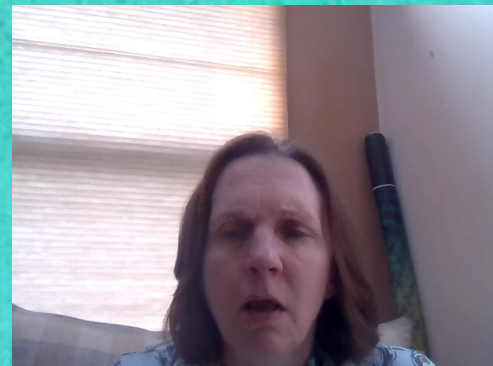


Comprehensive Review of Digestive Issues in Prader-Willi Syndrome

**Ann Scheimann MD MBA
Department of Pediatrics
Johns Hopkins School of Medicine
Adjunct Faculty, Baylor College of Medicine**



Disclosures:

Research support:

Co-Investigator:

Past: Millendo, Insys

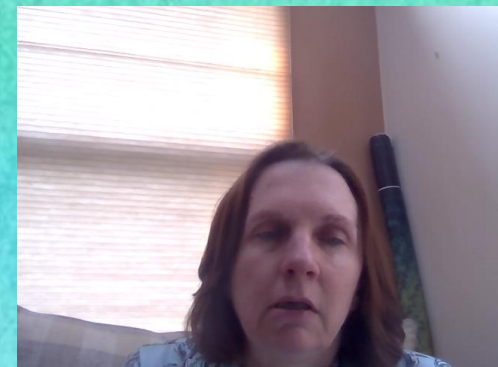
Current: Harmony, Saniona

Grant Support:

FPWR

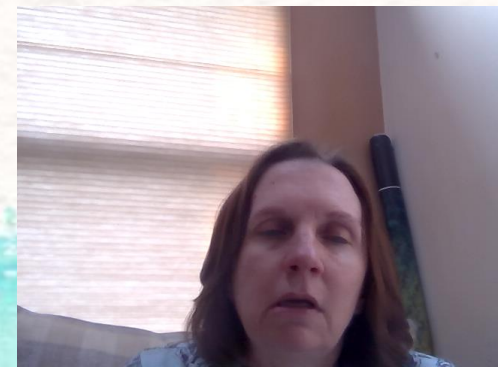
NIH/NIMH, NHLBI, NIDDK

Off-label use of medications



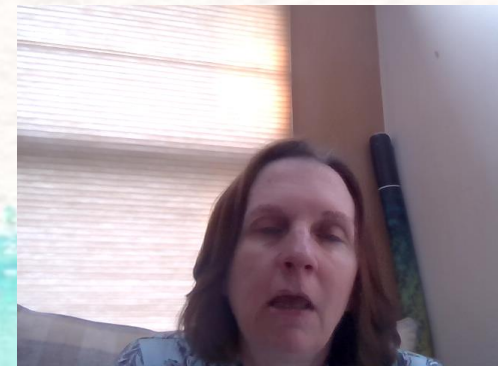
Outline of Presentation

- **Prevalence of gastrointestinal (GI) symptoms in Prader-Willi Syndrome**
- **Review of published clinical data, management approaches (evidenced-based and experiential in Prader-Willi syndrome)**
 - **Feeding/swallowing oral health**
 - **Gastric emptying/gastric dilation**
 - **Constipation/rectal picking**

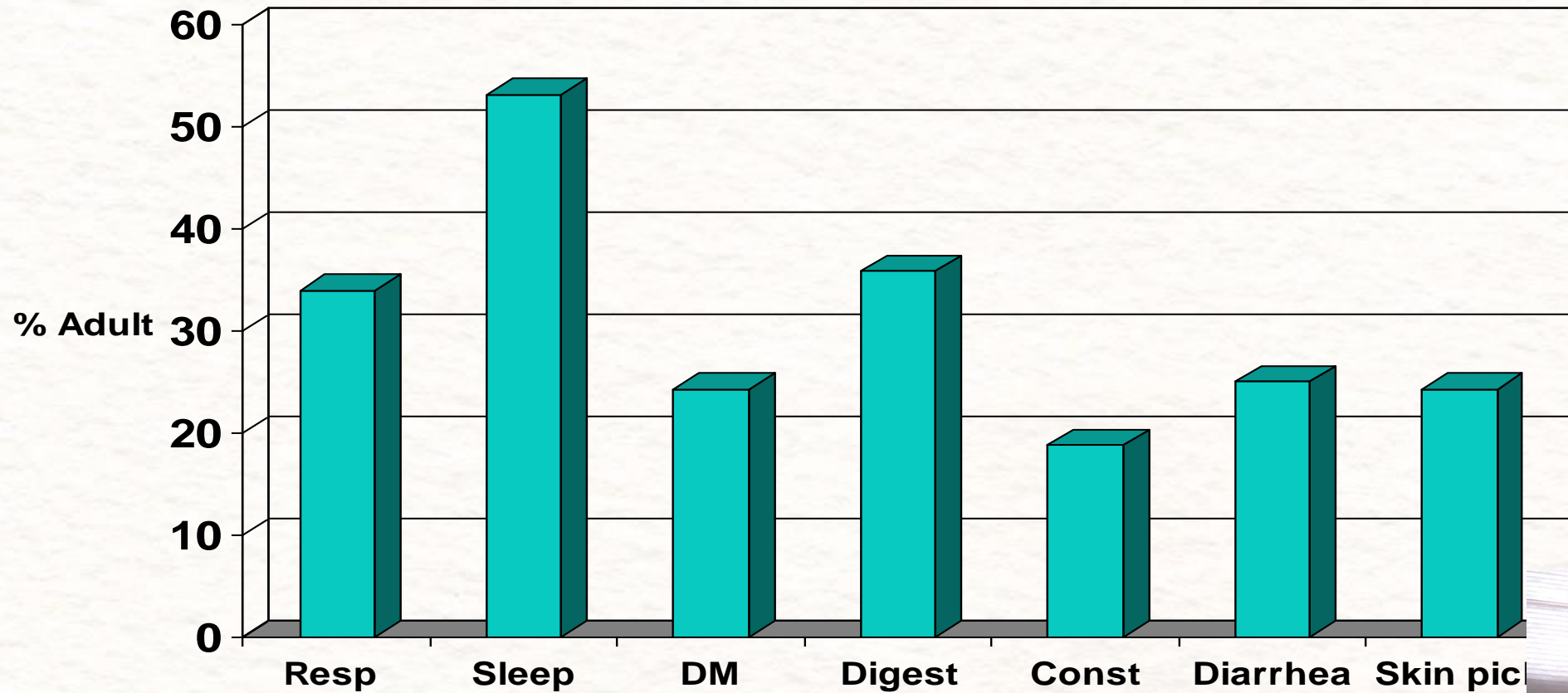


How Common Are GI-related Symptoms?

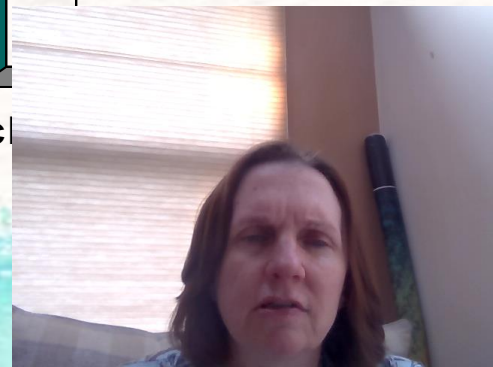
- Early feeding difficulties very common among infants with PWS
 - Major criteria for clinical diagnosis of PWS (Holm, et al., Pediatrics 1993)
 - Infant feeding problems seen in 93% of patients (Gunay-Aygun, Cassidy Pediatrics 2003)
- Frequent reports of reflux symptoms, and inability to vomit
 - Early deaths from aspiration (Reflux related?)
 - Significant morbidity from high pain threshold and vomiting threshold well documented



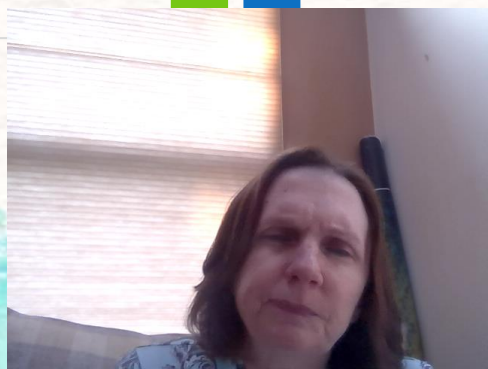
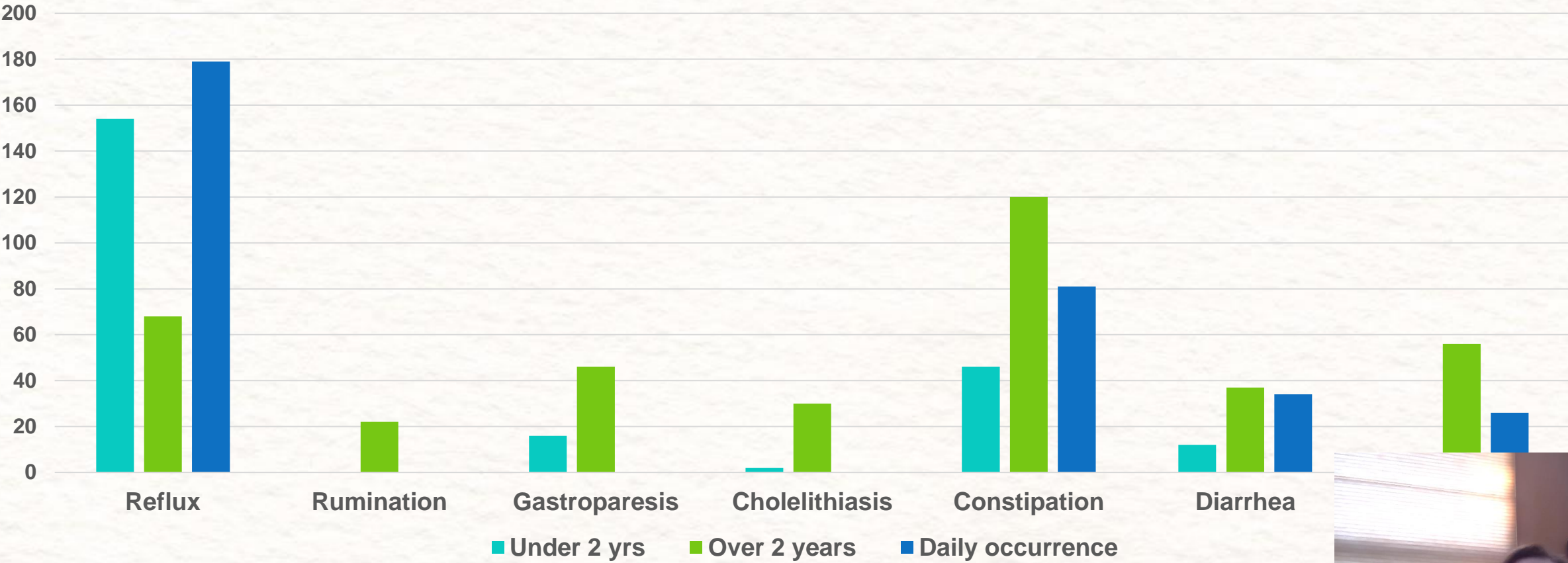
Symptom Prevalence Among Adults With Prader-Willi Syndrome



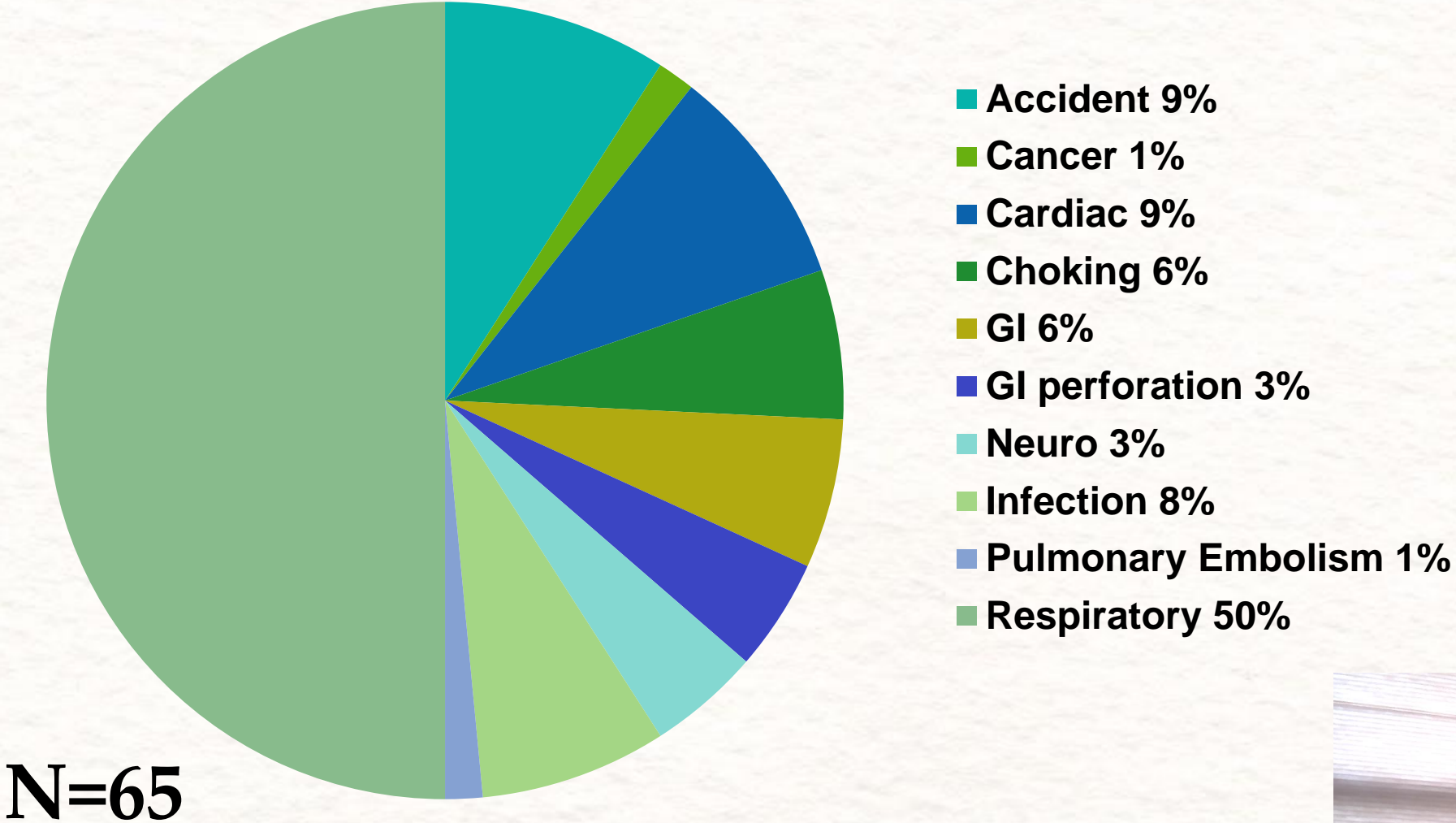
Combined data from JV Butler et al (2002), S Cassidy et al. (1995), and B. Whitman



FPWR Registry 2019 : Frequency of Gastrointestinal Symptoms



Pediatric Deaths: PWSA USA Data

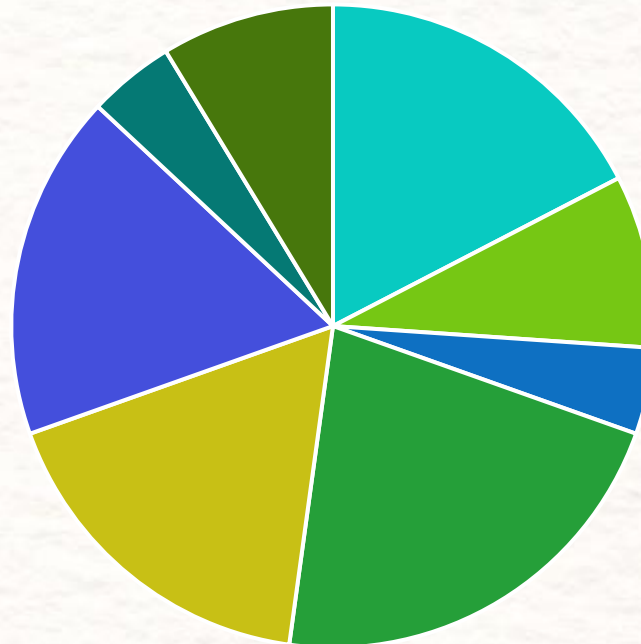


Courtesy of Jim and Carolyn Loker and



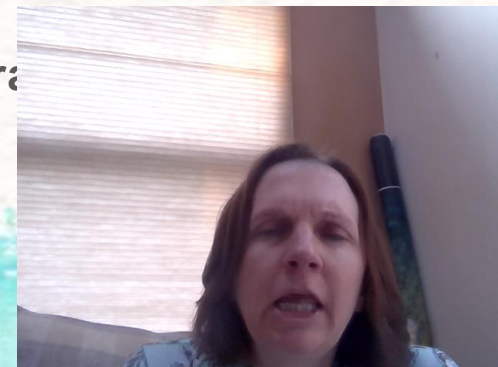
Mortality in Adults with Prader-Willi Syndrome: International Data

Cause of Death

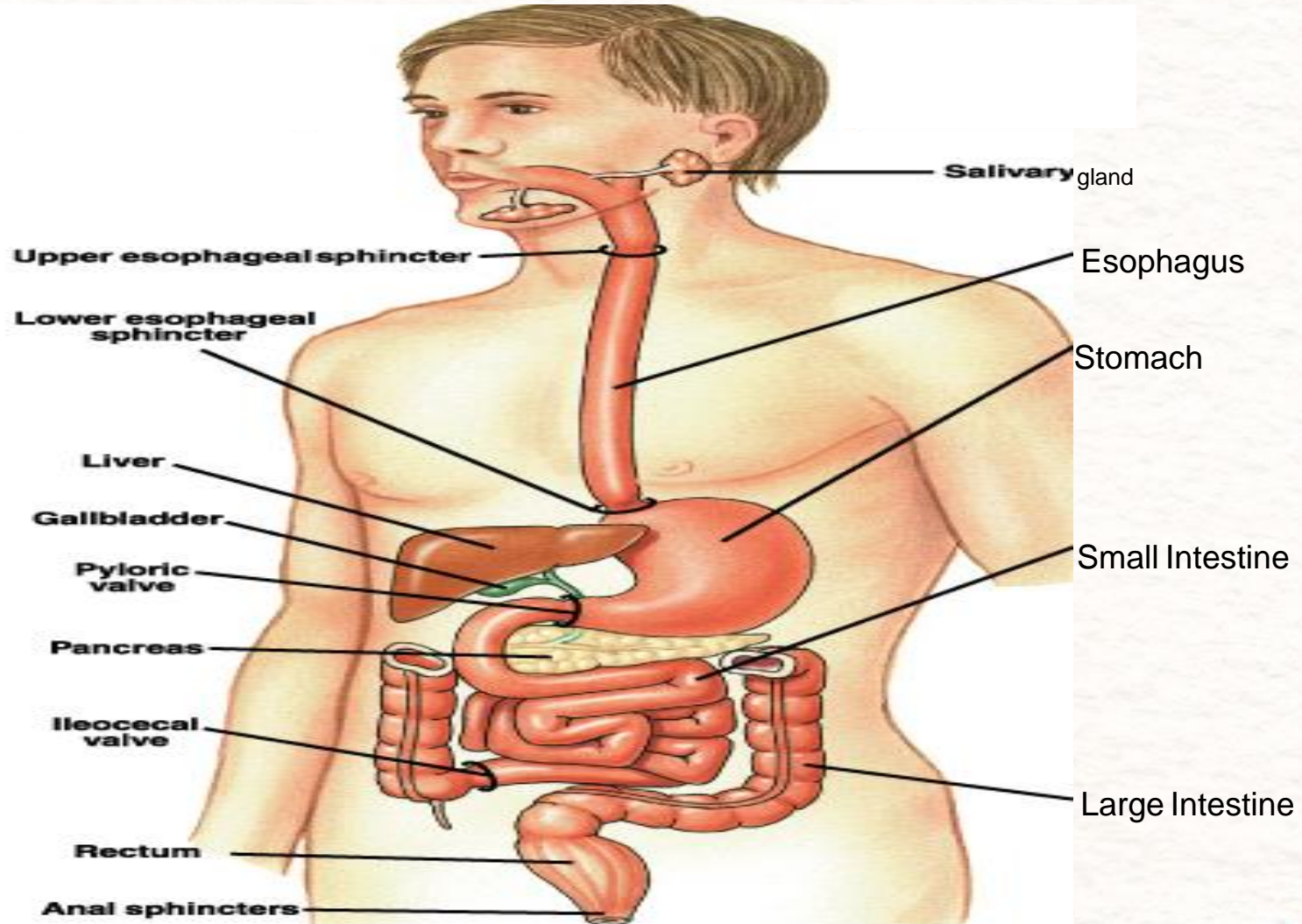


■ Obese/pneumonia ■ Accident ■ Unknown ■ Obese/OSA ■ Stroke/PE ■ Heart ■ Aspiration

Pooled published data from Europe, Australia, Japan, US



Overview of GI Anatomy

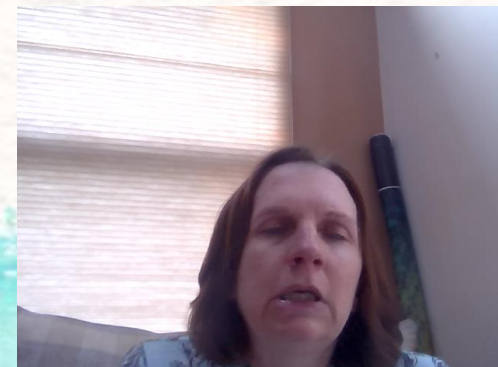
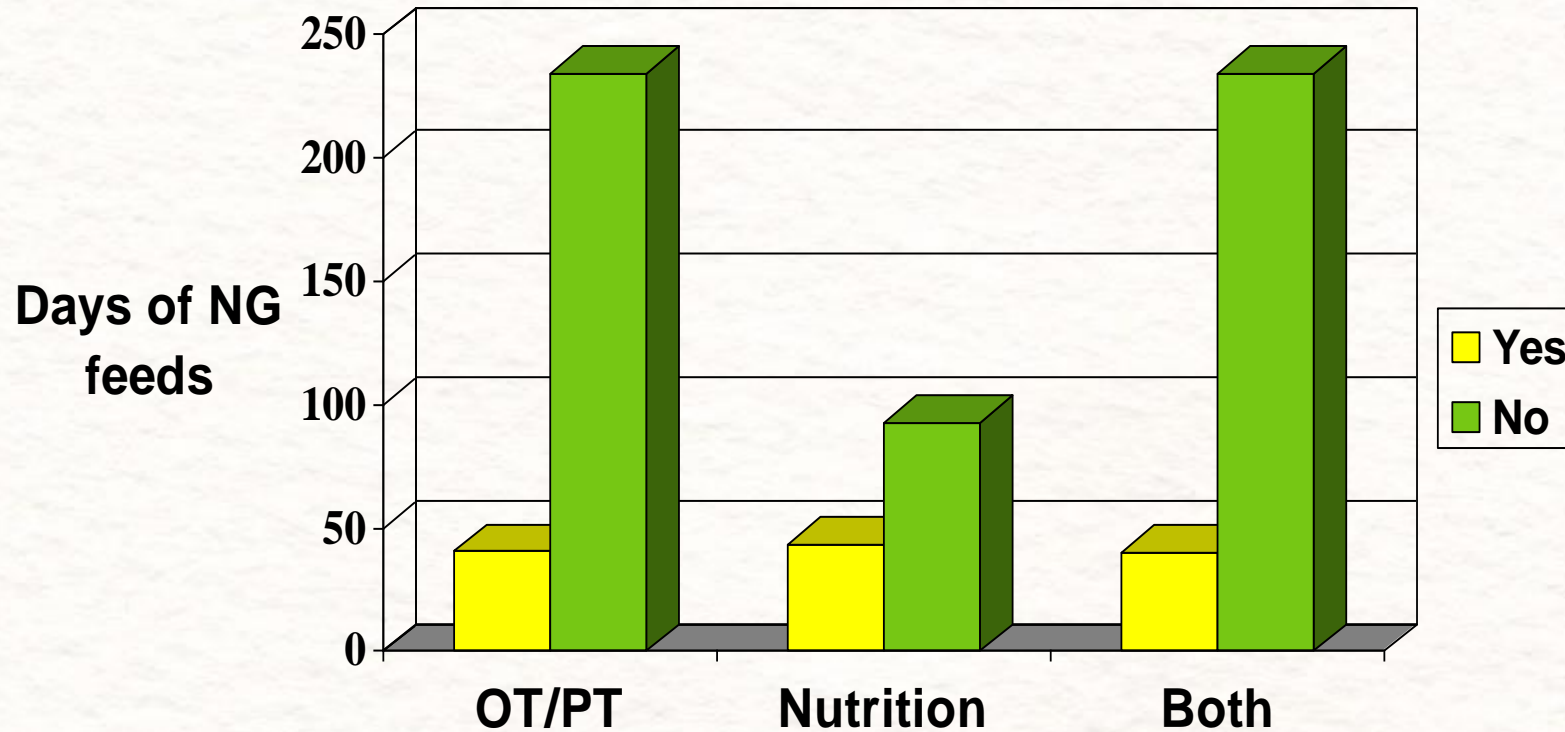


Common Oral Issues

- ▶ **Oromotor weakness**
 - ▶ Hypotonia
 - ▶ Palatal abnormalities
- ▶ **Dental abnormalities**
 - ▶ Micrognathia (Small jaw)
 - ▶ Microdontia (small teeth), delayed eruption and hypoplastic (weak) enamel, dental crowding and erosions from rumination
- ▶ **Salivary abnormalities (xerostomia-thick saliva)**
 - ▶ Salivary flow is only 20-50% of normals (PS Hart, *Ann NY Acad Sci* 1998 and Saeves et al *Arch Oral Biol* 2012)

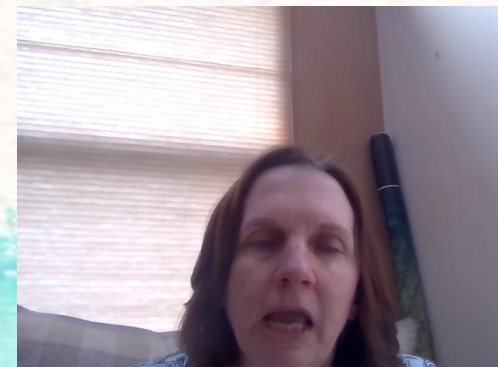


Feeding and Swallowing Interventions : Nutritional Intervention and Oromotor Therapy on Nasogastric Tube (NG) or Gastrostomy Feeds in Texas Children's Infants



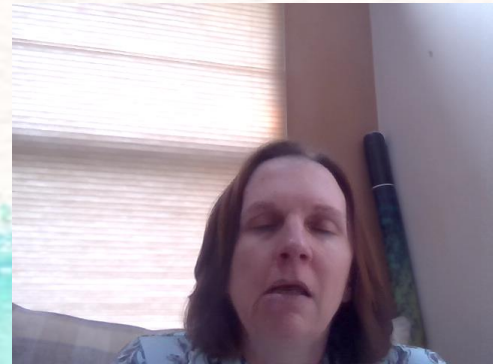
Swallowing Issues Among Adults and Children with PWS

- Study (2014) funded by PWSAUSA by Gross, Gisser and Cherpes published in Dysphagia 10/2015
- VFSS Swallow Studies using thin liquids and barium cookies in 30 adults with PWS
 - Significant, sometime substantial pharyngeal residue was present in 97% of subjects
 - Moderate to severe esophageal stasis was detected in 100% of participants
 - ***None could feel pharyngeal residue or esophageal stasis, regardless of the quantity***



Choking/Prader-willi Syndrome

- Review of data provided by families and collected through the PWSA bereavement program
 - 39% of families reported history of choking among the 52 families who completed questionnaires
 - Choking listed as cause of death in 12/152 patients (7.9%)
 - Average age 24 years (3-52 years)
 - 92% of patients were male



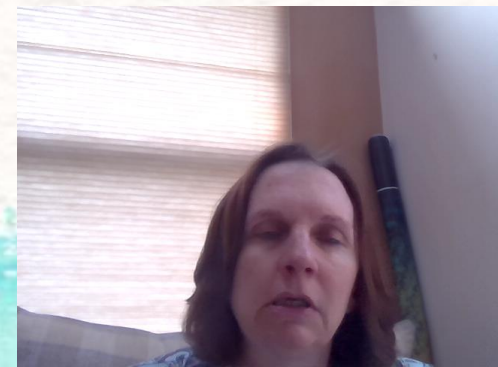
Choking/Prader-willi Syndrome

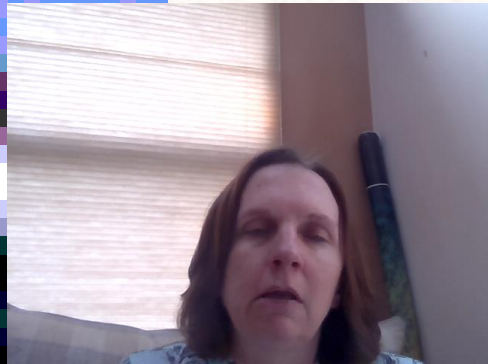
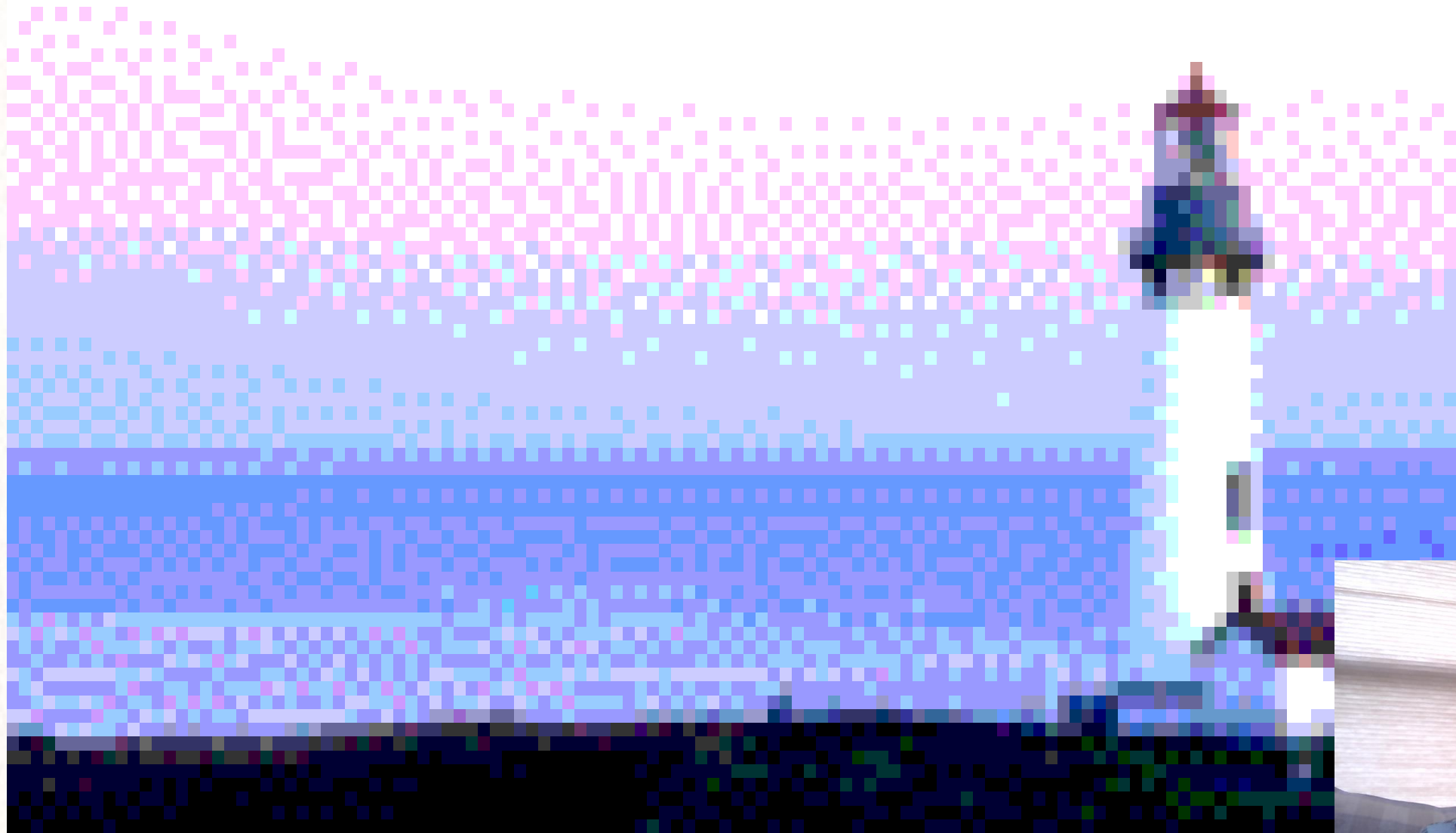
- Factors predisposing to choking
 - Hyperphagia/Foraging
 - 25% of patients were food-stealing
 - Thick saliva
 - Weakness of pharyngeal muscles
 - Gastritis/Gastroesophageal Reflux
 - Gastritis noted in 38% at autopsy (3/8)



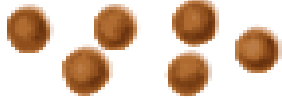






Choking/Prader-willi Syndrome

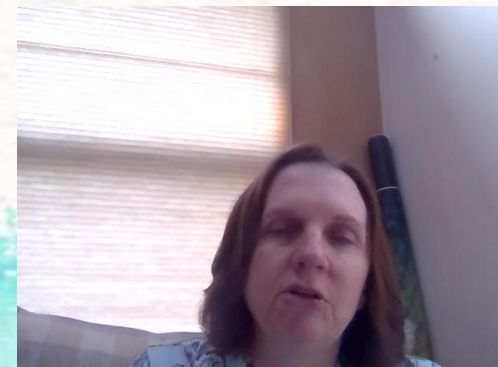
- ▶ Current Interventions
 - ▶ Heimlich maneuver training
 - ▶ Diet interventions
 - ▶ Supervised meals
 - ▶ Holiday monitoring
 - ▶ Meal pacing/Chewing prompts
 - ▶ Fluid intake with self regulation (straw)
 - ▶ Treatment of Gastritis/Reflux





Bristol Stool Chart

Type 1		Separate hard lumps, like nuts (hard to pass)
Type 2		Sausage-shaped but lumpy
Type 3		Like a sausage but with cracks on the surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear-cut edges
Type 6		Fluffy pieces with ragged edges, a mushy stool
Type 7		Watery, no solid pieces. Entirely Liquid



Frequency of Constipation in PWS

- ▶ 21 patients with PWS (median age 32 with median BMI 23.6) at Aarhus Center

- ▶ Constipation history, rectal exam, rectal diameter by ultrasound, transit time

- ▶ 30 healthy volunteers (median age 26 and BMI 23.1) controls

- ▶ Symptoms

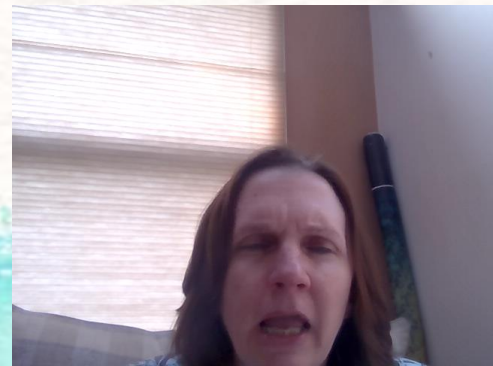
- ▶ Infrequent stools (<3/week) 47%

- ▶ Straining 37%

- ▶ Hard Stools 32%

- ▶ No difference in rectal diameter or transit time between PWS and controls

- ▶ 29.3% of PWS adults through questionnaire study



Anorectal Motility - Defecation

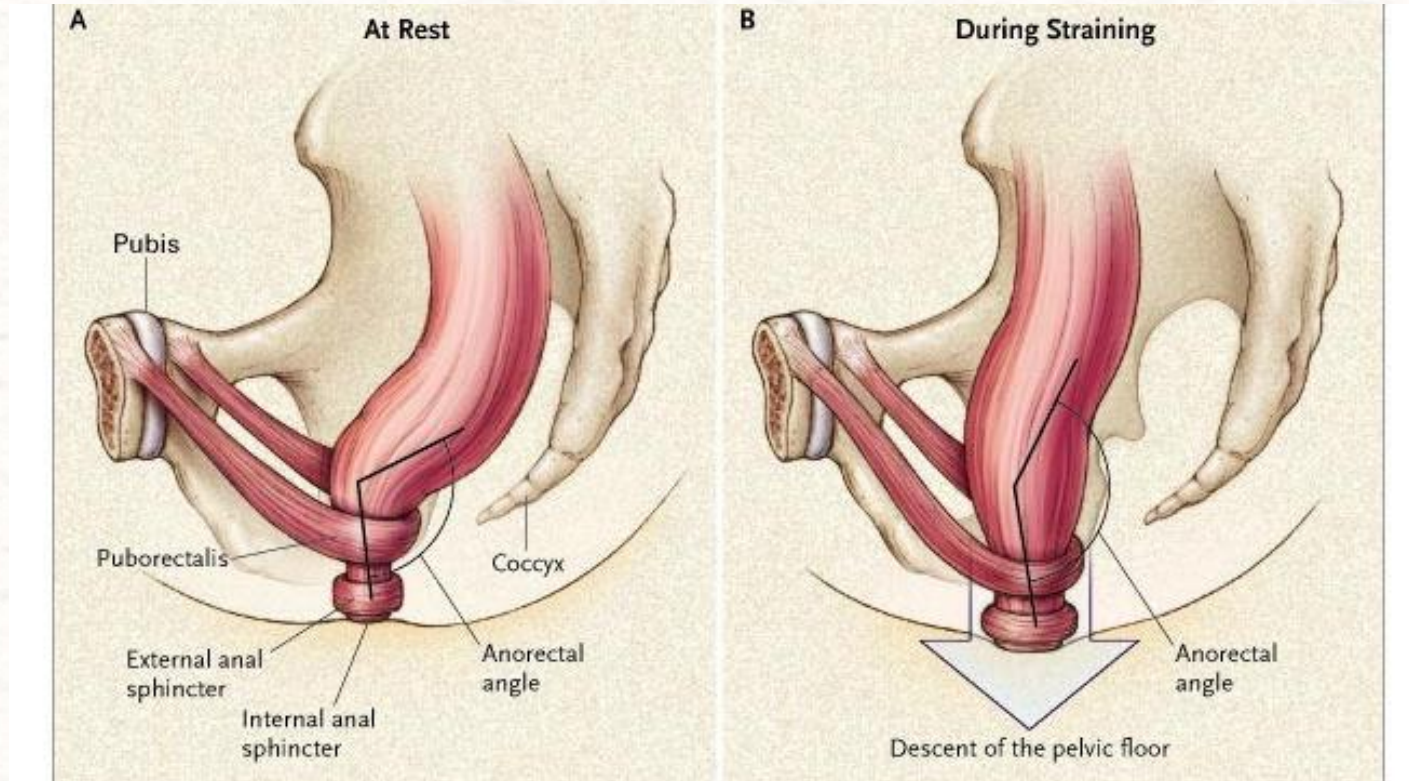
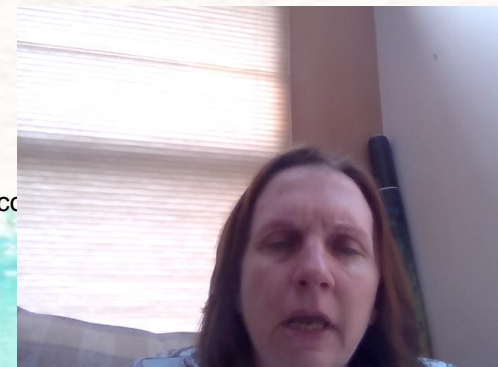
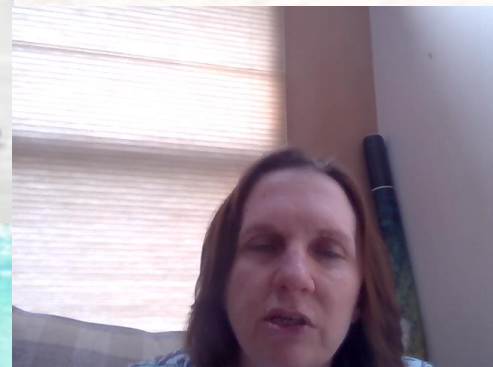


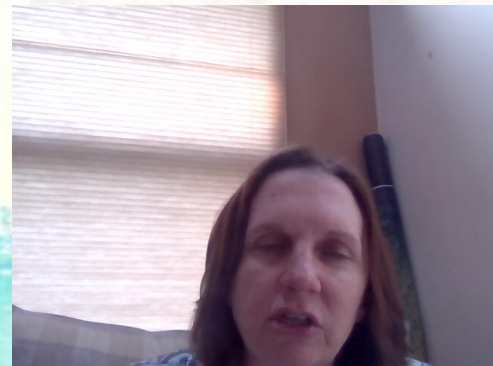
Image from <http://msk-anatomy.com>



Toilet Seating- Not This



Toilet Seating- but this!



Interventions for Constipation



Flaxseed
-Adjunct
-EFA

Magnesium compounds

Normal renal function



Treatment for Rectal Ulcer

- Relieve constipation and avoid straining during defecation
 - Consider stool softeners- titrate to keep stools soft
 - Decrease symptoms of pruritus ani from fecal bile acids
- Behavioral modification to decrease digging behavior
 - Supervised timed bathroom privileges
 - Reversed clothing to decrease anal access
 - Biofeedback/physical therapy to address toileting posture



PWSA-USA Constipation Alert

- Medical Alert on Constipation In Individuals with Prader-Willi Syndrome
 - James Loker MD
 - CAB PWSAUSA
 - “Failure of standard methods to clear stool in a timely manner in the setting of pain, distension, decreased appetite warrants surgical or GI consultation.”



Gastric Dilation



Gastric Dilation/Necrosis

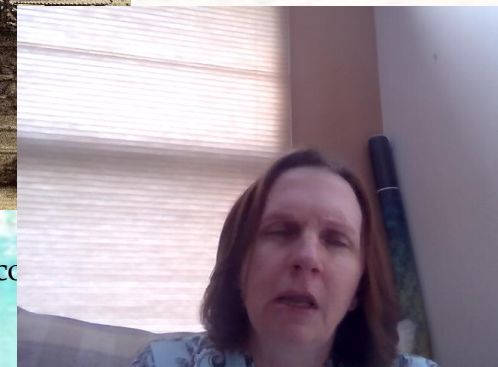
- ▶ Severe acute gastric dilatation described by Simone-Emmanuel Duplay in 1883
- ▶ In dogs related to stretching then twisting of stomach along axis
- ▶ 1859- Brinton suggested atony- inhibition of gastric motor nerves allowing progressive gastric distension
- ▶ Some models suggest feedback problem with solitary nucleus



Duplay, wikipedia



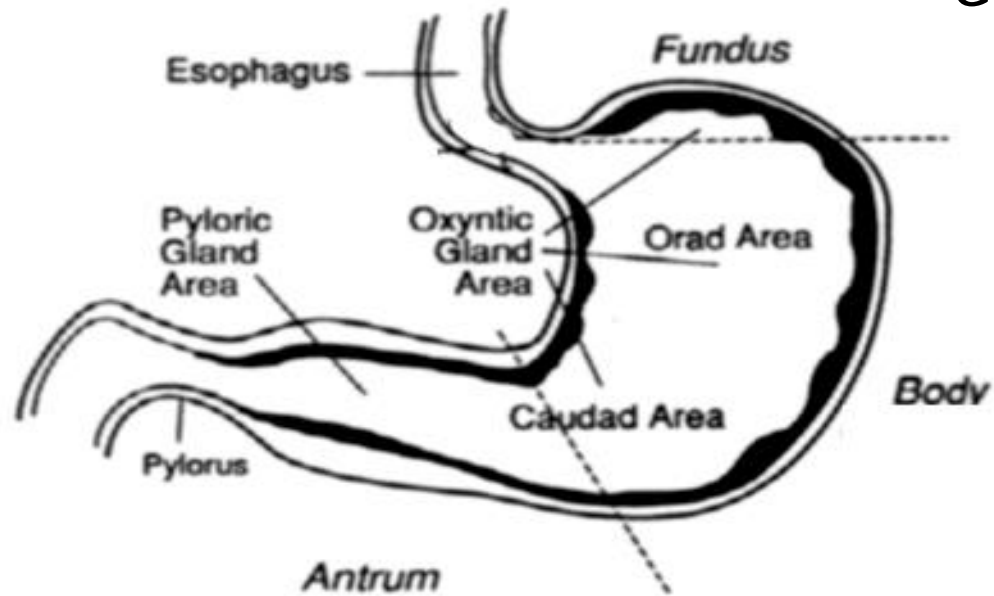
William Brinton, welcc



Gastric Motility

Proximal stomach

Gastric reservoir



Distal stomach

Peristalsis

Low distensibility

Grinding of solids



Gastric Dilation/Necrosis

- In dogs related to stretching then twisting of stomach along axis
- Previously reported in anorexia and bulimia patients
 - Undernourished patients complain of abdominal pain after meals
 - Attributed to significant binge eating
 - Possible role of bacteria producing gas and wall injury
 - Gastric wall becomes thin; vascular compromise
- Some models suggest feedback problem with solitary nucleus

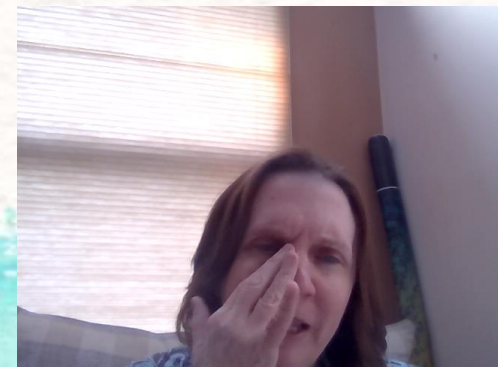


Acute Gastric Dilatation with Gastric Necrosis in PWS

- Series of 6 women with vomiting and gastroenteritis developed rapidly progressive gastric dilatation followed by necrosis*
 - 2 Pediatric cases had spontaneous resolution
 - 1 patient died of sepsis
 - 3 patients had massive dilatation requiring gastrectomy in 2
- Another series of laparoscopic gastric banding reported one death in a patient with Prader-willi Syndrome 45 days post procedure⁺

*RH Wharton et al., *Am J Med Genet* 1997, 73: 437-41

⁺E Chelala et al., *Surg Endo* 1997, 268-71



Gastric Rupture/Necrosis: Recent Data

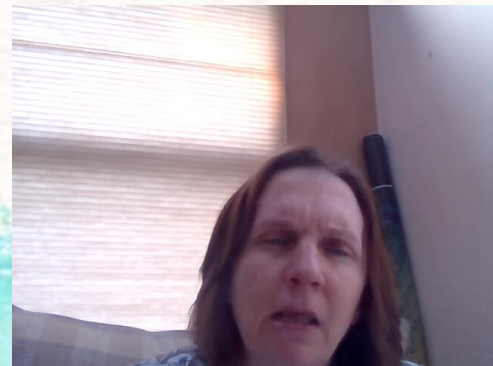
- ▶ 4 patients out of 152 died from gastric rupture/necrosis; 3 additional suspected
 - ▶ Teen (BMI 22) binge eating on holiday followed by abdominal pain and vomiting
 - ▶ 2 Young adults (not obese) with abdominal pain and vomiting
 - ▶ Middle-aged obese adults with history of ulcer and gastritis
 - ▶ Child with abdominal pain and hematemesis

Stevenson D, Scheimann A, et al., JPGN

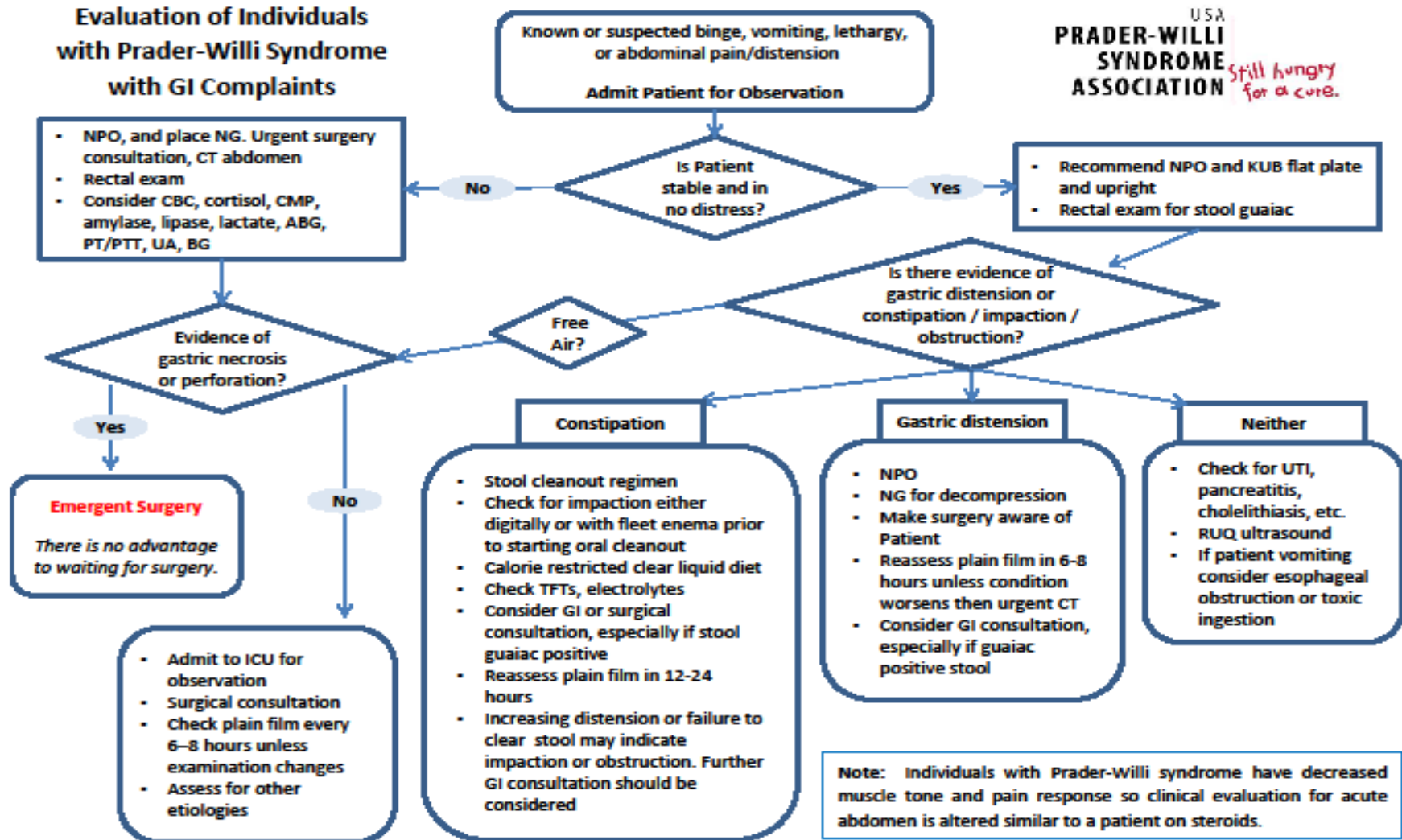


Gastric Dilation/Necrosis

- Difficult to diagnosis
- High index of suspicion
- Clinical features include change in diet before development of abdominal distension and vomiting
- Abdominal films show large dilated stomach
- Treatment is gastric decompression and supportive care with careful monitoring for possible rupture

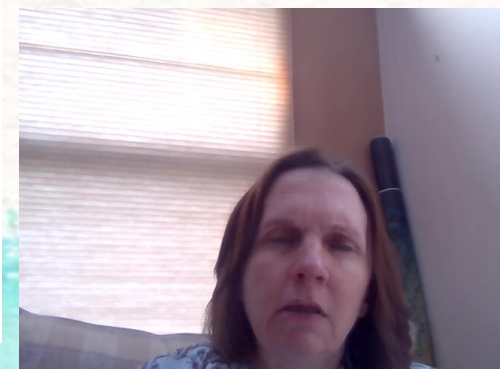


PWS GI Algorithm (Loker et al)



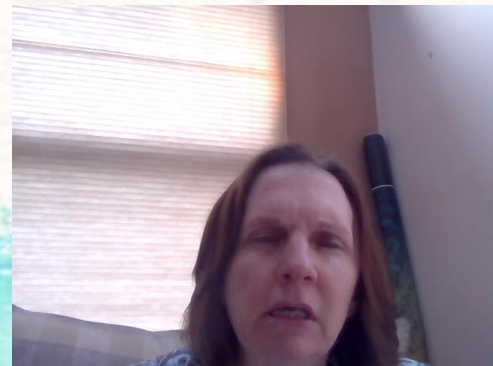
Credits: James Loker, M.D., Pediatric Cardiologist • Ann Scheimann, M.D., M.B.A., Gastroenterologist • PWSA (USA) Clinical Advisory Board Members

www.pwsausa.org



Medications/Treatment

- Current
 - Erythromycin
 - Metoclopramide
 - Domperidone- limited access in US
- Treat constipation!



Acknowledgements

- Collaborators
- Mentors
- Texas PWS Clinic Staff
- PWSAUSA, FPWR
- IPWSO
- Families of Children with PWS

