatty acid oxidation defects
**Treatment:** Blood glucose levels should be closely monitored in newborns at high risk for hypoglycemia. This may be measured soon after birth, every 2 hours after that, prior to feeding, and also at the time of any suggestive symptoms. In the preterm or sick neonate, where enteral nutrition is not possible, an intravenous dextrose infusion should be administered to provide a glucose infusion rate of at least 5 mg/kg/min. In the acute setting, prior to commencing a dextrose infusion, a slow bolus of 10% dextrose may be given. The glucose infusion rate is titrated to keep blood glucose levels above 70 mg/dl.

In addition more specific management to address the underlying etiology needs to be initiated. This may include: hydrocortisone therapy for adrenal insufficiency; growth hormone treatment for growth hormone deficiency; specific treatment for any underlying inborn errors of metabolism. If there is evidence of hyperinsulinism medical management is initiated. If the neonate is tolerating oral feeds, diazoxide at a dose of 5-15 mg/kg/day divided into three doses may be initiated. Fluid retention is a possible side effect of therapy. If there is no response, octreotide at a dose of 5-25 µg/kg/day as a continuous infusion or subcutaneously divided into three or four dose per day may be used (19). For intractable hypoglycemia, a glucagon drip at a dose of 1-20 µg/kg/hr may be effective (20). Hypokalemia and vomiting are potential side effects of this therapy.

If medical management is not successful, surgical intervention in the form of partial or sub-total pancreatectomy may need to be undertaken. Potential complications include development of diabetes later in life.

**Hyperglycemia**

Neonatal hyperglycemia is not clearly defined however; in healthy term babies a glucose level of greater than 126 mg/dl is unusual. Hyperglycemia is uncommon in term infants. It is more common in very preterm or small for gestational age babies. Factors such as impairment of insulin secretion and/or insulin resistance coupled with an immaturity of the liver enzymes contributing to gluconeogenesis can contribute to its occurrence in preterm and small for gestational age (SGA) babies.

Neonatal diabetes mellitus is a very rare disorder with its incidence occurring between 1:400,000-1:500,000 live births that may cause hyperglycemia (21). Other common causes of neonatal hyperglycemia include: iatrogenic from excessive intravenous glucose delivery, impaired glucose homeostasis in preterm/small for gestational age babies; sepsis; stress; and the use of drugs such as corticosteroids, theophylline, caffeine, dopamine and diazoxide.

Neonatal diabetes mellitus may be classified into the following two main types based on the resolution or persistence of the condition by 18 months of age:

- Transient neonatal diabetes (TNDM)
- Permanent neonatal diabetes (PNDM)

Most patients (70%) with TNDM have anomalies in chromosome 6q24. In contrast, the etiology of PNDM is more heterogeneous with causes including mutations in the gene encoding the ATP-sensitive potassium channel subunit Kir 6.2. This mutation is noted in 32-64% of cases and it may be associated with neurological manifestation in the DEND (developmental delay, epilepsy, and neonatal diabetes) syndrome (22). In other cases various transcription factors contribute to causing a defect in insulin production and diabetes in this case may present with non-pancreatic problems such as can be seen in the IPEX syndrome (Immune dysregulation, Poly-endocrinopathy, Enteropathy, X linked) which is a syndrome characterized by exfoliative dermatitis, diarrhea with villous atrophy, hemolytic anemia, autoimmune thyroid disease, and neonatal diabetes mellitus (23).

It is important to make an accurate diagnosis to ensure appropriate treatment. Details of the history should include body temperature pattern, gastric aspirate quantification if the infant is feeding and any changes in the peripheral perfusion of the infant. Important also, are history of medication use in the infant as well as in the mother and a familial history of diabetes. Maternal drugs such as diazoxide may contribute to neonatal hyperglycemia whereas the use of caffeine, theophylline, corticosteroids and phenytoin in the infant may be associated with hyperglycemia. Pertinent features on physical
examination such as skin mottling may be seen in babies with underlying sepsis.

**Laboratory:** Serial blood glucose measurements are important. Glucose infusion rate should be calculated in order to exclude excessive glucose delivery as the cause. Insulin level, c-peptide, and ketone bodies are important in neonates with diabetes. Genetic testing should be considered if hyperglycemia presents prior to 6 months of age, as neonatal diabetes which is a distinct entity from Type I diabetes is a strong possibility. Diabetes antibodies including: insulin auto-antibodies, islet cell antibodies (ICA512 antibodies), and glutamic acid decarboxylase (GAD) antibodies are helpful for diabetes presenting greater than 6 months of age as auto-immunity is the major cause of diabetes in these cases.

**Treatment:** If hyperglycemia is caused by sepsis, then the cause of the sepsis should be treated. Consideration should be given to an insulin drip if blood glucose remains greater than 180 mg/dl. Blood glucose should be monitored every hour if an insulin drip is in place and serum potassium levels should also be followed closely. Diluted rapid acting insulin may be administered subcutaneously for definitive management. Other options for treatment include continuous subcutaneous insulin infusion (CSII) which may achieve better control.

**Disorders of sodium metabolism**

Hyponatremia is defined as a serum sodium level of less than 133-135 mEq/L. Several homeostatic mechanisms influencing sodium balance may be immature thus predisposing this age group to hyponatremia. Prematurity is associated with high insensible water losses through the skin and respiratory tract. Environmental factors such as vapor pressure and humidity may also contribute to water loss through the skin (24). Renal immaturity also manifests with a reduced number of sodium transporters and a lower re-absorptive capacity causing sodium loss in the urine and contributing to hyponatremia. The clinical correlate of this is that preterm babies have a higher fractional excretion of sodium than term infants. Premature babies less than 32 weeks gestation also have defects in sodium re-absorption at the proximal tubular level causing natriuresis (25). In the neonatal period, there also exits partial physiological resistance to aldosterone (26). Neonatal kidneys have limited urine concentration capability which gradually normalizes by 3-6 months of age. Diminished medullary urea accumulation, increased medullary blood flow, decreased tubular ADH responsiveness coupled with a short loop of Henle are also other features which contribute to an inefficient countercurrent multiplier system (27).

Therefore sodium abnormalities in the neonate may be related to: postnatal age as this may affect glomerular filtration rate (GFR) and; gestational age which contributes to renal maturity which may be associated with a risk of salt loss. The factors contributing to hyponatremia can be classified under:

- **Factors associated with excess free water:** These include: iatrogenic causes such as maternal IV fluid administration prior to delivery, renal failure, and Syndrome of Inappropriate ADH (SIADH) which may result from intracranial pathology as may be seen with central nervous system injury from meningitis and birth asphyxia.
- **Factors associated with salt depletion:** These include: immaturity, congenital adrenal hyperplasia, renal impairment such as may be seen in acute tubular necrosis (ATN), Bartter syndrome (may be associated with hypokalemia), gastrointestinal tract losses (secretory diarrhea), and aldosterone deficiency (28).

Important factors in evaluation include assessment of previous fluid intake with attention to the newborns age and maturity and close monitoring of urine output. Serial measurements of serum sodium and serum osmolality are critical in assessment. Urine sodium, potassium, and creatinine paired with plasma osmolality and creatinine also may be useful in some disorders of sodium regulation.

**Treatment:** The aim of treatment is to normalize serum sodium and identify and treat the underlying etiology of the hyponatremia. Fluid restriction may be the first line of intervention. Careful sodium replacement with attention to fluid volume is instituted. If hyponatremia is due to a renal disorder
the treatment is dependent on the underlying abnormality. Salt supplementation will be required in infants with pseudo-hyporaldosteronism and aldosterone resistance. Mineralocorticoid (fludrocortisone) and glucocorticoid (hydrocortisone) replacement is required for treatment of hyponatremia due to congenital adrenal hyperplasia (CAH).

Hypernatremia

Hypernatremia is defined as serum sodium of greater than 145 mEq/L. The causes of hypernatremia may be classified into:

- Factors associated with inadequate fluid intake: These include: Breast feeding infants; premature infants in whom the fluid intake is inadequate to meet the high insensible losses occurring via the respiratory tract.
- Factors associated with excessive fluid loss: These include: Excessive fluid loss in urine such as in diabetes insipidus; osmotic diuresis as seen in glucosuria, gastrointestinal losses such as seen in vomiting, nasogastric aspirates, and secretory diarrhea; excessive water loss through the skin such as seen in cystic fibrosis.

Further discussion in this section will be focused on diabetes insipidus (DI) as a prototype for hypernatremia. History details need to evaluate patterns of feeding, presence of vomiting, quantification of urine output including number of wet diapers. Also important is a history of consanguinity.

Physical examination should include an assessment for signs of dehydration and the presence of midline defects and congenital anomalies such as cleft palate, cleft lip, and micropenis which may indicate hypopituitarism. Important factors in evaluation include an assessment of weight loss or weight gain of the infant with careful consideration to the intake and output. Serial measurements of serum sodium, creatinine, and serum osmolality along with urine osmolality are crucial in assessment.

Treatment: The aim of treatment is to normalize the serum sodium, identify, and treat the cause of hypernatremia. If there is strong suspicion for DI, a test dose of aqueous vasopressin may be administered. The response of the urine osmolality to this dose may prove useful in distinguishing between central versus nephrogenic DI. In the acute management of central DI, aqueous vasopressin may be administered via continuous infusion. For the subsequent management of central DI, desmopressin (DDAVP) may be administered via different routes: subcutaneous, intranasal, or orally. A referral to a pediatric endocrinologist should be made for treatment and follow up. For the management of nephrogenic DI in infancy, one should consider referral to a pediatric nephrologist.

Disorders of calcium metabolism

Calcium homeostasis is under the complex interplay of the calcium-parathyroid hormone-Vitamin D axis. Defects at any of these levels may result in hypocalcemia or hypercalcemia.

Hypocalcemia

This is defined as a serum total calcium of less than 8.8 mg/dl or ionized calcium less than 4.9 mg/dl in infants up to three months old (29, 30). Hypocalcemia may be asymptomatic on presentation and may be detected inadvertently on routine blood investigation. A common presentation includes neuromuscular irritability with jitteriness, myoclonic jerks “twitching” exaggerated startle response and seizures. Other neonatal presentations include apnea, cyanosis, tachypnea, vomiting, laryngospasm and heart failure (31).

Hypocalcemia may be classified depending on the age of the neonate at presentation into:

- Early onset hypocalcemia: usually presents within the first 4 days of life
- Late onset hypocalcemia: usually presents at 5-10 days of life
Table 8. Common causes of hypocalcemia in neonates and infants

- Early onset of hypocalcemia:
  - Infant of a diabetic mother
  - Perinatal asphyxia
  - Preeclampsia
  - Perinatal stress of trauma
  - Respiratory distress syndrome (RDS)
  - Maternal hyperparathyroidism

- Late onset hypocalcemia:
  - Vitamin D deficiency
  - Excess phosphate load (cow’s milk intake)
  - Hypomagnesemia
  - Transient hypoparathyroidism
  - Transient parathyroid hormone resistance

- Congenital hypoparathyroidism:
  - 22q11 deletion/DiGeorge syndrome/velocardiofacial syndrome
  - Agenesis of parathyroid glands
  - Metabolic syndromes (Kenny-Caffey syndrome, Kearns-Sayre syndrome)

- Iatrogenic
  - Phosphate deficiency
  - Citrated blood products
  - Lipid infusions
  - Bicarbonate therapy
  - Loop diuretics
  - Glucocorticoids

- Alkalosis

The various common causes of hypocalcemia are listed in Table 8 (28). History for time of onset and associated clinical features is important for investigation of the underlying etiology. Physical examination should include an assessment for a hyperactive startle response, facial anomalies such as hypertelorism, antimongoloid slant eyes, low set and notched ears, short philtrum of lip, and micrognathia. Laboratory studies for hypocalcemia include evaluation of the calcium-parathyroid Vitamin D axis and for possible underlying etiology and are listed in Table 9.

Table 9. Laboratory work up for hypocalcemia and hypercalcemia

- Blood
  - Total and ionized calcium
  - Phosphate, magnesium
  - Alkaline phosphatase, liver function tests
  - Albumin, serum pH
  - Electrolytes
  - Parathyroid hormone level
  - 25 OH Vitamin D, 1,25 OH Vitamin D

- Cytogenetics:
  - For hypocalcemia: 22q11 deletion, mitochondrial defects
  - For Hypercalcemia:
    - mutations associated with the CaSR gene
    - mutations associated with elastin gene - William’s syndrome
    - mutations of the Vitamin D receptor

- Urine: Calcium and phosphorus

- Radiology: as needed
  - X ray for evidence of rickets or osteopenia
  - Echocardiogram
  - Skeletal survey
Treatment: Intravenous infusion of calcium salts is used to treat severe symptomatic hypocalcemia. 10% calcium gluconate at a dose of 0.5 ml/kg (maximum of 2 ml/kg) may be given as a bolus IV push over 5-10 minutes with EKG monitoring. If a central line is available, a continuous infusion can be used over the next 24 hrs. However, if the latter is not available, boluses may be administered every 4-6 hours. Extra bolus may be given to maintain an ionized calcium level of greater than 1 mmol/L.

If there is concurrent hypomagnesemia, 50% magnesium sulphate at a dose of 100 mg/kg/dose as slow IV infusion over 30 minutes is administered. Treatment with Vitamin D supplementation at 200-2000 International Units/day is initiated presumptively to increase calcium absorption although improvement may take several days. For severe or persistent hypocalcemia, calcitriol 50-100 ng/kg/day in two to three divided doses may be used.

Hypercalcemia

Hypercalcemia is defined as defined as total calcium of greater than 9.2 mg/dl in premature infants and greater than 10.4 mg/dl in term infants (32). The causes for hypercalcemia are listed in Table 10 (29).

Evaluation. History details should include assessment of calcium and phosphorous intake assessment in the neonate. This is especially important in preterm infants receiving breast milk without phosphate supplementation and also in infants on low phosphate parental nutrition. Vitamin D and intake of fortified dairy intake should be assessed. A history of birth trauma may be associated with traumatic fat necrosis. Positive family history of hypercalcemia may be indicative of possible disorders like familial hypocalciuric hypercalcemia. Physical examination should assess for dysmorphism associated with Williams syndrome and for findings of a murmur of supravalvular aortic stenosis or peripheral pulmonary stenosis. Laboratory studies for hypercalcemia are listed in Table 10 (29).

Table 10. Common causes of hypercalcemia in neonates and infants

- Iatrogenic
  - Hypophosphatemia
  - Vitamin D excess
  - Vitamin A excess
  - Excess calcium supplementation
  - Extracorporeal membrane oxygenation
  - Thiazide diuretics
- Functional hyperparathyroidism
  - Maternal hypocalcemia
  - Congenital parathyroid hyperplasia
  - Inactivating mutations in the calcium sensing receptor
  - Jansen’s metaphyseal chondrodysplasia
  - Disorders of Vitamin D metabolism
  - Williams’ syndrome
- Hypophosphatasia
- Endocrine disorders
  - Congenital hypothyroidism
  - Thyrotoxicosis
  - Adrenal insufficiency
- Down syndrome
- IMAGe association (intrauterine growth retardation, metaphyseal dysplasia, adrenal hypoplasia and genital anomalies)

Treatment: After confirmation of hypercalcemia vitamin D and calcium intake should be minimized. A low-calcium formula (Calcilo XD) should be used as compared to the standard infant formula. This contains less calcium and no vitamin D. Serum and urine calcium should be monitored regularly as
confirmation of the efficacy of treatment and in order to prevent the induction of rickets. For severe hypercalcemia, treatment options include loop diuretics which may enhance calciuresis. Dehydration should be avoided since a decrease in glomerular filtration rate (GFR) may perpetuate the hypercalcemia and nephrocalcinosis may result. Severe hypercalcemia (may be asymptomatic) as seen in neonatal severe hyperparathyroidism, may be treated with bisphosphonates such as pamidronate (0.5-2 mg/kg). Prior to the availability of pamidronate, parathyroidectomy was the only therapeutic option available.

**Conclusion**

We have presented an approach to the newborn with endocrine problems due to pituitary, thyroid and adrenal conditions. We reviewed abnormalities in sexual differentiation and discussed metabolic problems including those due to glucose, sodium and calcium homeostasis.

**References**


