Striped Horses

John Kroger, MD, FAAFP

Islands Community Medical Services, Vinalhaven, ME

Yes, I have 9 children (plus 1 godson, 1 son-in-law and 3 daughters in law…
I put the Family in Family Medicine…

Striped Horses

- When you hear hoofbeats, think horses, not zebras

- **Theodore Englar Woodward** (March 22, 1914 – July 11, 2005)

Striped Horses

- When you hear hoofbeats….

- You are more likely to find an uncommon presentation of a common illness than a common presentation of an uncommon illness

Striped Horses

Based on clinical experience at Swift River Family Medicine and Rumford Hospital I added the caveat when working with medical students and residents:

"Just remember, Rumford has many ***striped horses***"

Striped Horses

- Striped horses – zebras found where you initially would not expect to encounter them…
- Rare disease:
  - A disease or condition that affects < 200,000 Americans (National Organization for Rare Disorders, Genetic and Rare Diseases Information Center)
  - Some European countries define a rare disease as one that affects < 1 in 2,000 people
- Rare diseases:
  - over 10,000 rare diseases
  - rare diseases are estimated to affect more than 30 million people in the United States
  - One in 10 Americans has a rare disease
    - and about half of them are children
  - Of the more than 6,800 rare diseases that have been identified, 72% are genetic.

Case 1

- 2 year, 8-month-old male admitted to hospital (Patient W)
  - Abscess in skin, R anterior chest wall near axilla
  - Bacteria: pseudomonas
  - Previous History:
    - Recurrent URIs, including multiple otitis media, bronchitis, sinusitis diagnoses
    - Pediatrician who had seen the child routinely prescribed amoxicillin for every presentation and ordered CBC.
      - WBC count varied from 2 – 5; differential varied with neutrophil % ranging from 10% - 40%
  - CBC at admission:
    - WBC 1.0
    - Total neutrophils reported by lab tech: 1%
    - Pathologist then reviewed: 0% neutrophils

Case 1 (continued)

- Child started on IV antibiotics, transferred to Maine Medical Center, Pediatric Hematology became involved
- Bone Marrow Biopsy was performed
  - Complete absence of B lymphocytes
  - Diagnosis: Bruton's X-linked agammaglobulinemia
  - Due to absence of B-lymphocytes, inability to make antibodies

Case 1 (continued)

- **SYNONYMS**
  - Bruton type agammaglobulinemia
  - Bruton's agammaglobulinemia
  - XLA
  - Agammaglobulinemia, BTK
  - Agammaglobulinemia, Bruton tyrosine kinase
  - BTK-deficiency

XLA

DISEASE OVERVIEW

X-linked agammaglobulinemia is a primary immunodeficiency characterized by very low levels of immunoglobulins .

People affected by this condition generally begin developing frequent and recurrent bacterial infections from about 6 months of age.

Commonly diagnosed infections include lung infections (pneumonia and bronchitis), middle ear infections, conjunctivitis, sinus infections, various skin infections, and infections that are associated with chronic diarrhea

X-linked agammaglobulinemia is caused by changes (mutations) in the BTK gene and is inherited in an X-linked recessive manner

Treatment aims to boost the immune system, which may be accomplished by administering immunoglobulins through a vein (IVIG) or subcutaneously (SCIG).

Frequent infections are generally treated with antibiotics.

XLA - continued

- XLA is a rare disorder, primarily affecting males. Females may be carriers but have no clinical manifestations. Its prevalence in the United States is **1 in 379,000 live births and 1 in 190,000 male births**.

- Forty percent of affected individuals have a positive family history while in **60% of the individuals the mutation is spontaneous**. Thus individuals with a typical phenotype but negative family history should be suspected to have XLA and tested adequately.

- XLA is caused by mutations in the *BTK* gene which is present on the long arm of the X-chromosome. *BTK* is a member of the Tec family of nonreceptor protein-tyrosine kinases which are signal transduction molecules. **Nearly 544 mutations have been associated with the disease**.

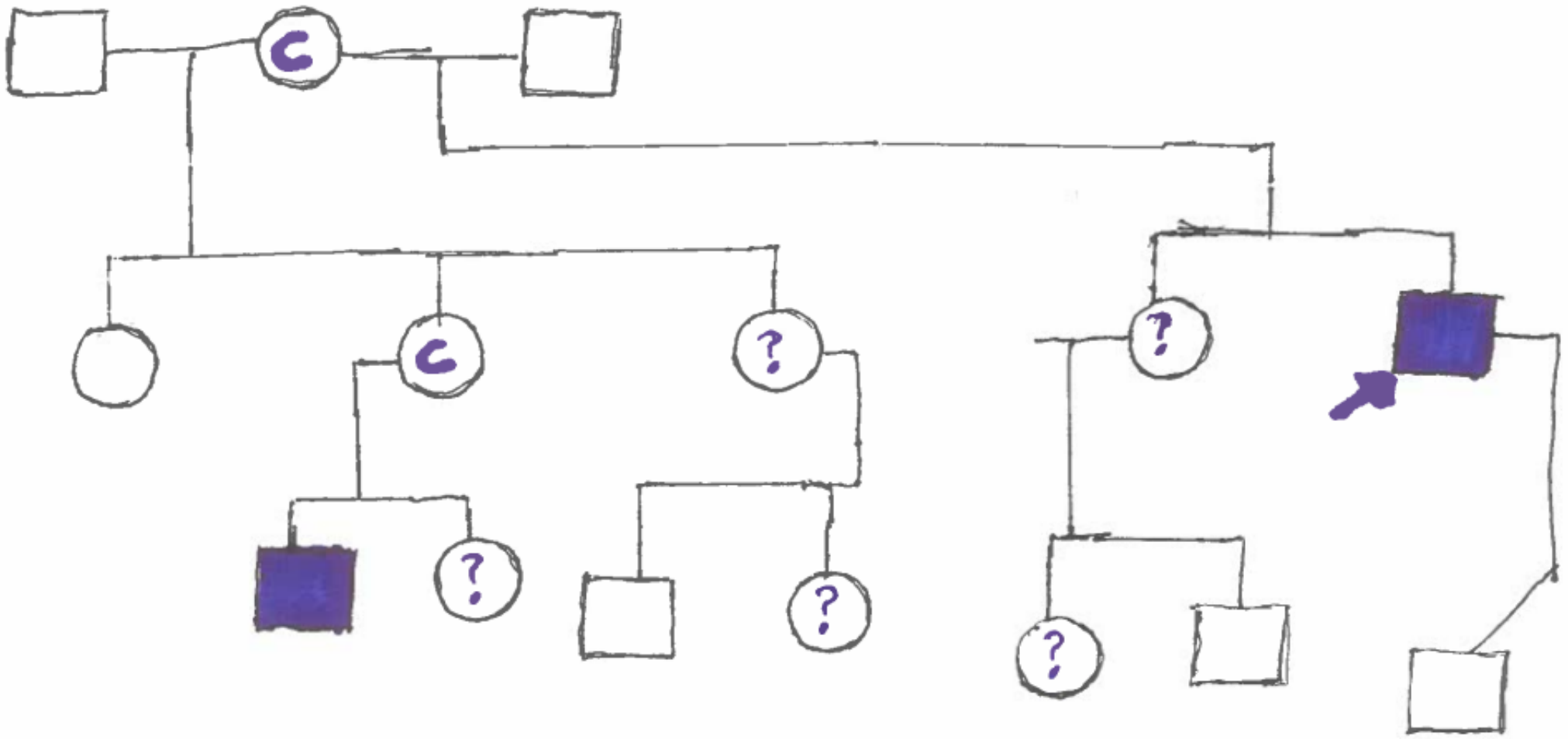
- Due to lack of B cell maturation, differentiation, and storage, lymphoid organs like the tonsils, spleen, adenoids, Peyer patches in the intestines, are poorly developed. The lymph nodes can, however, appear normal due to hypertrophy of T-cell areas.

XLA – case 1 continued

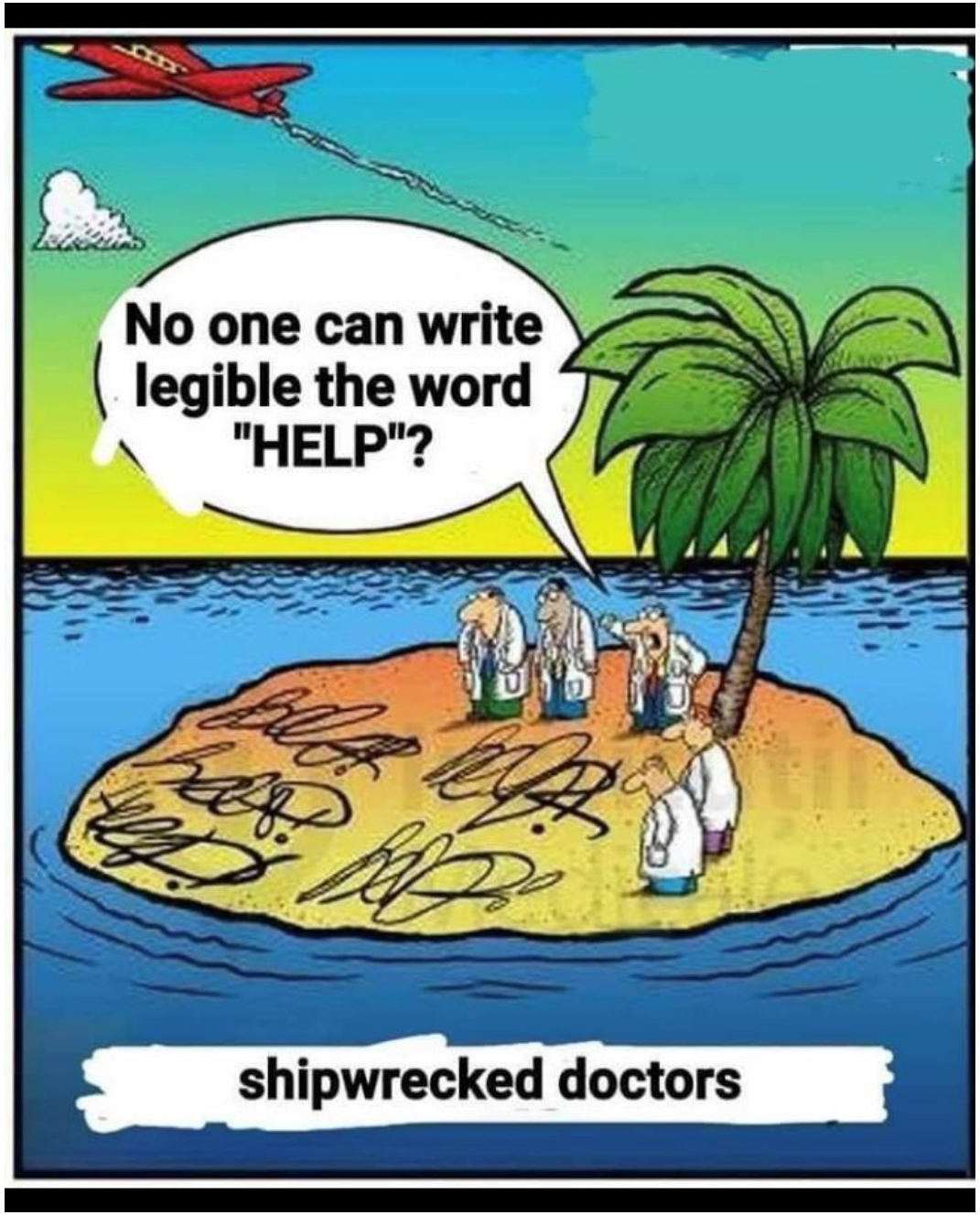
- How common is XLA?
- In December 1993, this was the first case diagnosed in Maine.
- X-linked disorder.

XLA - continued

- Patient W: has 4 older sisters
- Second oldest sister was pregnant about 9 years later
  - I delivered a healthy male infant
  - Cord blood
    - Cell typing – no B lymphocytes
    - Patient referred to Pediatric Immunology (who had been co managing my first case with me)



XLA GENOGRAM


No one can write legible the word "HELP"?
shipwrecked doctors

Case 2

- 48-year-old woman
  - Healthy
  - No tobacco use
  - History of Crohn's disease, which had been stable and not requiring any treatment for many years
  - Presents to ER with sudden onset chest pain
    - No diaphoresis
    - No dyspnea
    - EKG: STEMI
  - Patient transferred to CMMC via Lifeflight

Case 2 continued

- CMMC: patient brought to cardiac cath lab

- Diagnosis: SCAD Spontaneous Coronary Artery Dissection
  - She was treated with blood thinners – Eliquis for 12 months

SCAD

- Spontaneous coronary artery dissection is an emergency condition that occurs when a tear forms in a wall of a heart artery. Spontaneous coronary artery dissection also is called SCAD.

- SCAD can slow or block blood flow to the heart, causing a heart attack, heart rhythm problems or sudden death.

- SCAD most commonly affects **women in their 40s and 50s**, though it can occur at any age and can occur in men. People who have SCAD often don't have risk factors for heart disease, such as high blood pressure, high cholesterol or diabetes.

SCAD

- SCAD can cause sudden death if it isn't treated promptly. Get emergency medical help if you have heart attack symptoms — even if you think you aren't at risk of a heart attack.
- Risk factors for SCAD include:
- **Being female.** SCAD can happen to anyone. But it tends to affect women more than men.
- **Childbirth.** Some women who have had SCAD have recently given birth. This may be due to changes in hormones and stress on the blood vessels. SCAD has been found to occur most often in the first few weeks after delivery. But SCAD also can occur during pregnancy.
- **Extreme stress.** SCAD can happen after extreme stress. This includes intense physical exercise and severe emotional distress.
- **Fibromuscular dysplasia (FMD).** This condition causes weakening of the body's medium-sized arteries. FMD may lead to artery problems such as aneurysm or dissection. Women are more likely to have it than men.
- **Genetic conditions affecting connective tissue.** Ehlers-Danlos and Marfan syndromes have been found to occur in people who have had SCAD.
- **Very high blood pressure.** Severe high blood pressure can raise the risk of SCAD.
- **Illegal drug use.** Using cocaine or other illegal drugs might increase the risk of SCAD.

SCAD

- The true prevalence of SCAD remains uncertain, primarily because it is an underdiagnosed condition.
  - Missed diagnoses are driven by a low suspicion of ACS in young women even in the presence of classic presenting symptoms, limitations of current coronary angiographic techniques, and lack of clinician familiarity with the condition.
  - SCAD most commonly occurs in patients with few or no traditional cardiovascular risk factors.
  - Recent series using careful diagnostic criteria that exclude iatrogenic, traumatic, and atherosclerotic dissection suggest that SCAD may be a cause of up to 1% to 4% of ACS cases overall

SCAD

- Although there are wide ranges of clinical presentations and severities of SCAD, patients who survive and present for initial evaluation almost universally experience ACS and increased levels of cardiac enzymes.
- As many as 2% to 5% of patients present in cardiogenic shock.
- Among available series of patients presenting for evaluation, 26% - 87% of patients with SCAD present with STEMI, and 13% - 69% present with non STEMI.
- Presenting symptoms are consistent with atherosclerotic ACS, with chest pain being the most prevalent
- Ventricular arrhythmias or sudden cardiac death account for SCAD presentation in 3% to 11% of reported series

SCAD - continued

- Clinical presentation
  - STEMI
  - Non-STEMI
  - Ventricular tachyarrhythmias
  - CHF
  - Sudden Cardiac Death
- Most common cause in general population:
  - rupture of atherosclerotic coronary plaque leading to superimposed thrombosis, obstruction to the distal coronary flow, and coronary ischemia
  - SCAD leads to the formation of an intramural hematoma, compression of the true lumen, and obstruction to the distal coronary flow, resulting in ACS

SCAD - continued

- Etiology: is unclear and hypothesized to be multifactorial
  - Since SCAD occurs predominantly in young females, including peripartum, it is hypothesized that female sex hormones, environmental stressors, or underlying arteriopathies like fibromuscular dysplasia (FMD) contribute to its occurrence. FMD is a non-atherosclerotic and non-inflammatory vascular disease, common in younger women and can present with an aneurysm, stenosis, and dissection and affect the coronary circulation. A study showed that 10.5% of patients with FMD had an arterial dissection, and 2.5% had SCAD

SCAD – pregnancy related

- Women with pregnancy-related spontaneous coronary artery dissection have a poor prognosis.
  - Studies have shown they have
    - larger infarcts
    - more tendency to have left main and multivessel disease
    - reduced left ventricular ejection fraction
    - cardiogenic shock
    - STEMI,
    - ventricular arrhythmias

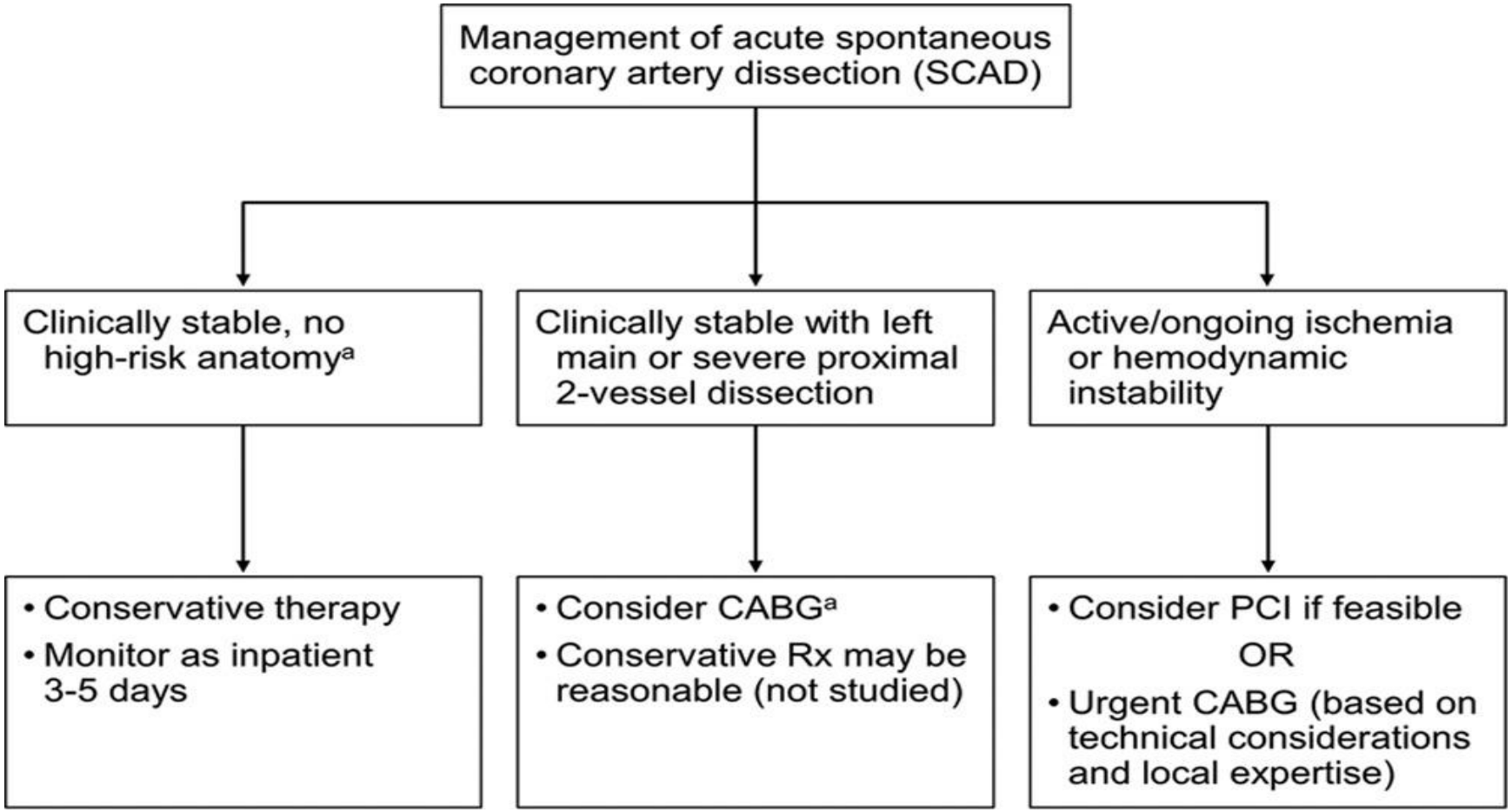
SCAD

- Spontaneous coronary artery dissection can affect both sexes
  - but the incidence is overwhelmingly higher in women in their fifth and sixth decades of life (about 90%) than in men
  - The risk factors for atherosclerotic coronary artery disease risk are lower in these patients than those who have ACS due to plaque rupture.
  - SCAD is a rare cause of acute coronary syndrome overall and constitutes only <1% of all myocardial infarctions.
  - As the condition is rare in men, data is limited for men

SACD - management

- Conservative management
  - usually the initially preferred modality of treatment for stable patients.
  - Studies have demonstrated angiographic healing in more than 90% of the patients with spontaneous coronary artery dissection, usually within a month.
  - However, recurrent MI due to propagation of the dissection is not uncommon.
  - A large-scale retrospective cohort study has shown that the recurrence rate is about 18%, and about half of the returning patients presented within the first week.

SCAD - Management



Case 3

- 3-month-old male infant
  - Previously healthy
  - Uncomplicated pregnancy and delivery
  - Mom with no medical issues or risks
  - Presentation: mother thinks she saw her child having a seizure in his car seat

- Exam:
  - Completely normal exam: neurologic, cardiac, pulmonary, etc.
  - Ordered labs
  - Mother brought child to have labs drawn at RH, then went to do errands with her child with her

Case 3

- 3-month-old infant, ? Seizure activity
  - Normal CBC, ESR, CRP
  - CMP normal except for BG 24
  - Called mother and asked her to return with child to hospital immediately

  - IV D5 started, child transferred to MMC
  - Continued with low blood sugars despite IV glucose

Congenital Hyperinsulinism of Infancy – Pancreatic Insulinoma

- Imaging at MMC showed 1 cm pancreatic mass
- Child sent by LifeFlight to CHOP (Children's Hospital of Philadelphia)
- CHOP – leading center for pancreatic tumors for children
- Insulinomas are extremely rare, with an estimated incidence of 1 to 4 cases per million persons per year; most insulinomas are diagnosed in adults.

Insulinoma

- Functional neuroendocrine tumor
  - Manifests with hypoglycemia caused by inappropriately high insulin secretion
  - Most commonly: solitary benign tumor
    - Can sometimes be associated with MEN1
  - Hypoglycemic episodes
    - Most often as fasting hypoglycemia
  - Usually diagnosed by biochemical testing when there is high clinical suspicion
  - Surgical resection – treatment of choice

Insulinoma

- Incidence: 1 – 4 per million per year
- Most commonly – single benign tumor
  - Can co-exist with other benign tumors (7% of cases)
  - Associated with MEN1 in 6-8% of cases
  - Surgical diagnosis happens at a median age of 47 – 50 years old

Insulinoma

- Hypoglycemia presentation:
  - Sympathoadrenal activation symptoms
    - Palpitations
    - Tremulousness
    - Diaphoresis
  - Severe hypoglycemia can occur
    - Neuroglycemic symptoms
      - Blurry vision
      - Confusion
      - Seizures
      - Behavioral changes
    - Amnesia of the hypoglycemic event is common

Case 4

- 1994
- 8-year-old girl
- Sore throat for 24 hours
- Upon entering the exam room, child is tripoding, leaning forward and drooling

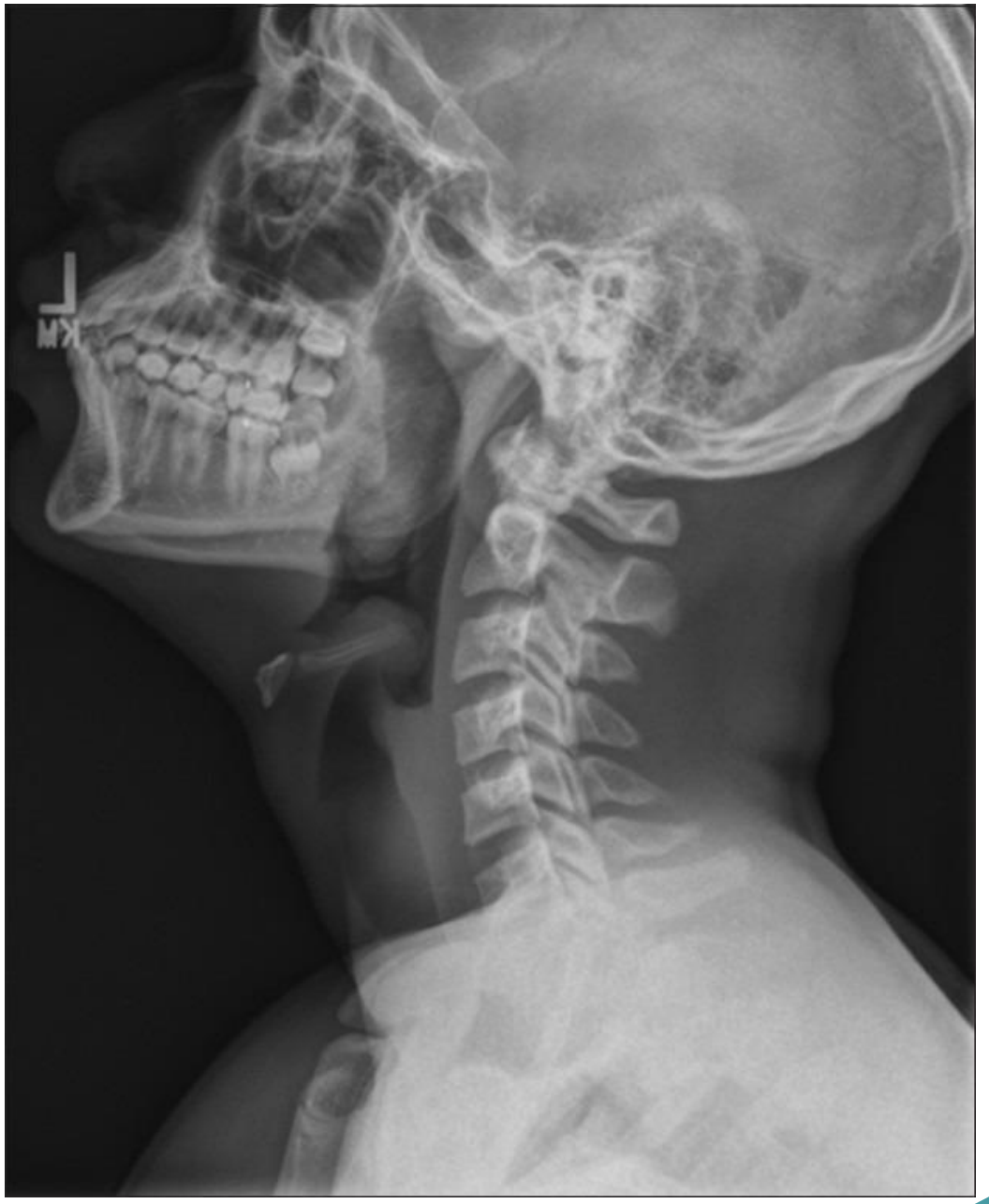
- Exam: NOT Performed

Case 4 - Epiglottitis

- 8-year-old girl
  - Lateral neck x-ray – classic thumb print sign
  - Brought to OR
  - Once arrangements were made for child to be accepted in transfer at CMMC and EMS crew was present, and surgeon present in the OR, the nurse anesthetist then performed a successful intubation
  - 2 days later child was extubated
  - Did well, no complications

Epiglottitis

Classic Thumb Print sign on lateral x-ray



Epiglottitis

- Acute epiglottitis is a life-threatening disorder
  - with serious implications to the anesthesiologist because of the potential for laryngospasm and irrevocable loss of the airway.
- Acute epiglottitis can occur at any age.
- Early diagnosis with careful and rapid intervention of this serious condition is necessary in order to avoid life-threatening complications

Epiglottitis

- inflammatory edema of the arytenoids, aryepiglottic folds and the epiglottis
- supraglottitis may be used instead or preferred to the term acute epiglottitis

Epiglottitis

- Before the development of the Haemophilus influenzae type b vaccine, the majority of cases were caused by H.influenzae and the condition was far more common.
- In the post-vaccine era, the pathogens responsible are more varied and can also be polymicrobial. For this reason, the term "supraglottitis" is often preferred, as the infections may affect the supraglottic structures more generally.
- Edema due to infection of the epiglottis and supraglottic structures can be gradually progressive until a critical mass is reached, and the clinical scenario can rapidly deteriorate and lead to airway obstruction, respiratory distress, and death.

Epiglottitis

- Acute epiglottitis can occur at any age.
- The responsible organism used to be Hemophilus influenzae type B (Hib), but infection with group A b-hemolytic Streptococci has become more frequent after the widespread use of Hemophilus influenzae vaccination.
- There are differences in trends, occurrences and management of acute epiglottitis between children and adults.
- There is also more diversity in the cause of epiglottitis in adults
  - The incidence of acute epiglottitis in adults ranges from 0.97 to 3.1 per 100,000, with a mortality of approximately 7.1%. The mean annual incidence of acute epiglottitis per 100,000 adults significantly increased from 0.88 (from 1986 to 1990) to 2.1 (from 1991 to 1995) and to 3.1 (from 1996 to 2000).

Epiglottitis

- Symptoms can be exacerbated by patient discomfort and agitation, particularly in children
  - so any patient with a diagnosis of true supraglottitis must have their airway secured under the most controlled circumstances possible, and every attempt should be made to keep the patient as calm and comfortable as possible until an airway is secured.
- The airway should not be instrumented for oral exams or endoscopy in the clinic or Emergency Department, and no patient with a potentially unstable airway should be sent to the radiology department for imaging.

Epiglottitis

- Since the addition of the HIB vaccine to the infant immunization schedule in many countries worldwide, the annual incidence of epiglottitis in children has decreased overall.
- However, the incidence in adults has remained stable, or increased.
- Additionally, the age of children who have had epiglottitis has increased from three years old to six to twelve years old in the post-vaccine era

Epiglottitis

- While in the past epiglottitis was thought to be primarily a disease of young children, it is now much more likely practitioners will encounter epiglottitis/supraglottitis in adults as well.

Epiglottitis

- The singular, most important, aspect of treatment is to **secure the airway**.
- Experienced providers should intubate these patients since their airways are regarded as difficult.
- An individual capable of performing a tracheotomy should be available if needed.

Case 5

- 6-month-old girl brought to ER by parents due to apparent difficulty breathing, shortness of breath
- History:
  - Uncomplicated pregnancy and delivery
  - Normal exam at birth and well child visits
  - Up to date on vaccines
- ER evaluation:
  - L pneumonia with complete white out of lung
  - Hypoxia
  - Transferred to MMC via LifeFlight

Case 5

- Hospital Course at MMC
- After 3 days of IV antibiotics, child is still requiring oxygen
- Repeat Chest x-ray shows persistence of Left lung white out
- CT of the chest is ordered
- Congenital absence of the L lung
- + tests for RSV
- In simple terms, a child with one lung can do quite well, unless they get an RSV infection

Case 5

- Family history:
  - Dad says: I had some sort of heart problem when I was a baby, they did surgery, and I have never had a problem since
- Genetic work up for this young girl
  - Partial deletion of the short arm of chromosome 22
  - Chromosome 22q11.2 deletion
  - DiGeorge Syndrome

DiGeorge Syndrome

- Chromosome 22q11.2 deletion syndrome (22q11.2DS) is a disorder caused by a small piece of chromosome 22 missing.
- 22q11.2DS is associated with a range of problems including:
  - congenital heart disease
  - palate abnormalities
  - immune system dysfunction including autoimmune disease
  - low calcium (hypocalcemia) and other endocrine abnormalities such as thyroid problems and growth hormone deficiency
  - gastrointestinal problems, feeding difficulties
  - kidney abnormalities
  - hearing loss
  - Seizures
  - skeletal abnormalities
  - minor facial differences
  - learning and behavioral differences.
  - The symptoms of this condition are extremely variable, even among members of the same family.

DGS – DiGeorge Syndrome

- Microdeletion of 22q11.2 is the most common microdeletion syndrome, affecting approximately 0.1% of fetuses
- The rate of 22q11.2 microdeletion in live births occurs at an estimated rate of 1 in 4000 to 6000

DiGeorge Syndrome

- DiGeorge syndrome is easy to remember using the "CATCH-22" mnemonic:
  - **C**onotruncal cardiac anomalies
  - **A**bnormal facies
  - **T**hymic hypoplasia
  - **C**left palate
  - **H**ypocalcemia
  - **22**q11.2 microdeletion

DiGeorge Syndrome

- Parents of child with absence of left lung
- Father's medical records indicate he had repair of Tetralogy of Fallot as an infant
- Moved to Connecticut
  - Had another child
  - This daughter was born with:
    - Tetralogy of Fallot
    - Congenital Bell's Palsy of the L side of her face
    - Absence of the proximal phalanx of the 1st digit L hand
    - Hypoplastic L main stem bronchus
- Family moved back to Maine as they did not trust the specialists at Yale-New Haven


Shootin' S.T.A.R.

Other cases I have been involved with

- ITP in 22-month-old, 2 weeks s/p pneumonia
- 8-year-old presenting with knee pain – s/p sore throat 2 weeks prior
- Leptospirosis in 2 individuals, contracted from family dog which ended up being hospitalized at a veterinary hospital
  - 93-year-old male and his 69-year-old daughter recovered with appropriate antibiotic treatment
- Malignant tumor parotid gland in 34-year-old woman, 4 months after delivering a healthy baby
  - “worst neck exam I ever performed in my career”
- Stiff Person Syndrome

Other cases I have been involved with

- Congenital Indifference to Pain
- CREST syndrome patient with cardiomyopathy
- Von Willebrand's presenting in unusual way
  - Age 16, mono, severe nosebleed, elevated PTT – initially felt to be related to the EBV infection
  - 5 years later – had appendectomy – bleeding caused case to extend from 45 minutes in OR to over 2 hours – labs confirmed von Willebrand's at that time

Information on Rare Diseases

- National Organization for Rare Diseases
  - NORD
  - https://rarediseases.org/

- Genetic and Rare Diseases Information Center
  - GARD
  - https://rarediseases.info.nih.gov/


adidas

Inconceivable…

Live long and prosper…