Inborn Errors of Metabolism

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What are Inborn Errors of Metabolism?

- Genetic disorders that affect the breakdown of food
  - Food that is not broken down properly may cause products to either build up or be missing in various parts of the body, leading to medical problems, including intellectual disability and damage to specific organs, such as the heart, kidneys, liver, brain, etc.
  - May be life threatening if untreated
- Caused by an error in the DNA alphabet (sequence) in a gene (trait) → gene doesn't work properly → non-working enzyme, which is necessary to break down a specific part of the food eaten (fat, sugar, protein)

Categories of Inborn Errors

- Protein Disorders
  - Amino acids (Phenylketonuria, Maple Syrup Urine Disease)
  - Organic acids (Methylmalonic Aciduria, Biotinidase Deficiency)
  - Urea cycle (Citrullinemia, Argininosuccinic Aciduria)
- Carbohydrate (Sugar) Disorders
  - Galactosemia
- Fatty Acid (Fat) Disorders
  - Medium Chain Acyl CoA Dehydrogenase Deficiency (MCAD)
  - Very Long Chain Acyl CoA Dehydrogenase Deficiency (VLCAD)

Inborn Errors: Well-Suited for NBS

- Early recognition/treatment critical
- Early signs/symptoms often non-specific
- Neonatal response to overwhelming illness is limited
- Metabolic decompensation can lead to irreversible neurologic impairment

What Happens After a Positive Screen?

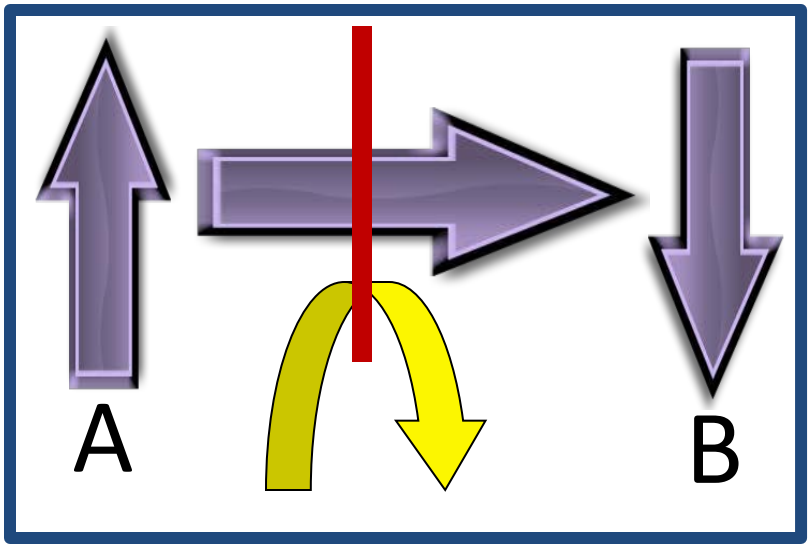
- Children's Hospital of Michigan Metabolic Clinic (CHMMC) is the State-designated referral center for all positive screens
- After notification:
  - CHMMC staff contacts primary medical doctor with recommendations, including "check health status", information on confirmatory tests, initiation of treatment/intervention, referral to CHM as indicated
  - If diagnosis confirmed, patient is followed at CHMMC - lifelong management – from birth through adulthood!
- Metabolic physician/dietitian/fellow on call 24 hours/7days/week to assist in either consultative management or transfer to CHMMC

Goals of Medical Management

- Two fold approach
  - Acute/emergency management
  - Long term management
- Maintain biochemical balance
- Careful monitoring to ensure adequate nutrition (protein and calories) for growth and development

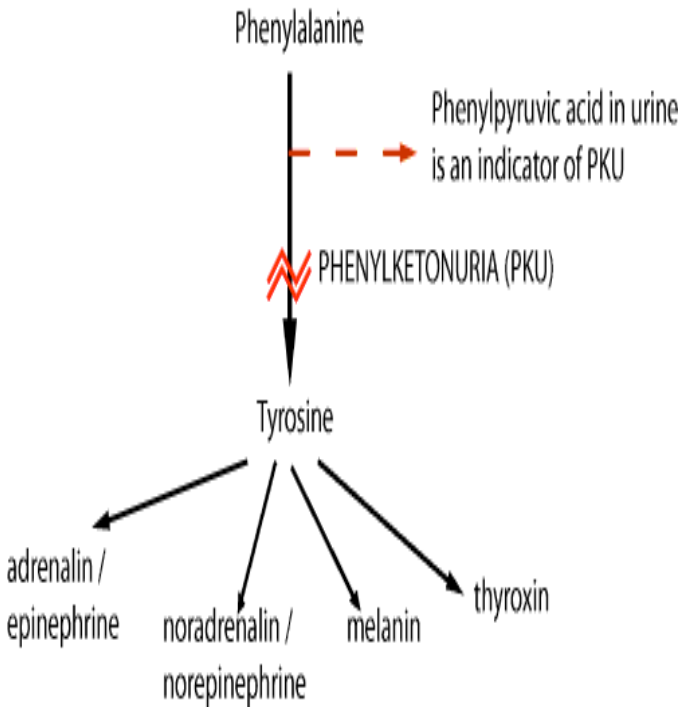
Current Treatment Strategies for Metabolic Disorders

- Accumulation of precursor or toxic substance (A)?
  - Treatment: Restrict amount available through special medical foods or diet
- Absence of product (B)
  - Supplement deficient product or missing vitamin cofactor
- Drugs to aid metabolic pathway



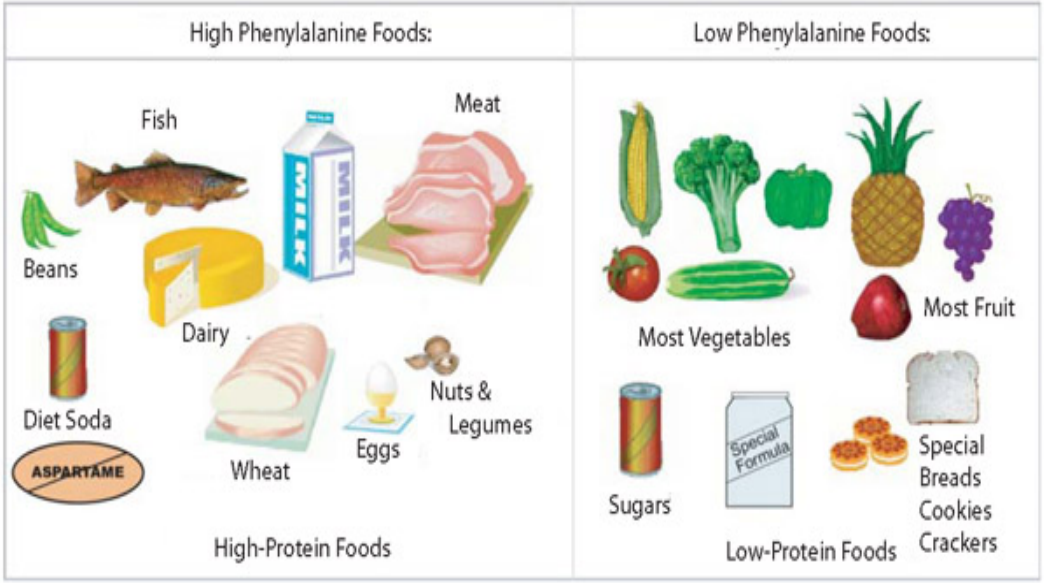
Amino Acid Disorders: Treatment "Diet for Life"

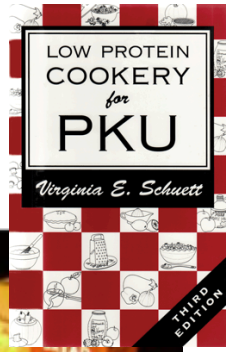
- Phenylketonuria: mutations in gene coding for *phenylalanine hydroxylase* → deficient enzyme activity
  - Excess phenylalanine
  - Phenylalanine →phenylpyruvic acid **(accumulation of precursor)**
  - Deficiency of tyrosine → deficiency of neurotransmitters dopamine and norepinephrine **(deficiency of product)**



Treatment of PKU – Diet for Life

- Prevent phenylalanine accumulation via phenylalanine-restricted diet
  - Provide enough phenylalanine for normal growth using phe-free metabolic formula + dietary restrictions/low protein products





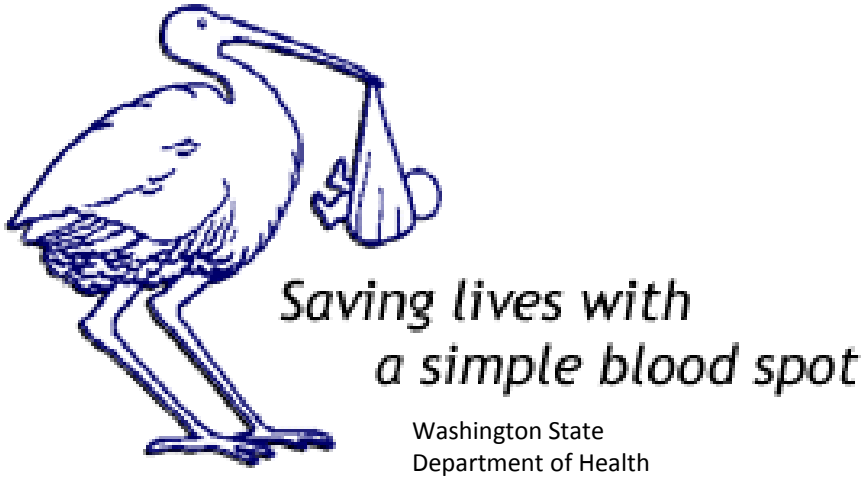
The Children's Hospital of Michigan Metabolic Clinic….it takes a village

DMC Children's Hospital of Michigan
always there just for them.

- Clinical Geneticists – Division of Genetic and Metabolic Disorders
  - Gerald Feldman, MD/PhD, Program Director
  - Robert Conway, MD, Clinic Director
  - David Stockton, MD, Chief, Division of Genetic and Metabolic Disorders
  - Leigh Ann Flore, MD, Clinical Geneticist
  - Vinod Misra, MD/PhD, Clinical Geneticist
- Genetic Counselor, Nurse Practitioners, Nurses, Dietitians, Social Worker, Psychologist
- Biochemical Genetics Laboratory (Lidong Zhai, PhD, Director), part of Detroit Medical Center University Laboratories (DMC-UL)
  - Provides 24/7 testing for confirmation of diagnosis and acute care and long term management on-site

Newborn Screening Saves Lives!

- More than 4 million newborns are screened annually in the United States
- Thousands of infants are rescued from disability and death
- Newborn screening offers life without physical disability
- What a gift!



Endocrine Disorders: Congenital Hypothyroidism and Congenital Adrenal Hyperplasia

Ram Menon, MD
Professor of Pediatrics
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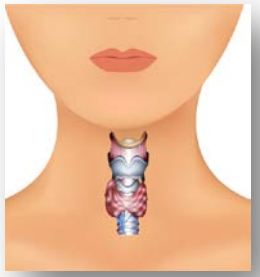
University of Michigan

Congenital Hypothyroidism

Congenital Hypothyroidism (CH)



Primary: Defect at the level of the thyroid gland.

Primary Hypothyroidism:

- 1/3000 - 4000 live births
  - Ectopic thyroid: 25 - 50%
  - Thyroid agenesis: 20 - 50%
  - Dyshormonogenesis: 4 - 15%
- Generally more severe
- Results in significant mental retardation / development delay if untreated

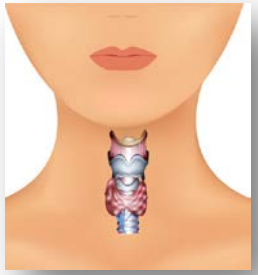
Secondary / Tertiary: Defect at the level of the pituitary gland / hypothalamus.

Secondary Hypothyroidism:

- 1/30,000 - 100,000 live births
- Generally milder
- Less likely to result in significant developmental delay

The MI NBS CH Program is designed to detect severe cases of Primary CH.

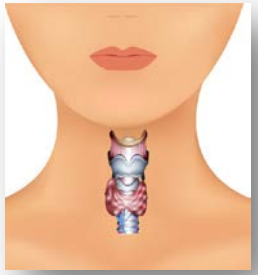
Congenital Hypothyroidism (CH)



- Newborns with severe CH do not exhibit signs and symptoms until later (weeks / months) in life.
- Early diagnosis and treatment (< 2 weeks of age) is key to a good prognosis for neurodevelopment and avoidance of mental retardation.
- MI NBS strategy - detection of elevated TSH in filter paper blood sample.
- Confirmation of CH is based upon elevated TSH in serum sample.
- Additional tests:
  - Low levels of serum Free T4 – also useful in titration of initiating dose of levothyroxine
  - Technetium-99m scan to assess location of thyroid gland
  - Thyroid ultrasound
  - Measurement of serum thyroglobulin

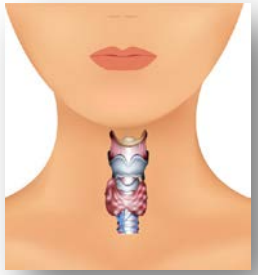
The goal of the MI NBS CH program is to prevent neurodevelopmental sequelae resulting from delayed diagnosis of Primary CH.

Congenital Hypothyroidism (CH)



- Treatment – Tab Levothyroxine (10 - 15 mcg/kg/day) administered orally once a day.
- Laboratory monitoring of dose every 3 - 6 months.
- Treatment is life long.
- Initiation of levothyroxine treatment in appropriate dose by 2 weeks of age is associated with normal neurodevelopmental outcome.
- Levothyroxine treatment is EASY, CHEAP, and EFFECTIVE.

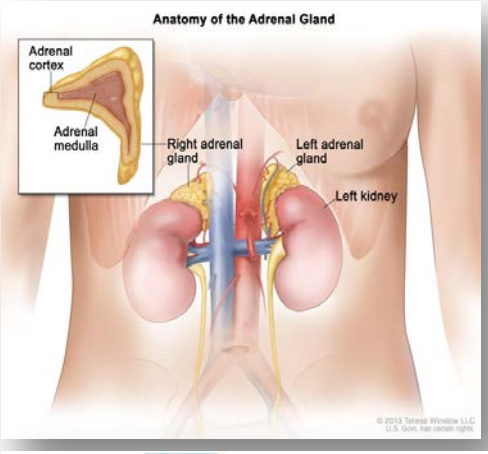
Congenital Hypothyroidism (CH)

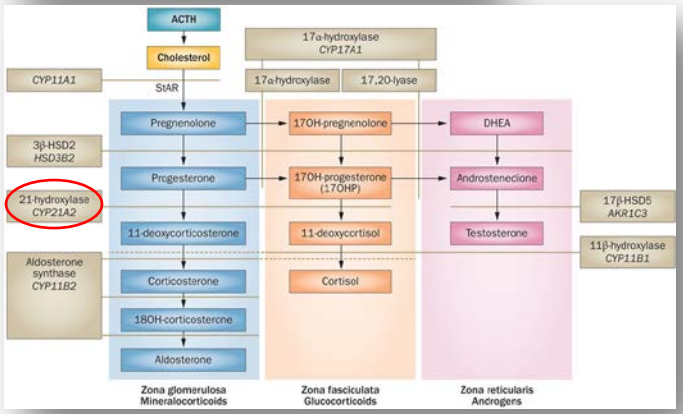


- In Michigan CH was added to NBS in 1977.
- On an average 75 – 100 babies with CH are diagnosed annually via NBS Program.
- Since inception 2050 babies have been diagnosed with CH via the NBS Program.
- Average time to treatment is 7 days.

Congenital Adrenal Hyperplasia

Congenital Adrenal Hyperplasia (CAH)





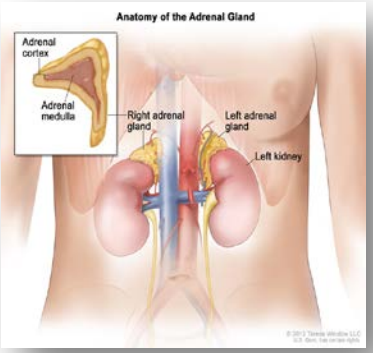
Group of autosomal recessive disorders, each of which involves a deficiency of an enzyme involved in the synthesis of cortisol, aldosterone, or both.

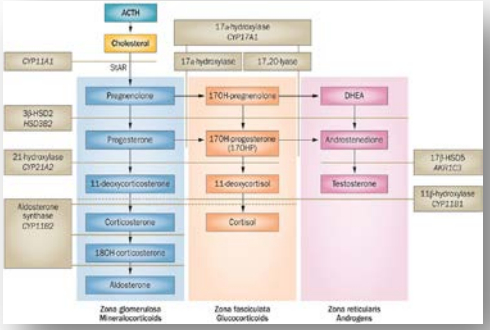
- 21-hydroxylase deficiency due to mutations or deletions of the CYP21A gene, accounts for > 90% of cases of CAH.
- Clinical types of 21-OH deficiency (in order of decreasing severity of presentation):
  - Salt-losing – neonatal death if untreated
  - Simple Virilizing
  - Non-Classical or Late-Onset

  } Classic Forms
- Incidence of classic forms of 21-OH deficiency in the general population = 1/20,000

The MI NBS CAH program designed to detect the Classic Forms of 21-OH Deficiency.

Congenital Adrenal Hyperplasia (CAH)



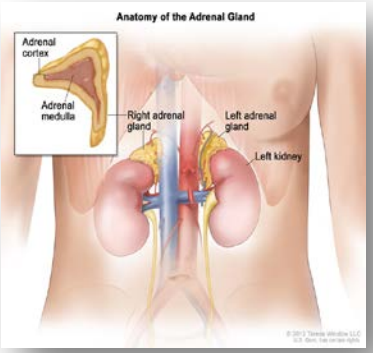


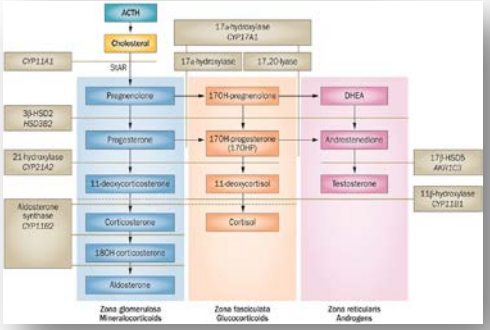
At birth:

- Males are phenotypically normal.
- Females exhibit variable degree of virilization.
- Symptoms and signs of cortisol and aldosterone deficiency evident only after a few days of life.
- Initial presentation can be hyponatremia, hyperkalemia, and cardiovascular collapse.

The goal of the MI NBS CAH program is to prevent neonatal mortality and morbidity secondary to delayed diagnosis of salt-losing CAH.

Congenital Adrenal Hyperplasia (CAH)

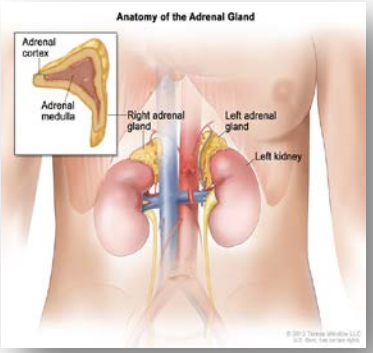


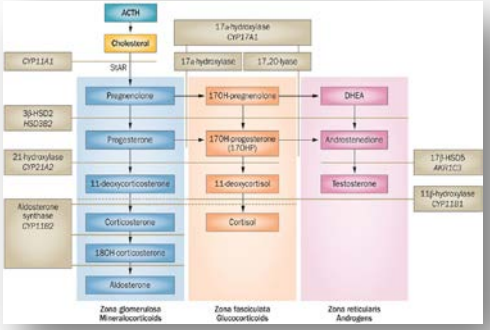


Diagnosis:

- 17-Hydroxyprogesterone (17OHP) levels elevated in filter paper blood sample.
- Repeat 17OHP in extracted blood sample.
- Second tier Tandem Mass Spec assay: (17OHP + Androstenedione) / Cortisol ratio (>2.5)
- Hyponatremia and hyperkalemia.
- ACTH Stim test is usually not required for diagnosing salt-losing CAH.
- DNA testing.

Congenital Adrenal Hyperplasia (CAH)

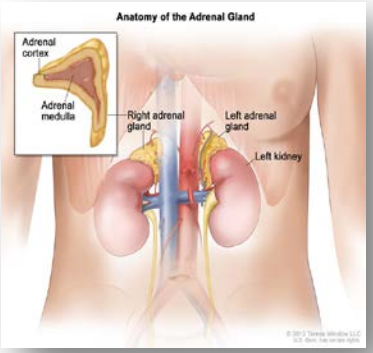


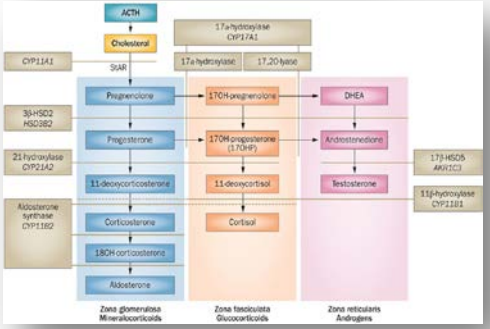


Treatment:

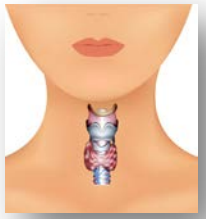
- Resuscitation and stabilization of circulatory and fluid & electrolyte status.
- Replacement of glucorticoid and mineralocorticoid hormones – lifelong.
- With appropriate management – normal growth, pubertal development, and reproductive function in adult life can be achieved.

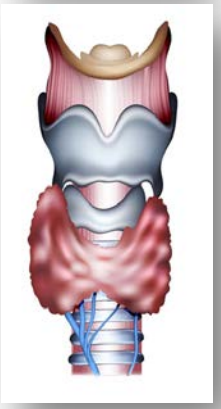
Congenital Adrenal Hyperplasia (CAH)

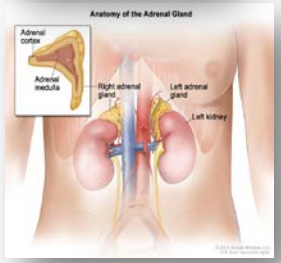


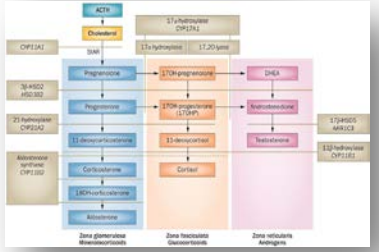


- In Michigan CAH was added to NBS in 1993.
- On an average 5 - 11 babies with CAH are diagnosed annually via NBS Program.
- Since inception 148 babies have been diagnosed with CAH via the NBS Program.









Acknowledgements

University of Michigan Endocrine Follow-Up Team

Chris-Hoeft Loyer – *Project Manager*

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Yolanda Henderson - *Coordinator*

Sandra Reinecke – *Administrative Assistant*

Karen Andruszewski - *Quality Assurance Coordinator*

Hemoglobinopathies

Wanda Whitten-Shurney MD

CEO/Medical Director

Sickle Cell Disease Association of America-Michigan Chapter

Hemoglobinopathies: An Inside Look

CAUSE – Genetic mutations

Hemoglobinopathies – Structure

Sickle Cell Disease SS

SC

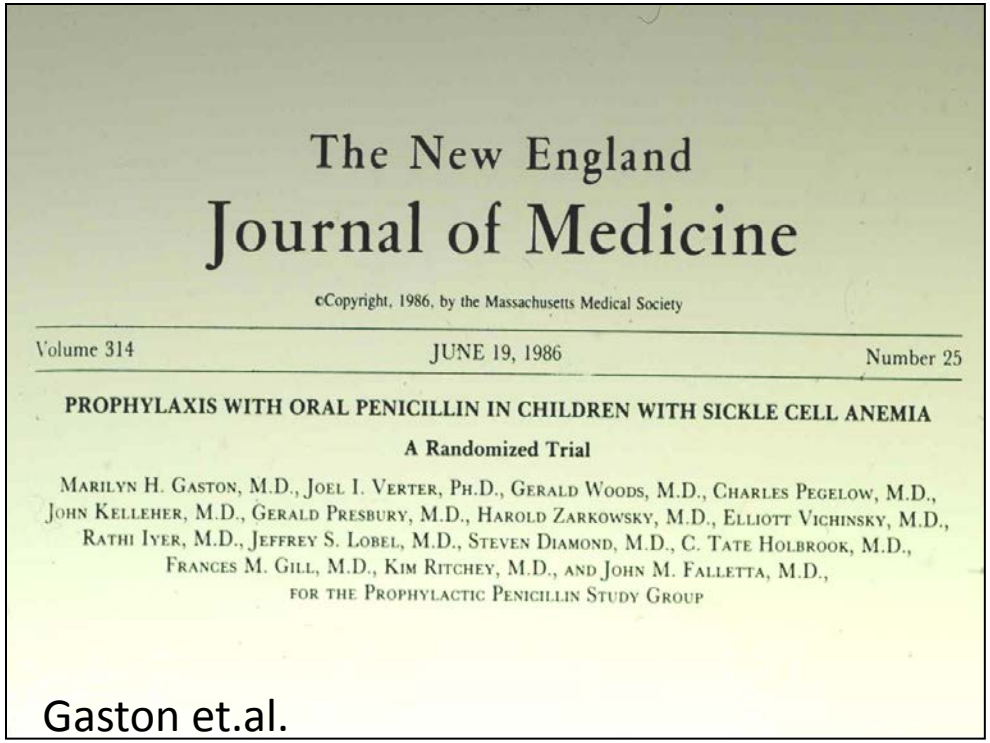
SThal

Thalassemias – Quantity

Alpha – Hemoglobin H disease

Beta - Cooley's Anemia

Hemoglobinopathies : Diagnosis & Treatment



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PROPHYLAXIS WITH ORAL PENICILLIN IN CHILDREN WITH SICKLE CELL ANEMIA

A Randomized Trial

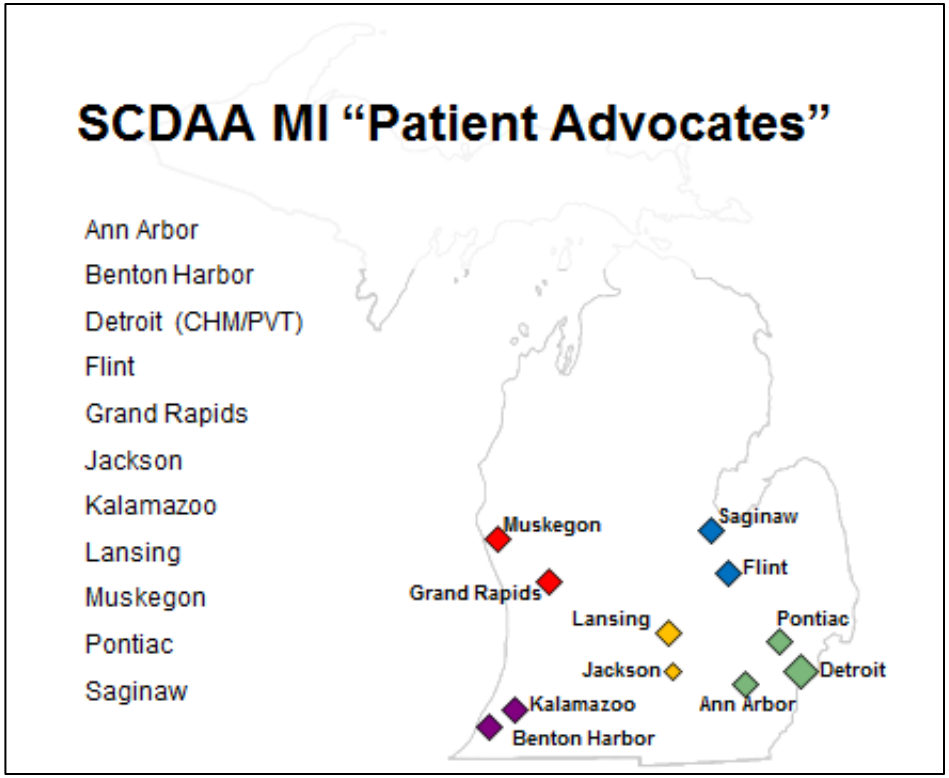
MARILYN H. GASTON, M.D., JOEL I. VERTER, PH.D., GERALD WOODS, M.D., CHARLES PEGELOW, M.D., JOHN KELLEHER, M.D., GERALD PRESBURY, M.D., HAROLD ZARKOWSKY, M.D., ELLIOTT VICHINSKY, M.D., RATHI IYER, M.D., JEFFREY S. LOBEL, M.D., STEVEN DIAMOND, M.D., C. TATE HOLBROOK, M.D., FRANCES M. GILL, M.D., KIM RITCHEY, M.D., AND JOHN M. FALLETTA, M.D., FOR THE PROPHYLACTIC PENICILLIN STUDY GROUP

Gaston et.al.

July 1, 1987

	Penicillin	Vitamin C
Total #	105	110
Deaths	0	**3**
Infection	2	**13**

Hemoglobinopathies : Diagnosis & Treatment



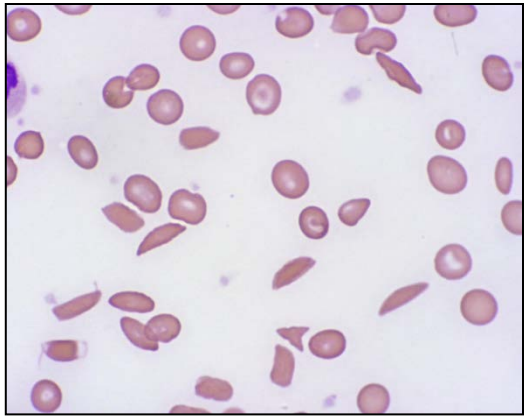
- ✓ Inform parents
- ✓ Obtain confirmatory test (2-3 months)
- ✓ Disease education
- ✓ Initiate penicillin prophylaxis
- ✓ Monitor penicillin compliance
- ✓ Refer to pediatric hem/onc
- ✓ Provide ongoing education and support

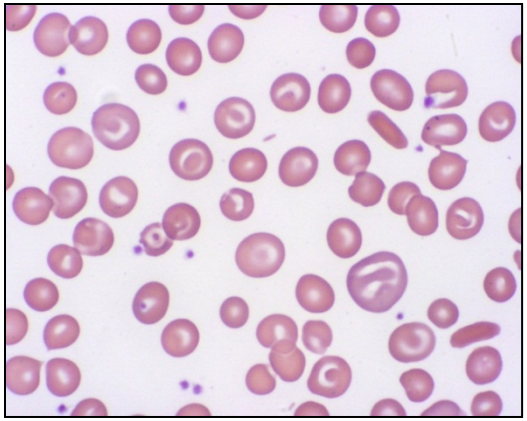
Hemoglobinopathies: Diagnosis & Treatment

Supportive care

Pain medication
Antibiotics
Blood transfusions

Hydroxyurea





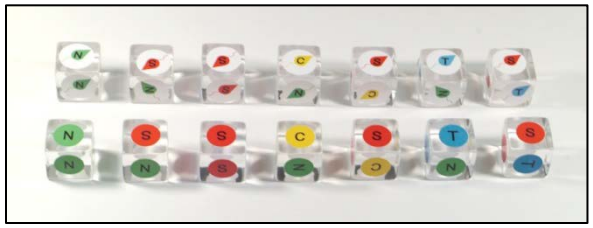
Stem Cell Transplant

Hemoglobinopathies : Outcomes

Prevention of pneumococcal sepsis

Early Education

Genetic Counseling



Cystic Fibrosis

Samya Z. Nasr, MD, CPI
Professor of Pediatrics
Director, Cystic Fibrosis Center
Coordinator, State of MI CF NBS Program
University of Michigan Health System

Cystic Fibrosis: Epidemiology

Most common autosomal recessive fatal genetic disease in Caucasians
Affects 30,000 children and adults in the U.S.; 70,000 individuals worldwide

Incidence*		Carrier Rate	
	White	1 in every 3,300 live births	29
	Black	1 in every 15,300 live births	62
	Asian	1 in every 32,100 live births	90
	Native American	1 in every 11,200 live births	53
	Hispanic	1 in every 9,500 live births	49

3-4% Carrier Rate
1 in 2,500 live births
1,000 new cases diagnosed a year

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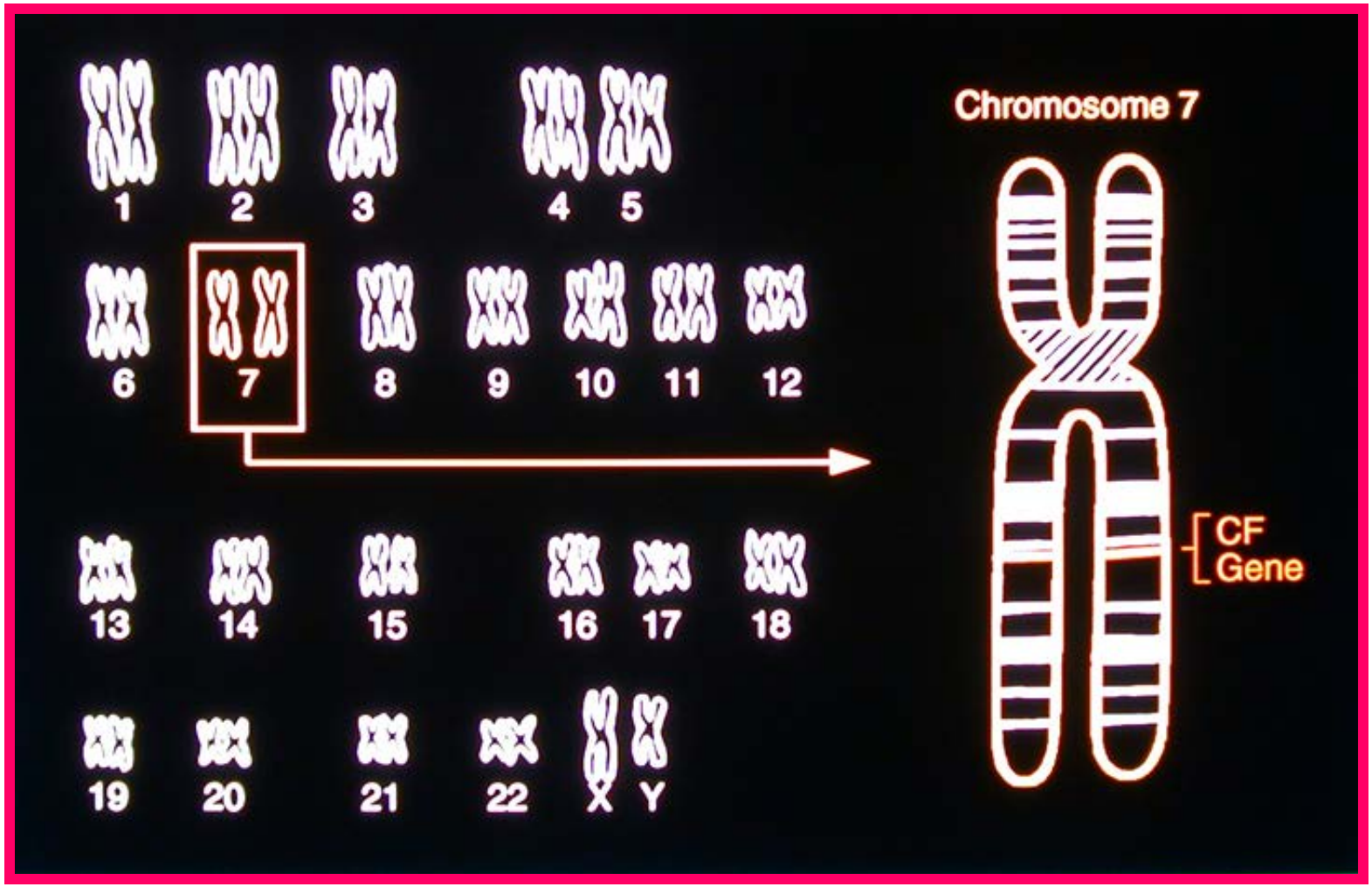
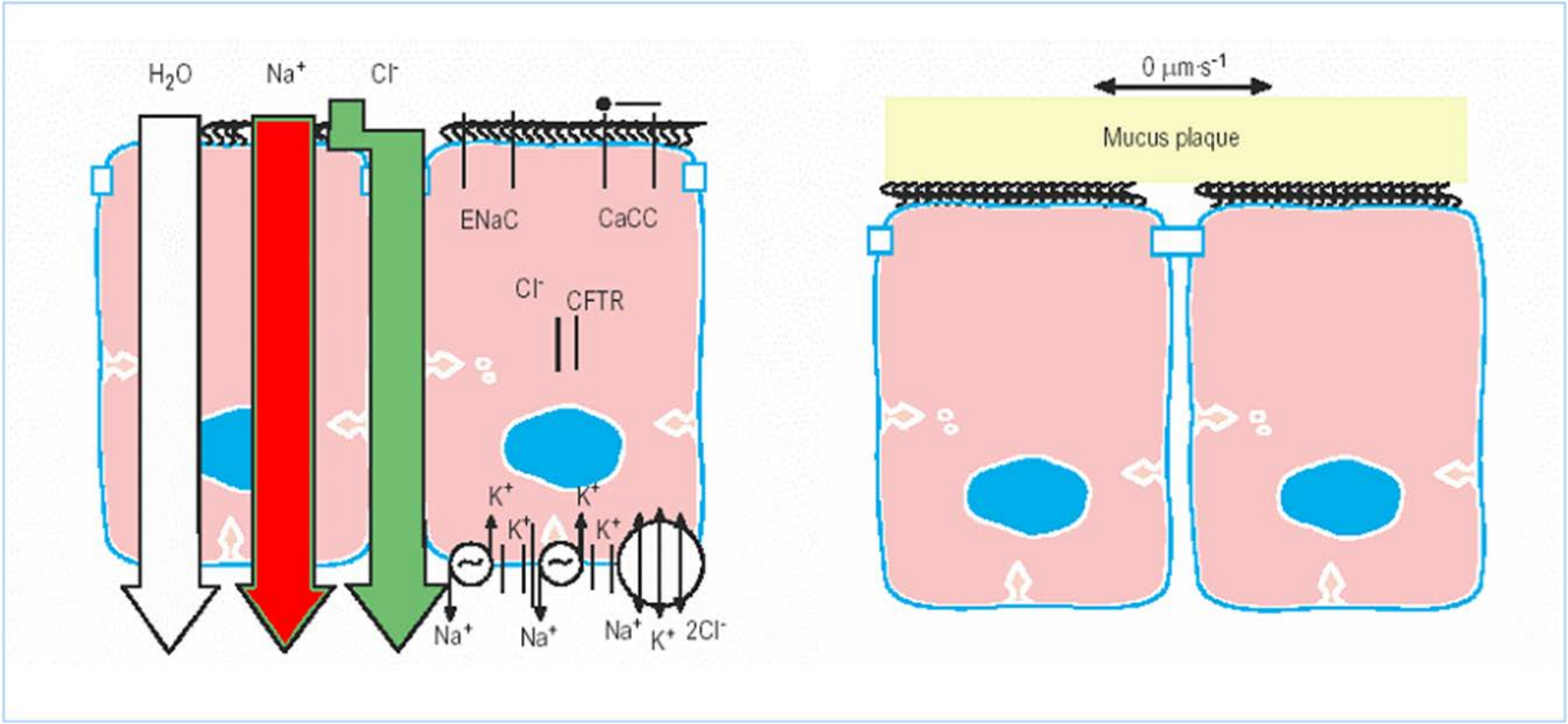
*Source: CF incident case reported to Cystic Fibrosis Foundation 1990-2014, NCHS Natality Statistics 1992, Hardy-Weinberg calculations in Thompson et al., Genetics in Medicine, Philadelphia, WB Saunders Co. 1991L 143-165

Cystic Fibrosis: Pathogenesis

Cystic Fibrosis: Site of CF Gene



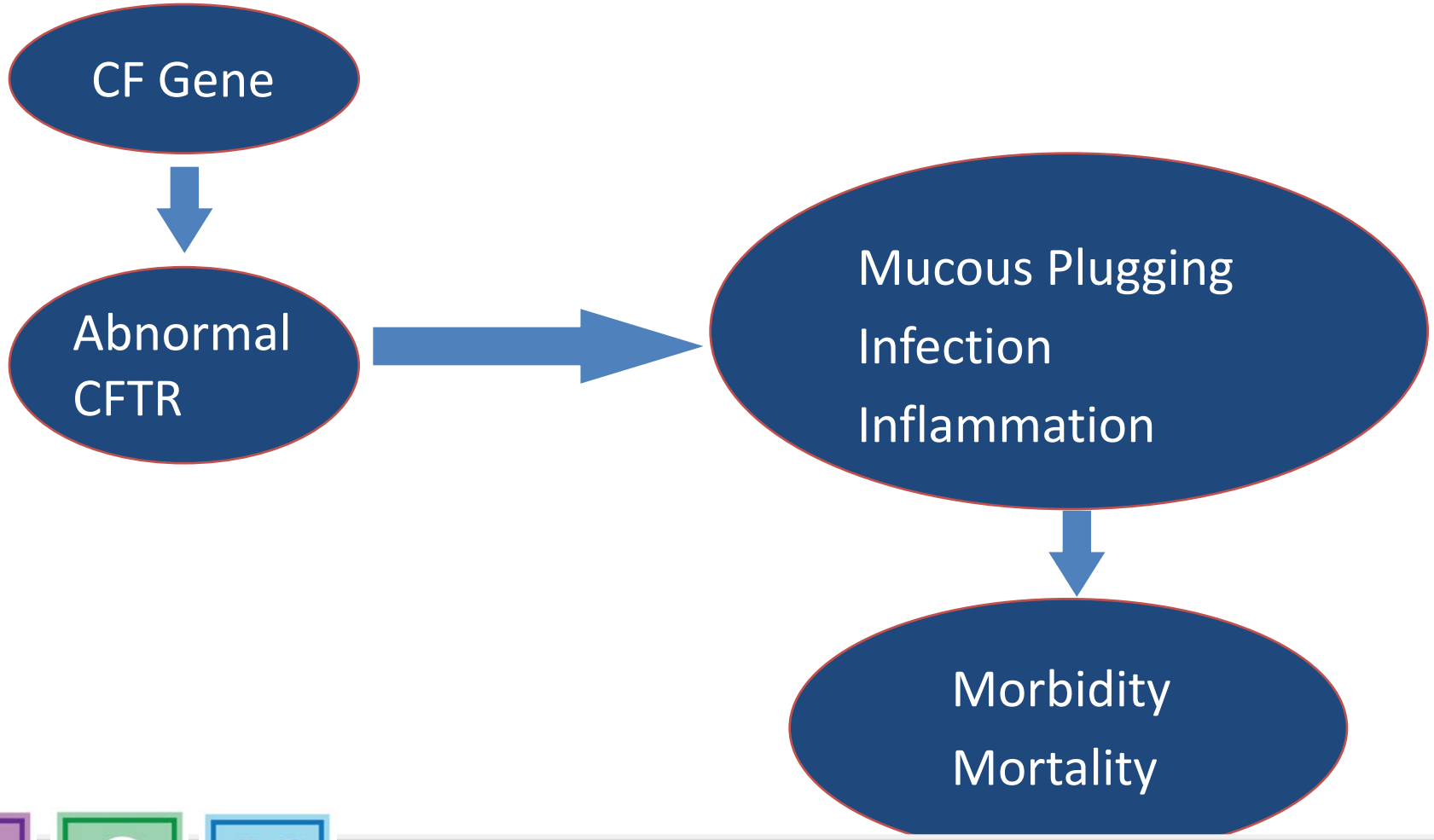
Cystic Fibrosis:
Abnormal Ion Transport and Mucus Stasis



Cystic Fibrosis: Mutational Basis of CF

- Over 2,000 sequence alterations identified in CFTR gene
- Most mutations identified in patients of Caucasian ancestry
- Some appear unique to populations of non-Caucasian ancestry
- Most non- delta F508 mutations are rare (occur in <1% of screened populations)

Pathogenesis of Cystic Fibrosis Lung Disease



Cystic Fibrosis: Diagnosis & Treatment

One or more characteristic phenotypic features

- A history of CF in a sibling
- A positive newborn screening

And abnormal CFTR function

- Elevated sweat chloride
- Nasal PD-CF pattern
- 2 CFTR mutations

Cystic Fibrosis: Newborn Screening

- All states have initiated universal screening programs for CF.
- Test for Immune-Reactive Trypsin (IRT) in dried blood spots.
- Follow-up with DNA assay for 23-40 mutations
- Repeat IRT

Cystic Fibrosis: Age at Diagnosis

Patient group	Median age at diagnosis in months
All patients with CF	5.3
Patients diagnosed at birth due to intestinal blockage (~15% of all patients)	<1
Patients diagnosed because they became sick from CF	14.5
Patients diagnosed by newborn screening	<1

Newborn Screening for CF in MI

- IRT/DNA
- Two tier screening process
- IRT ≥96%ile (Daily)
- DNA mutation analysis
- Update, 2/1/2009:
- IRT >99.9%ile /No CF MUT no longer screen positive
- Physician letter sent stating referral for ST only if signs of CF or family history of CF present.

Benefits of Screening

Does early diagnosis affect patient outcomes?

- Early Intervention
  - Improved growth and nutrition
  - Improved pulmonary health
  - Improved cognitive development
- Reduction of the “diagnostic odyssey”
    - Parental anxiety, frustration, trust
- Improved survival?

Potential Risks

- Stress of false positives
- Borderline results
- Counseling of carriers
- Early exposure to pathogens in CF clinics
- CF screening has more false negative in comparison to other screened diseases
- False negatives / Changes in health practices

Infant Presentation of Cystic Fibrosis

- Meconium ileus
- Steatorrhea
- Inadequate weight gain or failure to thrive
- Persistent cough, wheeze
- Recurrent pneumonia, bronchiolitis, etc.
- Other
  - Hypoelectrolytemic dehydration
  - Vitamin and or zinc deficiency
  - Rectal prolapse
  - Anemia/edema/hypoproteinemia

Multi-organ involvement in CF

Neurologic/Psychiatric
- Ototoxicity
- Adherance/Compliance

Cardiovascular
Acute/persistent respiratory symptoms
- Pulmonary hypertension

ENT
- Recurrent OM
- Chronic sinusitis
- Conductive hearing loss

GI
- Pancreatic insufficiency
- Meconium ileus
- Distal intestinal obstruction
- Cirrhosis
- Splenomegaly
- FTT

Allergy
- Allergic bronchopulmonary aspergillosis

Rheumatologic
- CF related arthritis

Renal/GU
- Nephrotoxicity
- Congenital absence of vas deferens

Endocrinology
- CF related diabetes
- FTT

Cystic Fibrosis: Management

Pulmonary Disease

The Vicious Cycle of CF Lung Disease

Inflammation

- Ibuprofen
- Corticosteroids

Obstruction

- Airway clearance
- Bronchodilators
- Dornase alfa
- Hypertonic saline

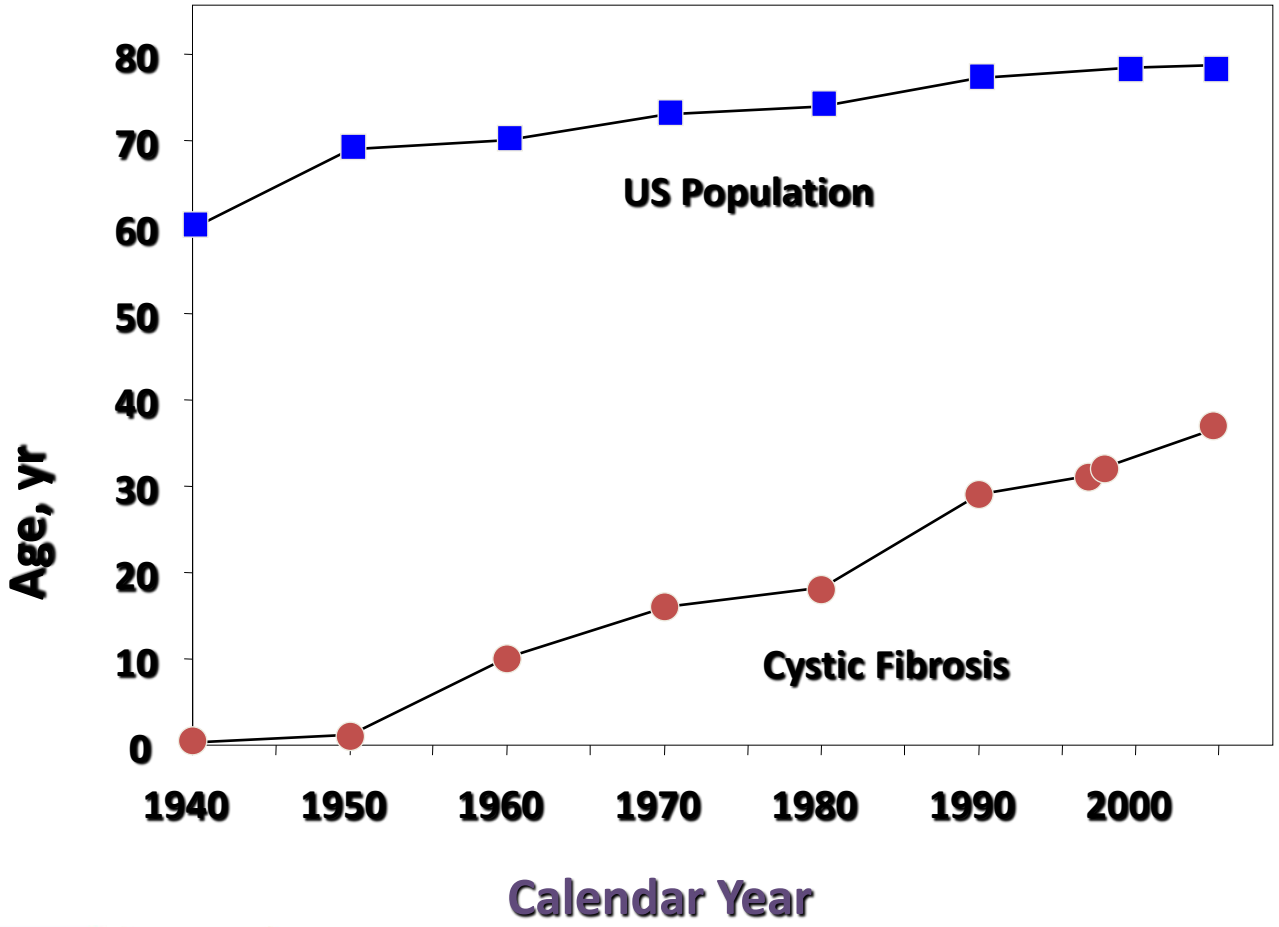
Infection

- Tobramycin
- Azithromycin
- Aztreonum

Cystic Fibrosis: Outcomes

- The diagnosis of CF is based on clinical presenting features and confirmed by laboratory tests.
- CF diagnosis based on symptoms is associated with delayed diagnosis and reduced survival
- NBS is associated with improved growth and nutritional status and may increase survival
- Despite linger ethical concerns, the consensus indicates that the moderate benefits and low risk of harm justify NBS for CF
- CDC and CFF endorse universal NBS
- MI to start NBS in October 2007, but don’t change clinical practice

Median Survival Rates



Clinical trial model for screening drug effects on rare alleles

Early Hearing Detection and Intervention

Dr. Colleen M. Barry, MD

Chapter Champion American Academy of Pediatrics

Sparrow Hospital

EHDI: An Inside Look

Three Broad causes of hearing loss:

Genetic

- Syndromic
- Single Gene

Infectious

- CMV cytomegalovirus
- TORCH infections

Environmental

- Ototoxic drugs
- Hyperbilirubinemia

EHDI: Diagnosis & Treatment

Importance of early diagnosis; general steps for confirmatory testing following a positive screen:

1. Screen in first few days of life, rescreen by four weeks of age
2. Diagnostic evaluation by three months of age if infant refers on rescreen
3. Intervention by six months of age to promote communication

EHDI: Diagnosis & Treatment

Basic overview of treatment modalities:
Communication is the Goal

- ASL
- Cued speech
- Hearing aides
- Cochlear implants

EHDI: Outcomes

How NBS has made a difference or impacted the population of children with hearing loss.

Primary Immunodeficiency

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Severe Combined Immunodeficiency

No adaptive Immune System

Unable to fight infections

Children with this disorder die before 2 years of age without intervention

Treatment?

Stem cell or bone marrow transplant

Best results if stem cell or bone marrow transplant before any infection occurs

Prior to age of 3 months

Michigan- 4th State to screen

- Now approximately half of all states are screening
- Pilot prior to screening revealed that we were absolutely missing cases in Michigan
- 4th year of screening
- T cell receptor excision circles or TREC screening assay is distinctly different in normals than in babies with SCID

Stats to Date

9 true SCID

- 7 transplanted
  - 1 deceased
- 1 being observed without transplant
- 1 being treated with gene therapy

Stats to Date

- Types of SCID not what would be predicted...
- Predictions would be more than 50% x-linked

What have we found?

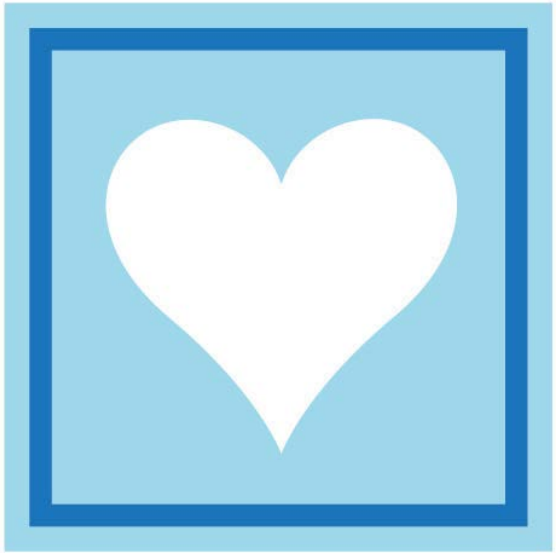
- 3 x-linked
- 2 radiosensitive
- 2 cartilage hair hypoplasia
- 1 IL7R deficiency
- 1 not yet determined

This means that the true incidence of SCID is closer to 1/40,000 rather than 1/200,000

The rarer forms were being missed prior to screening

SCID Screening

- Successful in identifying SCID
- Successful in getting children to early treatment
- Few false positives (severe illness or transient T cell lymphopenia or Digeorge syndrome)



Critical Congenital Heart Defects

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CCHD: An Inside Look

Classification of CCHD

- Critical congenital heart disease (CCHD) represents a group of heart defects which cause serious, life-threatening symptoms and requires intervention within the first days or first year of life.

Etiology of CHD

- Genetic duplications and deletions
- Gene mutations
- Multifactorial genetic lesions
- Environmental agents

Prevalence

- 7-9/1000 live births have CHD
  - ¼ of these have CCHD

CCHD: What Lesions?

- Coarctation of the Aorta
- Interrupted Aortic Arch
- Transposition of the Great Arteries
- Hypoplastic Left Heart Syndrome
- Single Ventricle
- Double Outlet Right Ventricle
- Truncus Arteriosus
- Pulmonary Atresia Intact Septum
- Tetralogy of Fallot
- Ebstein's Anomaly
- Totally Anomalous Pulmonary Venous Drainage

Physical Symptoms of CCHDs

- Tachypnea
- Tachycardia
- Weak pulse
- Very pale or blue skin color
- Poor feeding
- Drowsy

NBS for CCHD

Complete history and physical examination

– + Pulse oximetry screening

- At least 24 hours of age or before discharge
- Pass = SaO2 > 95%
  - 25% babies with CCHD will “pass” oximetry screen
- Fail
  - Refer to specialist congenital heart center for echocardiogram

Efficacy of Screening

- AAP, AHA, CDC, HHS all recommend universal screen for newborns
- Sensitivity 75%, Specificity 99%, False positive 0.14%
- Cost effective
- Lack of prospective data proving an improvement an outcomes

Screening improves outcomes?

- Prevent an asymptomatic CCHD baby being discharged home
- A false positive may detect another important illness
- Allows a timely transfer to a treatment center

But needs:

- Training
- Consistent protocol
- Equipment

Management of CCHD

Transfer to Congenital Heart Center

- Echocardiogram
- Symptomatic
  - Discuss urgent transfer with center
    - » NICU
    - » PICU
    - » Floor
- Asymptomatic
  - Transfer
  - Clinic appointment
  - Telemedicine

CCHD: Diagnosis & Treatment

Structural Heart Disease

- Cardiac Surgery
  - Coarctation
  - TGA
  - HLHS
  - Truncus Arteriosus
  - Single Ventricle

    Reduced pulmonary blood flow and ductus dependent

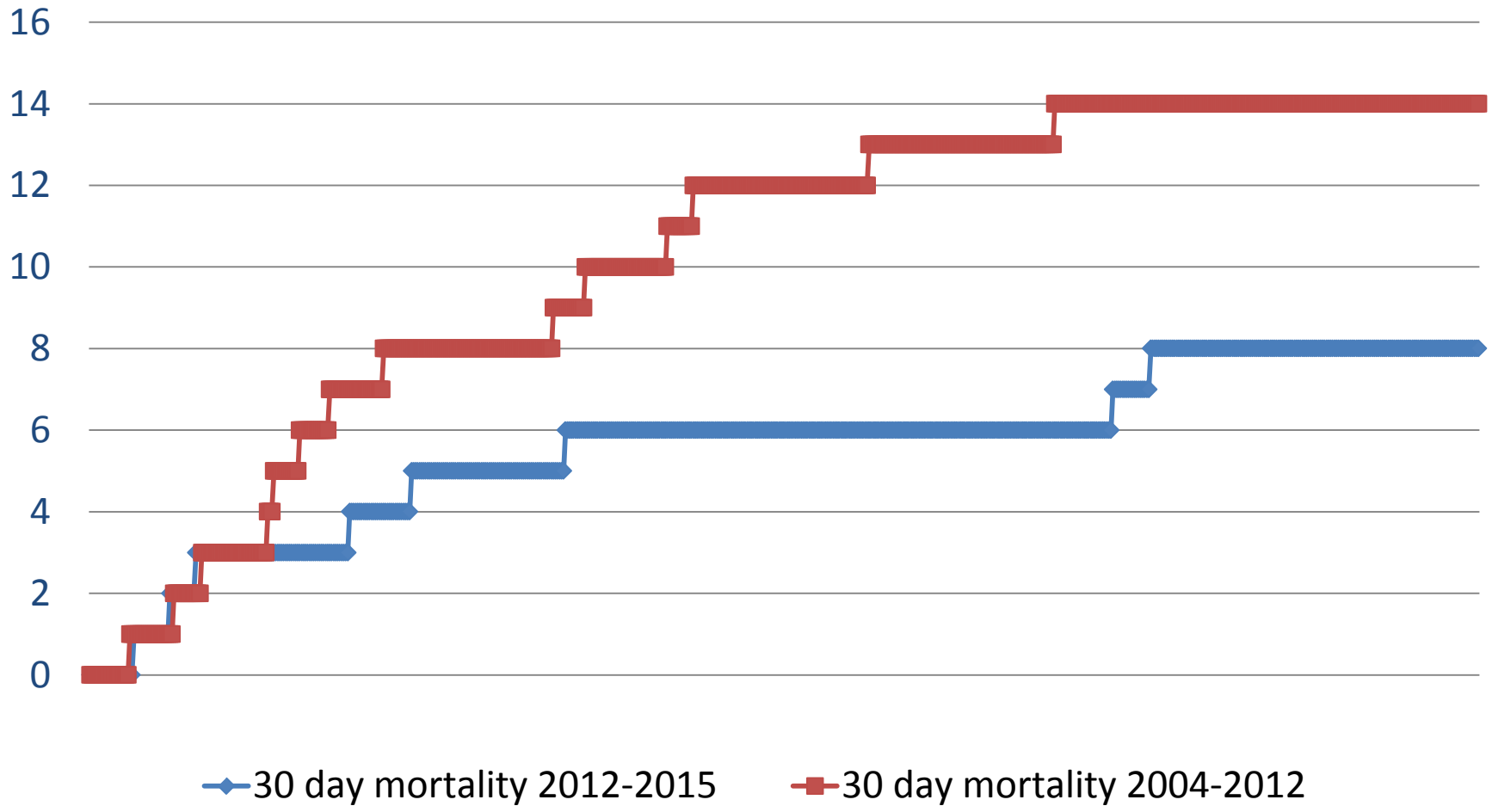
    - MBTS

    Increased pulmonary blood flow

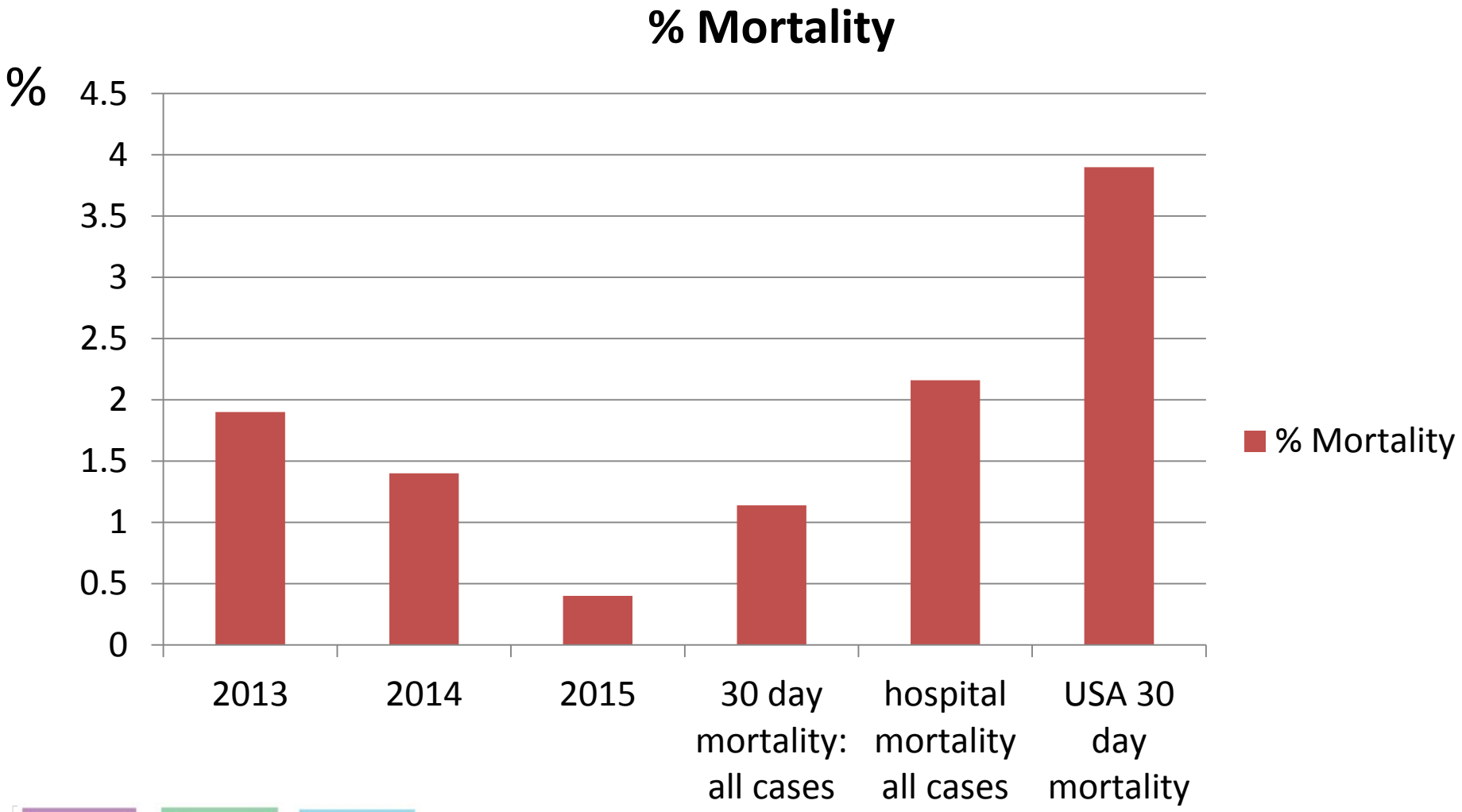
    - PAB

- Interventional Cardiology
  - Critical PS/Membranous Pulmonary atresia
  - Coarctation
  - Tetralogy of Fallot
  - Hybrid HLHS

HDVCH Mortality following cardiac surgery



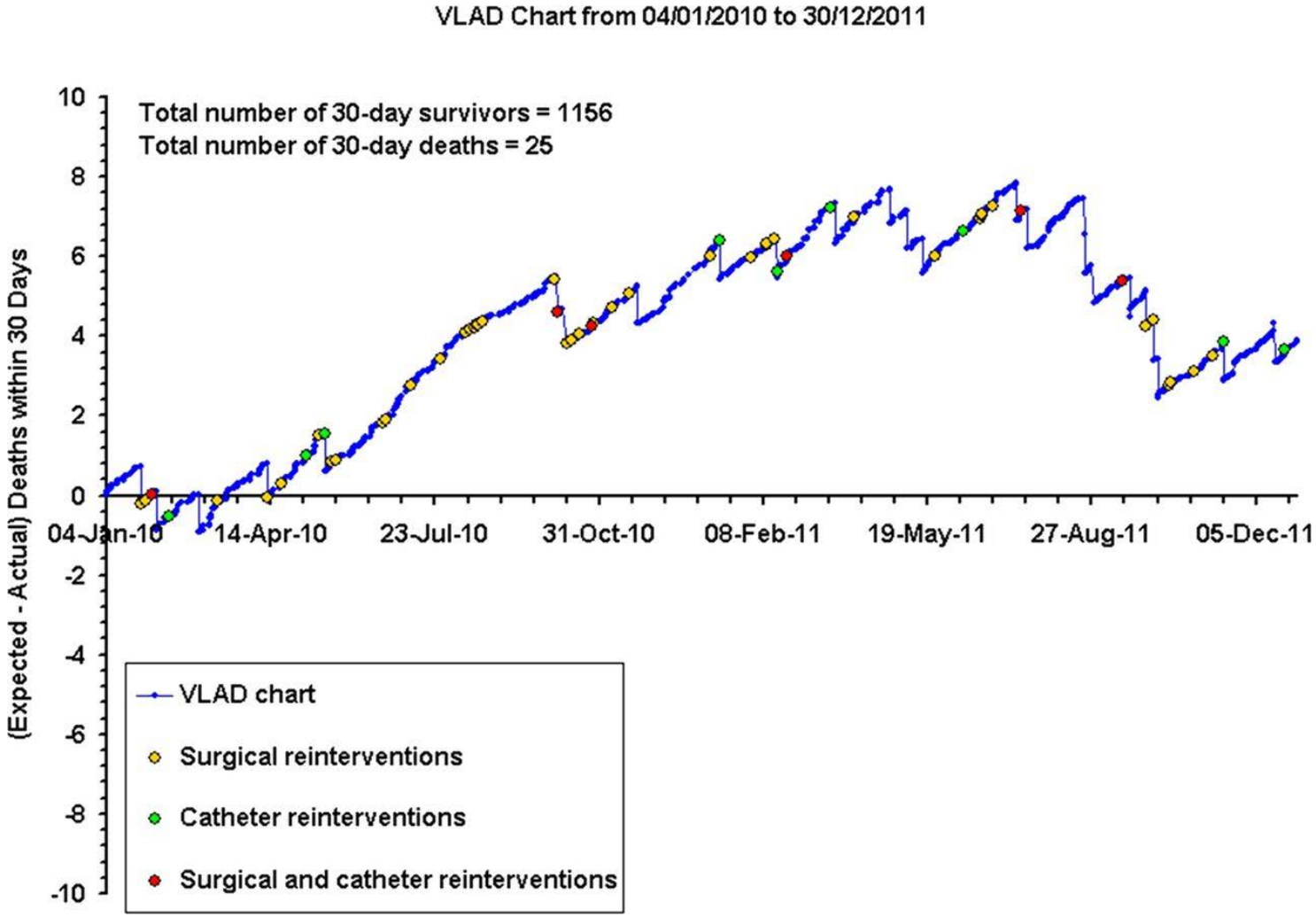
Surgical mortality: HDVCH



CCHD: Outcomes

- 1999–2006, congenital heart defects were listed as the **main** cause of death for 27,960 deaths
- Nearly half (48%) of the deaths due to congenital heart defects occurred during infancy
- Among those who survived the first year of life, 76.1% of deaths occurred during adulthood
- Males were more likely to die from congenital heart defects than females
- Differences between racial and ethnic groups persist

Real Time Surgical Outcomes



NBS for CCHD: Conclusions

- Most cases of CCHD can be operated with very low mortality risk provided they are diagnosed early
- NBS for CCHD is a valuable tool in identifying neonates with CCHD who at risk of being sent home or who have a home birth
- It includes a full clinical assessment in addition to oximetry
- 25% of screened babies will not be identified
- If universally adopted, it will undoubtedly save lives and reduce morbidity; the exact impact will remain obscure
- Prospective collection of surgical outcome data may allow an analysis over time of the impact of this intervention