Congenital Heart Disease: Classification Systems

- Anatomic
- Physiologic
- Surgical Procedures
- Familial or causal in which the developmental stage determines the extent of the defect: Cardiac looping occurs early in development so heterotaxias are associated with multiple, varied defects; VSDs may occur early or late and are, therefore, the most common defects.

Congenital Heart Disease: Prevalence

- 1.5-2.5/1000 live births.
- Bicuspid aortic valve in 1-2% live births.
- Estimated: 20,000 open heart procedures yearly for CHD.
- Post-op secundum ASD, pulmonary stenosis, patent ductus have normal life expectancy.
- Estimated > 500,000 adults in US with CHD.
Congenital Heart Disease: Etiologies

- 70-80% Multifactorial
- 6-12% Gross Chromosomal Anomaly
- 10-15% Single gene defect
- 1% Maternal Disease
- 1% Teratogen Exposure

Most cases (70-80%) are “multifactorial”

The Recurrence Risk with:

- 1 sib with CHD: 2-4%
- 2 sibs with CHD: 6-12%
- Mother with CHD: 6-12%
- Father with CHD: 2-4%

In 1/2 of these families the same defect recurs.
**Congenital Heart Disease: Etiologies**

6-12% have gross chromosomal anomalies

- Trisomy 21 (40% have CHD): AV canal
- Trisomy 18 (100% have CHD): VSD, PS
- Trisomy 13-15: VSD, ASD, TGV
- XO (Turner): Coarc, AS, VSD
- XXY (Klinefelter): Ebstein, Tetralogy

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**Trisomy 18**

100% have congenital heart disease
Trisomy 18

Trisomy 13
**Congenital Heart Disease: Etiologies**

10-15% Single gene defects

- Williams/elastin (del7q11.23): AS, PS
- Cri-du-chat (del5p15): VSD, AS, PDA
- Connexin 43: PS, heterotaxia
- Holt-Oram/TBX5 (12q24.1): ASD + limb
- Nkx2.5 (5q35): ASD + heart block
- DiGeorge/velo-cardio-facial syndrome
  22q11.2 hemizygous microdeletion
DiGeorge / velocardiofacial syndrome

Cardiac
Abnormal facies
Thymic hypoplasia
Cleft palate
Hypocalcemia
22nd chromosome

22q11.2 microdeletions are also found in isolated congenital heart diseases: interrupted aortic arch, truncus arteriosus, Tetralogy of Fallot, transposition, VSD, aortic coarctation, and double outlet RV.

DiGeorge / velocardiofacial syndrome (1 in 4000; 5% of CHD)

• Cardiac anomalies - 75%
• Abnormal facies - 41%
• Thymic hypoplasia – rare (but 75% have some immunodeficiency)
• Cleft palate – 11% (70% have some palatal anomaly)
• Hypocalcemia - 50%
DiGeorge syndrome; deletion of material from long arm of chromosome 22.

Fluorescence In-situ Hybridization (FISH) – normal. Green is an internal control labeling chromosome 22q13; Red labels 22q11.2 and has 2 copies (no deletion)
22q11.2 deletion syndrome

- Autosomal dominant
- 93% of probands have a *de novo* deletion
- 7% inherited from parent
- *Tbx1* (but mutations do not have CNS manifestations - cerebellar atrophy, polymicrogyria, neural tube defects, seizures)
22q11.2 deletion syndrome: congenital heart defects in 75%

- Tetralogy of Fallot – 22%
- Interrupted aortic arch – 15%
- Ventricular septal defect – 13%
- Truncus arteriosus – 7%
- Vascular ring – 5%
- Aortic arch anomaly – 3%

McDonald-McGinn, et al., Genet Couns 10:11-24, 1999

Congenital Heart Disease: Etiologies

- 1% Maternal Disease
  - Type I diabetes mellitus (2% affected)
  - Phenylketonuria (if not controlled)
  - Systemic lupus erythematosus (heart block & structural)

- 1% Teratogen Exposure
  - Alcohol (30% have some defect)
  - Anticonvulsants (2-3x increased risk)
  - Lithium
  - Retinoic acid
  - Rubella
AV Canal or Endocardial Cushion Defect

Aorta

LV

RV

AV valve leaflets draped over large defect
Atrial septal defect - Primum

Hypertrophied RV

ASD – Secundum type

RV
VSD-membranous type
Truncus arteriosus with VSD
Transposition of the Great Arteries

Aorta

Pulmonary artery

RV
LV

Double outlet right ventricle

Aorta

PA

RV
LV
Double outlet right ventricle

Aorta

PA

VSD