PRADER-WILLI SYNDROME
MEDICAL ALERTS

Prader-Willi
SYNDROME ASSOCIATION | USA
SAVING AND TRANSFORMING LIVES

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REVISED 2022

Prader-Willi
SYNDROME ASSOCIATION | USA
SAVING AND TRANSFORMING LIVES

PWSA | USA Mission

To enhance the quality of life of and empower those affected by Prader-Willi syndrome.

Prader-Willi Syndrome Association | USA
941.312.0400 | info@pwsausa.org | wwww.pwsausa.org

Find more valuable information on PWSA | USA's website, including a downloadable version of this Medical Alerts Booklet, by scanning the QR code below with your mobile device.

Prader-Willi Syndrome Medical Alerts
by
Clinicians of the PWSA I USA Clinical Advisory Board
and consultant experts

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INTRODUCTION

Characteristics and Common Medical Complications of PWS

This booklet was developed to alert medical practitioners in emergency departments, urgent care facilities and primary care practices to **severe medical complications that can develop rapidly in individuals with Prader-Willi syndrome (PWS).**

The booklet highlights medical issues that occur in some patients with PWS and hopefully assists in the recognition and management of problems that are uncommon in the general population but do occur with increased frequency among individuals with PWS. These findings may present at various ages and result in serious, sometimes urgent or even fatal outcomes. Common problems during hospitalization and medical procedures are also discussed.

The booklet also serves to alert families and other caregivers to potential PWS complications requiring specific management.

PWS is a variable and complex genetic neurobehavioral disorder resulting from an abnormality on chromosome 15. PWS occurs in approximately 1:10,000 to 1:15,000 births.

PWS affects the functioning of the hypothalamus and other aspects of the brain, and typically causes the following frequent findings:

- Generalized hypotonia evident prenatally and throughout life
- Decreased ability to suck in infancy leading to failure to thrive if not compensated. Swallowing abnormalities of oral secretions and food in all ages, often unrecognized
- Hyperphagia due to hypothalamically-driven lack of sense of satiety that can lead to dramatically excessive eating and, coupled with body composition abnormalities and metabolism with low caloric needs, can result in morbid obesity. Hyperphagia begins as early as ages 2-4 years and lasts throughout life. The presence of obesity can result in typical complications not usually present in those who are not obese, such as diabetes mellitus. Those with PWS who are not obese have had food intake carefully controlled by others.
- Short stature for the family if not treated with growth hormone
- Hip dysplasia, scoliosis, osteoporosis
- Delayed and incomplete sexual development
- Developmental delay and usually mild to moderate learning/cognitive deficits
- Chronic and significant problem behaviors; frank mental health conditions in some

In addition, some of the other common findings that may cause difficulties include:

- Adverse reactions to medications including anesthetics
- High pain tolerance leading to unsuspected issues such as fractures
- Gastrointestinal issues including decreased ability to vomit and chronic constipation. Occasional stomach necrosis and rupture often following binge eating
- Respiratory abnormalities such as hypoventilation or sleep disordered breathing in the form of obstructive or central sleep apnea
- Sleep problems such as excessive daytime sleepiness

- Temperature regulation abnormalities (hypothermia or hyperthermia)
- Misunderstanding or misinterpretation of information, necessitating clear and simple instructions

These findings are explained in more detail in the following pages, along with recommendations for evaluation and treatment for some of the problems in PWS. Information is based on literature review and experience of experts on PWS. The most emergent issues are discussed in the first section, inpatient, surgical and acute medical concerns in the second section, and additional medical issues and elaborations of some issues in the third section. A brief description of the genetic basis of PWS and how PWSA | USA can help in the event of death follow in sections IV and V.

Genetic testing is available for confirmation of diagnosis and to distinguish the three common causative genetic changes, which have a few distinctive findings (please see page 35 of this booklet, the section on Genetics.)

Recommended additional resources on medical issues in PWS include UpToDate® (www.uptodate.com) and GeneReviews (https://www.ncbi.nlm.nih.gov/books/NBK1330/). Members of the PWSA | USA Clinical Advisory Board are available for consultation with physicians through the Prader-Willi Syndrome Association | USA.

I. Emergency and Acute Medical Issues

Obesity and its related complications are the major causes of morbidity and mortality in Prader-Willi syndrome (PWS). Keeping the individual at a healthy weight will minimize these complications, but there are important medical and behavioral/mental health problems unique to PWS regardless of weight status.

Note that people with PWS have cognitive disability, and though it is usually mild they may misinterpret what is asked of or told to them. Instructions should be kept clear and simple.

Medical professionals can contact PWSA | USA to obtain more information and be put in touch with a specialist, as needed. UpToDate® (www.uptodate.com) and GeneReviews (https://ncbi.nlm.nih.gov/books/NBK1330) have excellent summaries of the syndrome.

Severe Gastrointestinal Concerns

- **Vomiting – Decreased ability to vomit.** Vomiting occurs infrequently in many people with PWS. Emetics may be ineffective, and repeated doses may cause toxicity. This characteristic is of particular concern in light of hyperphagia and the possible ingestion of uncooked, spoiled, or otherwise unhealthful food items. **The presence of new onset vomiting or vomiting accompanied by loss of appetite or lethargy may**

signal a life-threatening illness and may warrant immediate treatment. (See below and pages 24-25 as well as foldout on the last page of this booklet for more information on this topic.)

- **Severe Gastric Illness:** Gastric problems are very common in PWS due to decreased motility and gastroparesis. Abdominal distension or bloating, pain and/or vomiting may be signs of life-threatening gastric dilation, inflammation or necrosis. Rather than localized pain, there may be a general or vague feeling of being unwell. Anti-diarrheal medications may also cause severe colonic distension, necrosis and rupture and should be avoided. Any individual with PWS with these symptoms needs immediate medical attention. An X-ray, CT scan or ultrasound can help with the diagnosis and confirm if there is gastric necrosis and/or perforation.

  If distension is noted, these individuals need close clinical monitoring on an ongoing basis, to be made NPO, and may need decompression with an NG tube. **Gastric necrosis or perforation is a medical emergency requiring exploratory laparotomy or emergent surgery. Individuals with PWS may not have tenderness, rigidity or rebound normally associated with an acute abdomen.** Please see additional information on Gastric Necrosis on pages 24-25 of this booklet and see *an algorithm for evaluation of GI complaints in people with PWS at the end of this booklet.* See also **http://www.pwsausa.org/resources/medical-issues-a-z/** and view GI Problems-stomach and intestines.

- **Constipation and Rectal Bleeding:** Although only 20% of adults with PWS report constipation, a recent study found that 40% of adults with PWS fulfilled the diagnostic criteria for constipation. Abdominal and rectal pain, rectal fissures, and rectal bleeding may occur in association with disordered defecation. Rectal ulcers have occurred in individuals with PWS as a result of localized deep rectal picking aggravated by rectal irritation from constipation/anal pruritus and can present with mucoid rectal discharge, bloody stools, rectal pain, and tenesmus suggestive of emerging inflammatory bowel disease and warranting gastroenterology consultation. **Colonic impaction** may also occur and needs to be addressed. See also Constipation on pages 25-26 and at **http://www.pwsausa.org/resources/medical-issues-a-z/**

- **Other GI issues**: Stomach pain can also be due to gallstones or pancreatitis. An ultrasound, chemistry analysis of the blood and CT of the abdomen will help with the diagnosis.

Swallowing Dysfunction and Choking

People with PWS are highly likely to have an undetected swallowing problem that places them at risk for asphyxiation by a food bolus (choking). Many people with PWS cannot tell if they have cleared their throat or airway after swallowing, increasing the risk for aspiration. As a result, assessment requires a special kind of evaluation, a videofluoroscopic swallowing study with an esophageal

sweep. A clinical or bedside evaluation is not sufficient to detect dysphagia in this population. Choking can also occur with rapid ingestion of food and has caused numerous deaths in the PWS population. For more information on this topic, please see **http://www.pwsausa.org/resources/medical-issues-a-z/** and view Choking/Swallowing.

Respiratory Concerns

Individuals with PWS are at increased risk for respiratory difficulties. They have blunted ventilatory responses to hypoxemia and hypercarbia. This can cause problems related to anesthesia and sedation and complicate the diagnosis of obesity hypoventilation syndrome. Hypotonia, weak chest muscles, swallowing abnormalities, and central or obstructive sleep apnea are common. Anyone with significant snoring or other sleep problems, regardless of age or presence of obesity, should have a medical evaluation to look for sleep disordered breathing. This may include a sleep study. Infants commonly have central sleep apnea which generally improves spontaneously over time, but they may also have obstructive sleep apnea due to the hypotonia and other factors, as may individuals with PWS of all ages. Hypotonia can lead to diminished activity levels and low aerobic capacity. People with PWS at all ages are at risk for hypoventilation, which is central in origin. Hypersomnolence with or without cataplexy has been described in PWS.

In children with PWS, chronic stomach reflux and aspiration are emerging as common problems. Reflux should be considered in young children with chronic respiratory problems; videofluroscopy is the preferred test. Individuals with obstructive sleep apnea or obesity are at higher risk for reflux. At any age morbid obesity can be associated with obesity-hypoventilation syndrome. Children with PWS have been shown to have hypoventilation disproportionate to obstructive sleep apnea. (Please see pages 26-30 for recommendations for evaluation of breathing abnormalities associated with sleep disorders.)

Medications – Adverse Reactions

People with PWS may have unusual reactions to standard dosages of medications. Use extreme caution in giving medications, especially those that may cause sedation; prolonged and exaggerated responses have been reported. Metabolism of the drugs may be impaired in individuals with PWS. Abnormal body composition and metabolism may affect pharmacokinetics. In obese individuals, weight-based dosing guidelines often do not specify the use of actual body weight versus ideal or adjusted weight estimates, and multiple additional factors impacted by obesity must be considered for appropriate dosing. Consider additional focus on renal and hepatic function, medication lipophilicity, recommended dosing weight, and observability of medication effects. Special care should be taken with medications that have a narrow therapeutic window and for those in which the detection of harm may be delayed.

Pain Tolerance

A high threshold for sensing pain is common and may mask the presence of infection or injury. Someone with PWS may not complain of pain until infection is severe or may have difficulty localizing pain. Parent/caregiver reports of subtle changes in condition or behavior should be investigated for medical cause. Any complaint of pain by a person with PWS should be taken seriously.

Skin Picking and Bruises

Because of a compulsion that is common in PWS, open sores caused by skin picking may be apparent. Rectal picking/gouging is not uncommon. Individuals with PWS also tend to bruise easily. These lesions can cause serious life-threatening infections. Appearance of such wounds and bruises may erroneously lead to suspicion of physical abuse. There are approaches to help mitigate picking. Please see **http://www.pwsausa.org/resources/medical-issues-a-z/** and view Skin Picking.

Falls and Fractures

Individuals with PWS may have significant fractures from simple falls and require X-rays even if they do not complain of pain. Persistent pain, swelling, guarding, limping, or decreased movement of an extremity for more than a few days may warrant an X-ray.

Water Intoxication

Water intoxication has occurred in relation to use of certain medications with antidiuretic effects, as well as from excess (binging) fluid intake alone. For additional information see **http://www.pwsausa.org/resources/medical-issues-a-z/** and view Water Intoxication.

Temperature Abnormalities

Idiopathic hyperthermia and hypothermia can be noted in people with PWS. Hyperthermia may occur during minor illness and in procedures requiring anesthesia. Fever of unknown origin occurs. However, malignant hyperthermia does not appear to occur at increased frequency in PWS. On the other hand, fever may be absent despite serious infection. All individuals with PWS are at risk for mild hypothermia because of impaired peripheral somatosensory and central thermoregulation, poor judgment and cognitive inflexibility. Hypothermia is common in infants with PWS. See **http://www.pwsausa.org/resources/medical-issues a-z/** and view Temperature and Hypothermia.

Central Adrenal Insufficiency

Central adrenal insufficiency is a rare occurrence in people with PWS. A stress dose of cortisol may be indicated if the individual has problems after surgery or during times of stress. See page 34 in this booklet for more information. See also **http://www.pwsausa.org/medical-issues-a-z/** and view Adrenal or Cortisol Insufficiency.

Hyperphagia and Food Seeking

Individuals with PWS have a nearly constant drive to eat and must be continuously supervised in all settings to prevent access to excess food. In hospital settings, obtaining unguarded food can lead to rapid ingestion and fatal choking or gastrointestinal issues. Individuals who have normal weight have achieved this because of strict external control of their diet and food intake; these individuals are not less likely to ingest available food. There are currently no treatments for this constant urge to eat. Insatiable appetite may lead to life-threatening weight gain, which can be very rapid and occur even on a low-calorie diet.

II. Peri-Operative and In-Patient Issues

A. Hospital Experience and Pre-Anesthesia

Pre-Operative Preparation

When possible, pre-operative preparation to optimize nutritional status and address the common problems of diabetes control issues and constipation prior to significant elective surgical procedures should occur in patients with Prader-Willi syndrome.

Obesity Complications

A common finding in people with PWS, obesity can cause obstructive sleep apnea, pulmonary hypertension, diabetes, and right heart failure. These should be sought and addressed, as they affect illness, surgical and post-operative management.

Venous Access Difficulties

Many people with PWS will have difficult intravenous (IV) access due to increased fat mass and smaller than normal blood vessels. Ultrasound guided peripheral IV placement is helpful. IV lines are often more distressing to children with PWS than their actual surgery, therefore the lines need to be protected. In situations where hydration for more than 2-3 days is required, consider a peripherally inserted central catheter (PICC line) or tunneled central venous access, to avoid reinsertion.

Hyperphagia/Food Seeking

For people with PWS, complete safety from access to extra food is essential in any health care setting. Access to food storage or refrigerators should be prevented. Assume the individual has eaten unless verified by a caregiver. Complaints of hunger should not result in access to snacks or food. Patients in the hospital should have someone with them at all times. The individual may be on a calorie-restricted diet, and that should be conveyed to the nutritionist and kitchen. For elective procedures involvement of a dietician to help with pre-operative nutritional management along with planning for inpatient management of nutrition may be helpful. Patients with PWS should not be permitted to have "at your request" or "on demand" food ordering. A dietician should be involved in setting up the inpatient and discharge nutrition plans to ensure adequate protein intake along with appropriate vitamin/mineral supplementation to provide optimal healing.

Pain Tolerance

Unexplained tachypnea or tachycardia may be the only indication of pain. Behavior problems that are not typical for this person may also be evidence of pain. Individuals with PWS may not respond to pain in the same manner as others, masking the presence of underlying problems. Since pain may not be evident, other signs of underlying problems should be assessed.

Behavior Problems

Individuals with PWS are prone to emotional outbursts, obsessive-compulsive behaviors, and psychosis. These may be exacerbated by the stress of hospitalization or surgery. If possible, a pre-admission assessment should be performed, in part to consider 1-to-1 supervision in order to safeguard staff and the patient and prevent food foraging.

Psychosis

There is an increased risk of psychosis in individuals with PWS, which can be triggered by significant events such as changes in routines or serious illness. Prompt attention to hallucinations or reported change in typical behavior is essential. View Psychiatric Concerns at **http://www.pwsausa.org/resources/medical-issues-a-z/**

Skin Picking

Picking at sores and stitches is a common self-injurious behavior in PWS. It may complicate healing of IV sites and incisional wounds. Restraints or gloves may be necessary to protect wounds during healing. See Skin Picking at **http://www.pwsausa.org/resources/medical-issues-a-z/**

Temperature Instability

Low basal body temperature is typical in healthy individuals with PWS. Hypothalamic dysregulation can lead to poor temperature control during fever or hypothermia.

Respiratory Issues

The high incidence of central, obstructive and mixed apnea in people with PWS make it imperative to obtain a sleep study and/or pulmonology consultation prior to moderate or major surgical procedures in order to guide post-operative use of CPAP or BiPAP. The generalized hypotonia may include respiratory muscle weakness, which could complicate the ability to cough effectively and clear airways. See pages 26-30 in this booklet and **http:pwsausa.org/resources/medical-issues-a-z/** and view Breathing/ Respiratory concerns.

Cardiac Problems

Surprisingly, coronary disease is less in PWS than in individuals with similar obesity. Cardiac problems, if they do occur, usually are due to hypoventilation right heart failure, which can be associated with obesity. Non-pitting edema can often be seen in the obese individual even in the absence of heart failure and is treated with weight loss and ambulation. Diuretics are usually not very beneficial in treating the edema.

B. Anesthesia and Surgical Procedures

General Recommendations

Schedule procedures as early in the day as possible to prevent prolonged awake NPO status, so as to reduce patient anxiety and opportunities for food seeking behavior.

Anesthesia

People with PWS may have unusual reactions to standard dosages of anesthetic agents. Use caution in giving anesthesia. Outpatient procedures and conscious sedation may be especially problematic; the use of general anesthesia and airway management is often preferred but may warrant overnight observation for respiratory complications. Procedures done outside of the hospital settings should be carefully considered, with proper equipment for resuscitation immediately available. Ongoing assessment of breathing and oxygen saturation is critical in all outpatient procedures including dental work. Ongoing psychotropic medications may affect metabolism of anesthetic agents leading to shorter or longer duration of action. People with PWS may exhibit abnormal physiological responses to hypercapnia and hypoxia. There does not seem to be a higher incidence of malignant hyperthermia. Please see **http://www.pwsausa.org/resources/medical-issues-a-z/** and view Anesthesia**.**

Narcotic Sensitivity

Individuals with PWS may have an exaggerated response to narcotics. Use the lowest possible dose to achieve the desired state of anesthesia. Many individuals with PWS have delayed gastric emptying that can be compounded with narcotics.

Airway Access

A small airway, high palate, and/or obesity (neck and pharyngeal adiposity) may complicate ability to intubate. It can also make bag-mask ventilation difficult (mask fit challenges, increased airway resistance and reduced respiratory system compliance). Outpatient procedures and general sedation may be especially problematic. Care must be taken during procedures done in or out of hospital settings, and assurance that proper equipment for resuscitation is immediately available if needed. The possibility of doing such procedures in an operating room should be discussed. Procedures where more than light sedation is used may warrant overnight observation, particularly since sensitivity to medications is also an issue in PWS (see below).

Saliva Abnormalities

Thick sticky saliva complicates airway management especially during conscious sedation. It also increases the risk of caries. Dried saliva may not be an indication of hydration status. Voluntary water drinking is minimal in the majority of individuals with PWS.

Oro-Pharyngeal Surgical Concerns

With a significant number of infants and children with PWS undergoing sleep assessments prior to growth hormone treatment and the potential consequent rise in surgical procedures (e.g., tonsillectomy) requiring intubation and anesthesia, it is important to alert the medical team about complications. These may include trauma to the airway, oropharynx or lungs due to possible anatomic and physiologic differences seen in PWS, including a narrow airway, underdevelopment of the larynx and trachea, hypotonia, edema, and scoliosis.

C. Post-Operative Period

General Recommendations

Patients with PWS who undergo deep sedation or general anesthesia should be recovered overnight in a monitored unit. Continuous monitoring of pulse-oximetry for 24 hours is important post-operatively, with attention to airway and breathing. Infants and children may require intensive care monitoring. A conservative approach to pain management should be used, limiting the use of narcotic agents. Consider direct supervision (1:1) for those patients at risk of food foraging post-operatively. Patients may exhibit altered temperature regulation, where fevers may be absent despite the presence of infection. Individuals with PWS are at risk for deep venous thrombi (DVT) and pulmonary embolism due to their hypotonia and obesity. DVT prophylaxis should be considered in all obese individuals with PWS, and prolonged bed rest is to be avoided. Please review the sections above under Hospital experience and Pre-Anesthesia (pages 12-15) and **http://www.pwsausa.org/resources/medical-issues-a-z/** and view Post-operative Monitoring.

Respiratory Considerations

Pre-operative pulmonary assessment should guide the use of CPAP or BiPAP. Respiratory therapy may be indicated to prevent atelectasis and/or post-operative lung infections.

Pain Insensitivity and Narcotics

Individuals with PWS characteristically display a decreased outward response to pain. The only indications of pain may be behaviors that are not typical for that individual, or unexplained tachypnea/tachycardia. Lack of a typical pain response may mask the presence of underlying problems. Conversely, many post-surgical patients with PWS seem to experience less pain, and they can be comfortable with lower doses of narcotic medications or with a narcotic-free regime. Those who do need post-operative narcotics may benefit from methylnaltrexone to decrease the duration of the post-operative ileus.

Gastrointestinal Issues

Post-operative ileus is characteristically more profound and long lasting in patients with PWS. When indicated, sips of clear liquids may be started immediately after surgery, but the advancement of diet should be delayed until there are non-subjective signs of digestive recovery. One strategy for moderate to extensive surgeries on older children or adults is 2 ounces of clear liquids every 4 hours to start. If the patient tolerates intake and bowel sounds are present, the intake can be increased to 4 ounces every 4 hours. Abdominal radiographs are done daily to confirm normal gas patterns before advancing to a soft diet. Any abdominal bloating is an indication to discontinue diet.

Skin Picking

Skin picking may represent a severe threat to post-operative incisions. Restraints or gloves may initially be necessary, followed by physical barriers such as braces or casts to protect wounds during healing. Post-operative anxiety may cause patients without a history of skin picking to begin the habit.

Hypotonia Consequences

Generalized muscle hypotonia is a constant feature of PWS. It may complicate ability to cough effectively and clear airways, affecting post-operative recovery.

Pulmonary Embolism

Individuals with PWS are at increased risk for pulmonary embolism. Deep vein thrombosis prophylaxis should be considered in all obese individuals. Prolonged bed rest should be avoided.

Orthopedic Concerns

Musculoskeletal manifestations, including scoliosis, hip dysplasia, fractured bones (which may be undetected), osteoporosis, and lower limb alignment abnormalities, occur at significant frequency in people with PWS. Care of this patient population from the orthopedic surgeon's

perspective is complicated by other clinical manifestations of PWS. Please see also **http://www.pwsausa.org/resources/medical-issues-a-z/** and view Orthopedic Issues**.**

Behavioral Disorder and Psychosis

People with PWS are prone to emotional outbursts, obsessive-compulsive behaviors, and in some cases psychosis. Psychosis can be triggered by significant events such as changes in routines and serious illness. Prompt attention to hallucinations, disorientation or reported change in typical behavior is essential. View mental health issues at **http://www.pwsausa.org/resources/medical-issues-a-z/** under Psychiatric Concerns.

Summary of Post-Operative Management

Patients with PWS are known to have increased morbidity after surgery due to:

- Abnormal physiological response to hypercapnia and hypoxemia
- Untreated central and/or obstructive sleep apnea
- Hypotonia
- Narrow oropharyngeal space
- High incidence of central, obstructive and mixed apnea
- Thick secretions
- Obesity
- Increased incidence of scoliosis with decreased pulmonary function

- Prolonged exaggerated response to sedatives
- Increased risk for aspiration
- Decreased pain sensation
- Possible challenges with compliance to pre- and post-operative treatment procedures due to:
  - Extreme food seeking behavior and hyperphagia
  - High incidence of gastroparesis and slow motility of the intestinal tract
  - Severe skin picking which may interfere with wound healing
  - Altered temperature regulation – fever may be absent in the presence of infection
  - The possibility of central adrenal insufficiency

Therefore, the following are recommended for post-operative management:

- Patients with PWS who undergo deep sedation and general anesthesia should be recovered overnight in a monitored unit. Infants and children may require intensive care monitoring.
- Continuous monitoring of pulse-oximetry for 24 hours post-operative with attention to airway and breathing.
- A conservative approach to pain management and use of narcotic agents.
- Full assessment of return of gastrointestinal motility prior to initiation of intake by mouth, often with abdominal radiographs, because of the predisposition to ileus after surgery.

- Scheduling procedure as early in the day as possible to prevent prolonged time period where food seeking could take place.
- Direct supervision (1:1) to prevent foraging post-operatively and exclusion from ad lib patient ordering of food from hospital dietary services.
- Monitor for picking at wounds and/or incisions. These may require additional dressings and other barriers including full time sitter to prevent access to surgical site and medical devices
- Close observation of wound for signs of infection
- Airway clearance to prevent atelectasis and/or post-operative lung infection.
- Due to the hypotonia and obesity, individuals with PWS are at risk for deep venous thrombi (DVT) and pulmonary embolism. Patients should be under the guidelines for DVT prophylaxis.

Please see also **http://www.pwsausa.org/resources/medical-issues-a-z/** and view Post-operative/Surgery.

III. Evaluation and Treatment of Special Issues

Risk of Stomach Necrosis and Rupture

A Cause of Death from Sepsis, Gastric Necrosis or Blood Loss

Signs and symptoms of stomach necrosis and rupture:

- **Vomiting-**Atypical vomiting accompanied by decrease in appetite or lethargy is unusual in PWS
- **Loss of appetite** (ominous sign)
- **Lethargy**
- **Complaints of pain, usually non-specific.** Pain sensation appears to be abnormal in PWS due to high pain threshold; affected people rarely complain of pain
- **Pain** is often poorly localized
- **Peritoneal signs** may be absent
- **Abdominal/stomach bloating** and **gastric dilation**
- **Fever** may or may not be present
- **Guaiac positive stools (chronic gastritis)**

An algorithm for Emergency Room evaluation of an individual with PWS and abdominal complaints is on a foldout page at the back of this publication.

History may include:

- History of **binge eating** within the week. Hyperphagia and binge eating are characteristic of people with PWS, regardless of whether obese or slim. This frequently occurs at holiday or social occasion with less supervision of intake
- History of **gastroparesis**, which is common in PWS, though often undiagnosed
- History of significant **obesity followed by weight loss**, which may leave the stomach wall thinned.
- See also **http://www.pwsausa.org/resources/medical-issues-a-z/** under GI Problems**.**

Constipation

Constipation is a common problem in individuals with Prader-Willi syndrome (PWS). Although only 20% of adults with PWS report constipation, a recent study found that 40% of adults with PWS fulfilled the diagnostic criteria for constipation. It takes longer for food to move through the GI system (gastroparesis) in Prader-Willi syndrome. This slower passage of food can lead to serious issues similar to the ones seen related to the stomach. Outpatient methods used to clear constipation in non-PWS patients may be ineffective due to poor fluid intake and hypotonia. Inpatient regimens frequently use large volumes of fluid which may cause problems. Reliance on these methods may lead to life-threatening conditions such as necrosis and perforation of the colon and subsequent sepsis. Due to decreased muscle tone and altered pain response, individuals with

PWS may not have the same clinical exam that a non-PWS patient would have. A heavier reliance on imaging may be necessary. Individuals with PWS may be at higher risk for impaction. Rectal examination and enema may be required in addition to oral cleanout regimen. This may also be problematic in some, leading to rectal picking.

Patients with PWS having constipation and receiving repeated regimens of oral PEG (polyethylene glycol) solution for bowel cleansing should be monitored closely for abdominal distention and retention. Use of laxative agents with sweeter flavoring, such as lactulose or chocolate-flavored senna preparations, should be avoided if possible.

Failure of standard constipation protocols to clear the stool in a timely manner, especially in the face of increasing abdominal distention, vomiting, decreased appetite, stoppage of food consumption, and/or abdominal pain, warrants surgical or GI consultation. Emergent surgical or colonoscopic intervention may be necessary.

Breathing Abnormalities Associated with Sleep

Problems with sleep and sleep disordered breathing have long been known to affect individuals with PWS. The problems have been frequently diagnosed as sleep apnea (obstructive [OSA], central or mixed) and/or sleep related hypoventilation with hypoxemia. Disturbances in sleep architecture (delayed sleep onset, frequent arousals and increased time of wakefulness) are also frequent. Sleep

problems in people with PWS are often underrecognized as they do not exhibit the most common symptoms such as snoring, witnessed apneas, etc.

Factors that seem to increase the risk of sleep disordered breathing include young age, severe hypotonia, narrow airway, morbid obesity, and prior respiratory problems requiring intervention such as respiratory failure, reactive airway disease and hypoventilation with hypoxemia. Due to a few fatalities reported in individuals with PWS who were on growth hormone therapy (GH), some physicians have also added this as an additional risk factor. One possibility (that is currently unproven) is that GH could increase the growth of lymphoid tissue in the airway thus worsening already existing sleep disordered breathing. Nonetheless, it must be emphasized that there is currently no definitive data demonstrating that GH causes or worsens sleep disordered breathing. However, to address this concern, as well as the historically well documented increased risk of sleep-related breathing abnormalities in PWS, **the Clinical Advisory Board of the PWSA | USA makes the following recommendations:**

1. **A sleep study or a polysomnogram** that includes measurement of oxygen saturation and carbon dioxide for evaluation of hypoventilation, obstructive sleep apnea and central apnea should be contemplated for all individuals with Prader-Willi syndrome. These studies should include sleep staging and be evaluated by experts with sufficient expertise for the age of the patient being studied.

2. **Risk factors that should be considered to expedite the scheduling of a sleep study should include:**
   - Severe obesity – weight over 200% of ideal body weight (IBW).
   - History of chronic respiratory infections or reactive airway disease (asthma).
   - History of snoring, sleep apnea or frequent awakenings from sleep.
   - History of excessive daytime sleepiness, especially if this is getting worse.
   - Before major surgery including tonsillectomy and adenoidectomy.
   - Prior to sedation for procedures, imaging scans and dental work.
   - Prior to starting growth hormone or if currently receiving growth hormone therapy.

Additional sleep studies should be considered if patients have the onset of one of these risk factors, especially a sudden increase in weight or change in exercise tolerance. **If a patient is being treated with growth hormone, it is not necessary to stop the growth hormone before obtaining a sleep study unless there has been a new onset of significant respiratory problems.**

Any abnormalities in sleep studies should be discussed with the ordering physician and a sleep specialist knowledgeable about treating sleep disturbances to ensure

that a detailed plan for treatment and management is made. Referral to a pediatric or adult sleep medicine specialist is strongly encouraged for management of the respiratory care.

In addition to a calorically restricted diet to ensure weight loss or maintenance of an appropriate weight, a management plan may include modalities such as:

- Supplemental oxygen
- Continuous positive airway pressure (CPAP) or Bilevel positive airway pressure (BiPAP)
- Oxygen should be used with care as some individuals may have hypoxemia as their only ventilatory drive and oxygen therapy may actually worsen their breathing at night.
- Behavior modification therapy is sometimes needed to gain acceptance of CPAP or BiPAP.
- Medications to treat behavior may be required to ensure adherence to the treatment plan.

If sleep studies are abnormal in the morbidly obese child or adult (>200% IBW), the primary problem of weight should be addressed with an intensive intervention — specifically, an increase in exercise and dietary restriction. Both are far preferable to surgical interventions of all kinds. Techniques for achieving this are available from clinics and centers that provide care for PWS and from the national parent support organization [PWSA | USA]. Behavioral problems interfering with diet and exercise may need to be addressed simultaneously by people experienced with PWS.

If airway related surgery is considered, the treating surgeon and anesthesiologist should be knowledgeable about the unique pre- and post-operative problems found in individuals affected by Prader-Willi syndrome.

Tracheostomy surgery and management present unique problems for people with PWS and should be avoided in all but the most extreme cases. Tracheostomy is typically not warranted in the compromised, morbidly obese individual because the fundamental defect is virtually always hypoventilation, not obstruction. Self-endangerment and injury to the site are common in individuals with PWS who have tracheostomies placed.

At this time there is no direct evidence of a causative link between growth hormone and the respiratory problems seen in PWS. Growth hormone has been shown to have many beneficial effects in most individuals with PWS including improvement in the respiratory system. Decisions in the management of abnormal sleep studies should include a risk/benefit ratio of growth hormone therapy. It may be reassuring for the family and the treating physician to obtain a sleep study prior to the initiation of growth hormone therapy and after 6-8 weeks of therapy to assess the difference that growth hormone therapy may make. A follow-up study after one year of treatment with growth hormone may also be indicated.

Endocrine Abnormalities

Hypothalamic dysfunction and its resultant hormone deficiencies are the presumed origin of many features of PWS.

- **Hypothyroidism** (thyroid stimulating hormone deficiency) has been reported to occur in up to 20%-30% of individuals and may be undiagnosed prior to surgery. Central and primary hypothyroidism can be seen in individuals with PWS. Levothyroxine treatment should not be routinely prescribed in children with PWS unless confirmed by thyroid function testing. Both plasma thyroid stimulating hormone (TSH), T_4 and free T_4 (FT_4) are low in central hypothyroidism, whereas TSH is elevated in primary hypothyroidism. It is recommended that baseline thyroid function testing (T_4/FT_4 and TSH) be done during the first 3 months of life (unless the newborn screening was normal) and annually thereafter, especially if the patient is receiving GH therapy. Please see Hypothyroidism at **http://pwsausa.org/resources/medical-issues-a-z/**

- **Growth hormone deficiency** is also related to hypothalamic dysfunction. All individuals with PWS should be considered to be growth hormone (GH) deficient. Currently, growth hormone is being used as early as one month of life with overall beneficial effect on body composition and growth. The recommended dose is 0.18 to 0.24 mg/kg of ideal body weight divided 7 days a week. The lowest dose is recommended in infants. Benzyl alcohol free-GH products such as Genotropin Miniquick should be first choice whenever possible during the first 6 months of life. Bone age, growth velocity, plasma IGF-1, $IGFBP_3$, glucose, HbA1C, insulin, and thyroid function testing should be monitored during GH treatment.

  Overall, GH therapy is generally safe and well tolerated in PWS children and adolescents. Extreme caution, however, is recommended during 3-12 weeks after initiating GH due to possible development of increased intracranial pressure, manifested by headache and papilledema. It resolves by stopping GH and restarting thereafter with low GH dose with gradual increase. Due to possible development of obstructive sleep apnea, polysomnography should be obtained prior to initiating treatment, within 3-6 months after starting GH therapy, and then annually. Scoliosis is not a contraindication for GH treatment.

  While GH is typically discontinued once bone maturation is achieved at a bone age of 14.5 and 16.5 in girls and boys, respectively, it is the consensus of experts that GH remains beneficial throughout the lifespan. An adult GH stimulation test is necessary to consider adult GH treatment. GH dose in adults is 0.2 to 1.2 mg daily. Lower extremity edema is the most common side effect, but it subsides after decreasing the GH dose. The same blood work as for children is needed to monitor GH treatment in adults, with bone mineral density instead of bone age. See Growth Hormone at **http://pwsausa.org/resources/medical-issues-a-z/**

- **Hypogonadism** occurs in both sexes. Both central or hypogonadotropic (low LH/FSH) and primary or hypergonadotropic (ovarian failure) hypogonadism have been reported in PWS.

Cryptorchidism is virtually universal in males with PWS. Although human chorionic gonadotropin (hCG) is only effective in 24% of infants, this modality of treatment should be considered before a surgical approach. Early treatment with hCG may result in better outcomes including improved development of the scrotal sac, growth of phallus length and muscle tone. The improved muscle tone may decrease the need for gastrostomy tube feeding and facilitate circumcision and orchidopexy.

The increase in onset of pubic and/or axillary hair before age 8 years in girls and 9 in boys is most commonly the result of premature adrenarche and should not be confused with an early sign of puberty. Testicular enlargement (4 ml) in boys and breast development in girls is the first sign of puberty.

No consensus exists as to the most appropriate regimen for sex hormone replacement in PWS. However, most experts recommend intramuscular testosterone replacement in males starting at a dose of 25-50 mg given every 28 days, usually by age 14 years, with gradual increase towards typical adult male doses. Behavior should be monitored during treatment. Other modalities of androgen therapy include daily patches or gel as well as testosterone enanthate, which is administered subcutaneously once a week, typically administered by the parents. Oligomenorrhea or amenorrhea is typical for females with PWS. In girls, usually by age 12-13 years, low-dose oral estrogens with gradual increase are recommended, with combined oral contraceptive pills used after the first vaginal bleeding has occurred. Monitoring of sex hormone replacement therapy should include LH, FSH and sex hormones (testosterone or estrogens).

Although rare, there have been six documented pregnancies in females with PWS. Therefore, counseling on reproductive health and contraceptive practices is warranted for all females with PWS. See Puberty/Sex Hormones at **http://pwsausa.org/resources/medical-issues-a-z/**

Central Adrenal Insufficiency

The possibility has been raised of unrecognized adrenal insufficiency as the responsible cause of unexplained death in some individuals with PWS. However, subsequent studies based on various means of dynamic testing revealed low rates of central adrenal insufficiency in PWS, ranging from 0 to 14.3%. It is currently considered rare.

In general practice, the first step in evaluating patients for possible central adrenal insufficiency is measuring a morning (8 to 10 a.m.) basal cortisol level. Dynamic testing should be considered if repeat cortisol is still below normal range. None of the dynamic stimulation tests can be considered completely reliable for establishing or excluding the presence of central adrenal insufficiency. Consequently, clinical judgment remains one of the most important issues for deciding which patients need assessment or reassessment of adrenal function.

IV. Genetic Basis of PWS

PWS is due to a genetic abnormality that, in the vast majority of cases, results from a new genetic change in the person with PWS. It is caused by lack of expression of a group of genes on the proximal long arm of chromosome 15 (15q11.2-q13). In about 2/3 cases, this expression deficiency is due to absence (**deletion**) of a segment of the chromosome 15 contributed to the affected individual by the father. In most of the remaining cases it is due to the presence of two maternally-contributed and no paternally-contributed chromosome 15 (**maternal uniparental disomy**). Normally the relevant genes in the PWS 15q region are only expressed when inherited from the father and not when inherited from the mother, a process called genomic imprinting. The third, least common cause is a defect in the imprinting center such that both parental copies of the relevant genes in the PWS region of chromosome 15 are suppressed (an **imprinting defect**).

Although most of the manifestations of PWS are the same regardless of the cause of absent expression of these genes, a few problems occur more frequently in the presence of one or the other of the genetic causes leading to somewhat different prognosis. Recurrence risk can also vary with genetic cause. All three of these genetic causes will result in an abnormal DNA methylation test, though determination of the exact genetic cause requires additional testing. Further discussion of the genetics of PWS and the manner in which they can influence medical problems is beyond the scope of this brochure but can be found in numerous sources including Gene Reviews: **https://ncbi.nlm.nih.gov/books/NBK1330/**

V. In the Event of Death

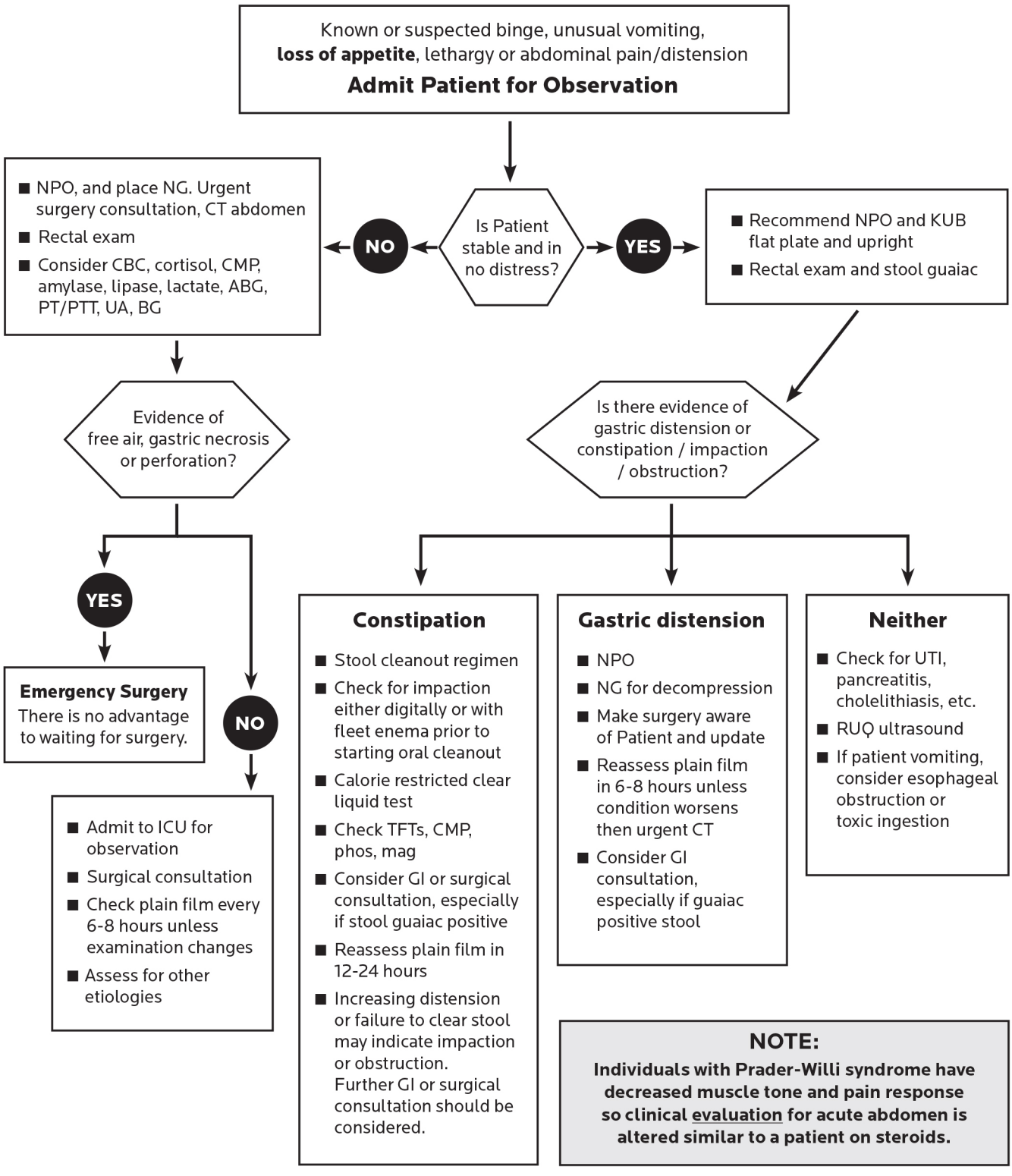
PWSA | USA collects information on mortality to help advance knowledge about causes of death. That knowledge can lead to future research and address critical areas of need for advancing treatment development and quality of life/longevity for those with PWS. We also partner with Autism BrainNet to facilitate the collection of postmortem brain tissue to identify new and effective treatments.

When the death of a loved one is near or has occurred, families may call Autism BrainNet's 24-hour, seven-day-a-week hotline to begin the donation process:

877.333.0999 or PWSA | USA **941.312.0400**

PWSA | USA also provides bereavement support to families who have lost a child with PWS. Please call PWSA | USA to report a death so that the family can receive grief counseling. Please contact Family Support (**941.312.0400**) in the event of death/near-death of an individual with PWS.

Evaluation of Individuals with Prader-Willi Syndrome with New GI Complaints



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Prader-Willi SYNDROME ASSOCIATION | USA
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and consultant experts

Prader-Willi Syndrome Medical Alerts
by
Clinicians of the PWSA | USA Clinical Advisory Board
and consultant experts

This life-saving Medical Alerts Booklet is dedicated to ***Janalee Heinemann, MSW*** *in appreciation for a lifetime of service to the PWS community and the truly thousands of lives that were saved and transformed by her skill, compassion, and dedication.*

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