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THE PRESSURE IS RISING
HYPERTENSION IN PREGNANCY

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History of Present Illness

A pregnant female in her early 30s with no recorded prenatal care was found unresponsive by Emergency Medical Services (EMS) at home thirty minutes after an unwitnessed event. The patient received two doses of intranasal naloxone on scene with minimal response. Upon arrival to the Emergency Department (ED), a Maternal-Fetal Medicine (MFM) physician performs a bedside ultrasound, which dates the pregnancy at approximately 28 weeks gestation and confirms intrauterine fetal demise (IUFD). The patient is intubated for respiratory failure, given two units of packed red blood cells for profound anemia, and started on norepinephrine for blood pressure support.

Past Medical History
Intravenous drug use
Chronic hepatitis C

Past Obstetric History
Placental abruption at 28 weeks in last pregancy
Rh isoimmunization

Past Surgical History
Cesarean section
Back surgery with rods for scoliosis

Medications
None

Allergies
No known drug allergies

Physical Exam

T	HR	BP	RR	SpO2	GCS
PRE-RESUSCITATION					
36.5	118	50/palp	28	55%	3
POST-RESUSCITATION					
35.8	109	145/83	22	100%	3

The patient is a woman who is intubated and sedated. Her pupils are sluggishly reactive. She is tachycardic but heart sounds suggest a regular rhythm with no appreciable murmurs. On lung exam, she has bilateral breath sounds with no wheezes, rhonchi, or rales. Abdominal exam reveals a gravid uterus with the fundus measuring 6 cm above the umbilicus, and her prior cesarean incision is noted. There is no vaginal bleeding noted on external evaluation; bimanual examination reveals cervical dilation at 1 cm. Her extremities are cold, clammy, and pale. The patient is unresponsive to painful stimuli.

Diagnostic Tests

ABG pH 6.74 / pCO2 61 / pO2 303 / BE -29 / Lactate 19.2
Alk Phos 111 AST 63 ALT 17 T Bili 0.2 INR 2.4 PT 26.8 Fibrinogen 93
Uric Acid 8.3
Peripheral Blood Smear: normocytic anemia, thrombocytopenia consistent with hemolytic/microangiopathic anemia
Rapid Thromboelastography (TEG): ACT 191s R Time 90s Time 250s Angle 55o Max amplitude 48mm Lysis 30 0%
CK 1,284 Trop 0.094
Kleihauer-Betke: 0% fetal maternal hemorrhage
Urine Protein : Creatinine Ratio 34.0 / Urine Drug Screen: Negative

CT/CTA head and neck: No acute intracranial abnormalities
EEG: no focal, lateralizing or epileptiform features appreciated

CT Abdomen and Pelvis: Intrauterine pregnancy, large placental abruption measuring 17.7 x 13.4 x 16.5cm
Obstetric Ultrasound confirmed IUFD, cephalic presentation, no hydropic changes, complete placenta abruption noted

Hospital Course

After initial resuscitation with blood product transfusion, vasopressors, and mechanical ventilation, the patient was noted to have systolic pressures of greater than 140mmHg, which was concerning for preeclampsia in the setting of pregnancy. She was transferred to the Surgical Intensive Care Unit (SICU) for continued management where induction of labor for IUFD was initiated. Shortly after transfer to the SICU, seizure activity was noted. Given the potential for eclamptic etiology, the patient was treated with intravenous lorazepam 2 mg, followed by a bolus of intravenous magnesium sulfate 6 g followed by a continuous infusion of 2 g/hour. Ultimately, the patient completed a spontaneous vaginal delivery of a phenotypically normal-appearing demised male infant. The delivery was complicated by postpartum hemorrhage of approximately 1400 mL, consistent with concealed placental abruption. The patient was extubated on postpartum day one and treated with magnesium sulfate for twenty-four hours post-delivery. Her coagulopathy was corrected by TEG-directed blood product replacement. After transfer out of the SICU, the patient proceeded to have a relatively uncomplicated postpartum course with discharge from the hospital.

Discussion

Definitions and Epidemiology

Preeclampsia is defined as hypertension plus proteinuria, or in the absence of proteinuria, signs and symptoms consistent with significant end-organ damage. Preeclampsia is believed to stem from endothelial dysfunction, possibly secondary to impaired placentation early in gestation, resulting in impaired balance of proinflammatory and antiangiogenic factors that worsens with increasing gestational age.[1] Although not entirely understood, this dysregulation is thought to progress and result in cerebral vasospasm leading to new onset generalized tonic-clonic seizures during pregnancy, formally known as eclampsia.[1,2] As such, preeclampsia is traditionally thought to be one part of a spectrum of disease, and if left undetected or untreated, it can progress to eclampsia. However, 25% to 40% of eclampsia cases are documented to occur in the absence of premonitory signs of preeclampsia.[3,4] Even in eclampsia cases that are preceded by elevated blood pressures, 33% of these cases have only mild elevation in blood pressures, less than the classic threshold of 160mmHg/110mmHg. Thus, this remains a difficult disease process to diagnose.

New-Onset Seizures in Pregnancy	
History of epilepsy	
Trauma	
Metabolic	Hypocalcemia Hyponatremia Hypoglycemia
Toxins	Drug or alcohol intoxication Drug or alcohol withdrawal
Neurologic	Stroke Intracranial hemorrage Brain mass
Infections	Meningitis Encephalitis Sepsis

Table 1: Differential diagnosis for new-onset seizures in pregnancy

Hypertensive disorders of pregnancy are amongst the most common obstetric emergencies, and represent some of the most significant causes of maternal and neonatal morbidity and mortality.[2] Among cases of eclampsia, studies show that approximately 23% of patients require mechanical ventilation and 35% have at least one other major complication such as the syndrome of hemolysis, elevated liver enzymes, and low platelets (HELLP); pulmonary edema; acute respiratory distress syndrome (ARDS); disseminated intravascular coagulation (DIC); renal failure; stroke; or cardiac arrest.[4] Risks to the neonate include premature birth, placental abruption, and growth restriction.[2] Furthermore, studies have demonstrated that women with hypertensive disorders during pregnancy have an increased risk for IUFD, although the pathophysiology is not fully understood.[2,5] Up to 33% of eclamptic seizures occur outside of the hospital, making early recognition of predisposing risk factors essential.[4] Emergency providers should have a high suspicion of eclampsia in any critically ill, pregnant patient who presents to the ED or requires admission to the ICU.[4,6]

Clinical Presentation

Pregnant patients presenting with headache, visual disturbances, abdominal pain, or shortness of breath should raise the suspicion for preeclampsia. However, patients can oftentimes present with asymptomatic hypertension; thus, blood pressure monitoring is paramount during pregnancy. In patients presenting with altered mental status or seizure activity, eclampsia should be suspected and managed quickly.

Diagnostic Considerations

The differential diagnosis for eclampsia can be vast, and other etiologies of altered mental status or seizure activity should be considered, including trauma, metabolic derangements, toxic exposure or ingestion, neurologic insults, and infectious etiologies.

In regards to diagnosing hypertension during pregnancy, the classic definition is systolic blood pressure greater than 140mmHg or diastolic blood pressure greater than 90mmHg on at least two occasions, or at least four hours apart, after a female has reached twenty weeks of gestation.[2] If this is new onset hypertension in the setting of pregnancy, this is termed gestational hypertension. If hypertension occurs prior to this gestational age, the patient likely has had pre-existing hypertension, and this also needs to be similarly managed during pregnancy. It is only if a patient has proteinuria or other signs or symptoms of end-organ damage that she is diagnosed with preeclampsia.

In addition to a detailed neurologic exam to assess for visual or cerebral symptoms, laboratory analysis is the cornerstone for diagnosing preeclampsia. A urinalysis is needed to assess for proteinuria (≥0.3 g in a 24-hour urine specimen or protein/creatinine ratio ≥0.3), a complete blood count to assess for anemia indicative of hemolysis or thrombocytopenia, a renal panel to assess for renal insufficiency, a hepatic panel to assess for

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Infantile Botulism

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History of Present Illness

The patient is a five-week old male presenting with poor feeding. The infant was born via spontaneous vaginal delivery at forty weeks to a Group B Streptococcus (GBS) positive mother who did not receive appropriate antibiotic therapy during delivery. The pregnancy was also complicated by oligohydramnios in the third trimester. Postnatal course has been uncomplicated, and the child has received all routine care. Patient is up to date on vaccinations.

The patient's mother reports that he has been fed breast milk exclusively since birth, however two days ago he began to exhibit difficulties with feeding. He was noted to have poor latching with both the breast and bottle, resulting in decreased number of wet diapers. He has also been more irritable and lethargic, with a constant but weak cry. The patient was taken to the pediatrician's office and was subsequently referred to the emergency department (ED) with concern for dehydration.

Past Medical History

None

Past Surgical History

None

Medications

None

Allergies

No known drug allergies

Physical exam

T 36.9 °C
HR 165
BP 95/73
RR 42
SpO2 99% on RA

The patient is a lethargic male infant who is quietly whimpering. His fontanelles are open, soft, and flat. He does not have a dysmorphic appearance. Mucous membranes are dry. Cardiopulmonary examination is unremarkable. Pulses are strong and symmetric in all extremities. Capillary refill is two seconds. There is globally decreased tone with weak suck but good grasp and normal reflexes. He is measured to be in the 50th percentile for height, weight, and head circumference.

Diagnostic Tests

14.3 / 5.1 / 420 / 40.9	138 / 4.5	106 / 21	15 / 0.24 / 59

Procalcitonin: <0.10
VBG: 7.36 / 36.7 / 21.2 / -4
UA: Negative
Influenza: Negative
CSF; Clear, RBC 11 / WBC 1 / gram stain negative
ECG: Normal sinus rhythm
CXR: Negative

Hospital Course

The patient's initial presentation was concerning for a serious bacterial infection (SBI). He was resuscitated with 20 mL/kg of normal saline and 4 mL/kg of dextrose-containing fluid with little improvement in appearance. Blood, urine, and cerebrospinal fluid (CSF) cultures were obtained, and the patient was started on ceftriaxone and ampicillin empirically. He was admitted to the Neonatal Intensive Care Unit (NICU) for further care.

While in the NICU, the patient's broad-spectrum antibiotics were continued. Respiratory viral panel was negative. Transthoracic echocardiography was obtained to evaluate for a cardiac etiology of the patient's symptoms and was unremarkable. On hospital day two, the patient's tone worsened and he was intubated for hypercarbic respiratory failure. Neurology was consulted and raised concern for infantile botulism. They also recommended obtaining an MRI of the brain, which was normal. Botulism stool studies were obtained and sent to the Ohio Department of Health for testing. The patient was started on baby botulism immune globulin (baby BIG). Antibiotics were discontinued after cultures showed no growth after forty-eight hours.

While awaiting results of botulism testing, alternative diagnoses were explored. Laboratory testing for spinal muscular atrophy and enterovirus were negative. Electromyography (EMG) demonstrated a presynaptic neuromuscular junction dysfunction consistent with botulism. The patient's respiratory status improved after receiving baby BIG and he was extubated on hospital day five. The following day stool studies returned positive for botulinum toxin B. The patient's tone and feeding gradually improved, and he was discharged on hospital day fourteen with mild residual hypotonia .

Discussion

Epidemiology and Pathophysiology

Botulism is a rare disease caused by exposure to neurotoxins from Clostridium botulinum, a spore-forming, gram-positive rod that is naturally present in soil, dust, and aquatic sediment. Botulism presents in several discrete clinical contexts, all of which cause symmetric flaccid paralysis.[1] Foodborne botulism is caused by the single consumption of food contaminated with pre-formed botulinum toxin (BT). It is a rare condition, with 109 outbreaks occurring in the United States (US) between 1920 and 2014.[2] Wound botulism is caused by the contamination and germination of C. botulinum within a wound. Although exceedingly rare, the number of cases has increased over the past two decades, primarily due to "skin popping" among intravenous drug users.[3]

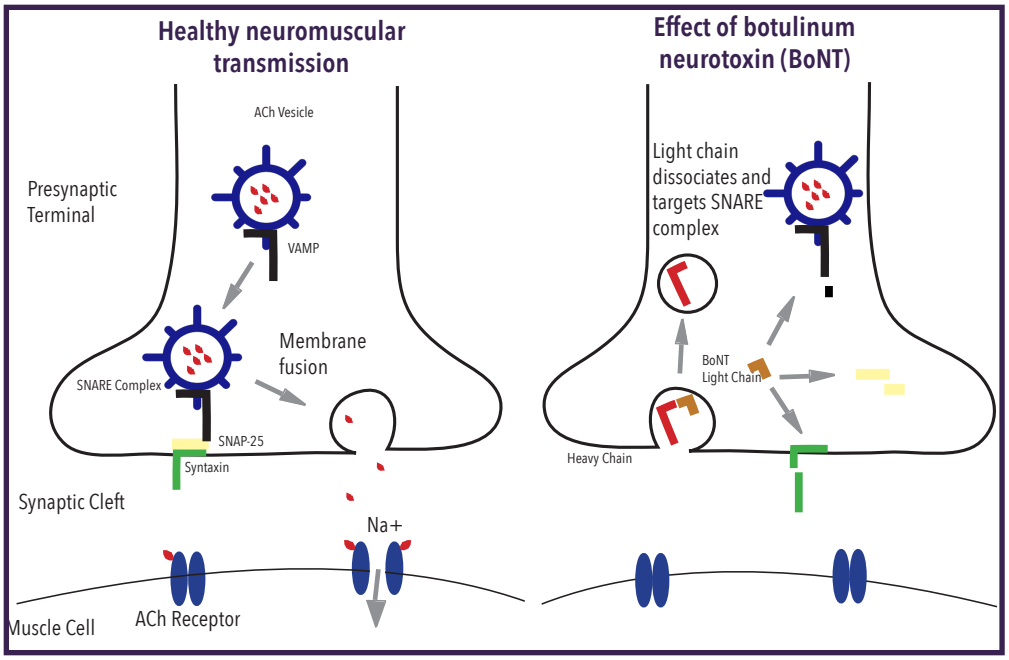

Figure 1: Figure depicting normal neuromuscular transmission (left) and the effect of botulinum neurotoxin (right).

Infantile botulism, the focus of this article, is by far the most common form of botulism, with 141 cases occurring in 2017.[4] The earliest reports of infantile botulism suggested an association with infant ingestion of honey. Epidemiologic data suggests honey ingestion-associated botulism occurs infrequently, though infants should still not be given honey until one year of age as a precautionary measure. Instead, a disproportionate number of cases occur in areas of recent soil disturbance such as agricultural regions and areas undergoing construction, raising the concern for transmission through repeated exposure to environmental spores.[5] Infantile botulism is caused by the gastrointestinal colonization and subsequent intra-intestinal toxin production of ingested C. botulinum.[6] Infantile botulism typically affects infants under six months of age, when the gastrointestinal flora is least developed. The well-developed gut flora found in adults and older children protects against intestinal colonization of C. botulinum, though cases of adult intestinal botulism have been described in patients with anatomic gastrointestinal tract abnormalities.[7]

All botulism infections are associated with production of BT, a potent neurotoxin that prevents the release of acetylcholine in the neuromuscular junction. Under normal conditions, depolarization at the pre-synaptic axon terminal causes acetylcholine to be released from the pre-synaptic membrane into the synaptic cleft. Acetylcholine release is facilitated by the soluble N-ethyl-maleimide-sensitive factor attachment protein receptor (SNARE) complex.[8] BT cleaves SNARE proteins within the pre-synaptic nerve, thereby preventing acetylcholine's release into the synaptic cleft.[8]

Clinical Presentation

Symmetric flaccid paralysis develops due to decreased acetylcholine within the synaptic cleft. Paralysis typically occurs in a descending fashion, with cranial nerve palsies oftentimes as the first presenting signs. Diplopia, one of the first presenting symptoms in adults, is difficult to detect in infants. Thus, cranial nerve dysfunction in infants is largely demonstrated by decreased gag and suck resulting in poor feeding. Diminished range of eye movement and ptosis can also be recognized on physical exam. Progressive hypotonia and weakness then follows. Autonomic symptoms such as constipation, decreased tearing, anhidrosis, dry mouth, and hypotension may also present early in the disease course. As the clinical course progresses, loss of deep tendon reflexes may invariably occur, and late stages typically involve paralysis of diaphragmatic muscles leading to respiratory failure. As expected, sensation is preserved given that the effect of BT is isolated to the neuromuscular junction. Clinical suspicion for infantile botulism should remain high in any patient presenting with cranial nerve deficits, hypotonia, constipation, or respiratory failure of unknown etiology.[9]

Diagnosis

Though a thorough history and neurologic examination are usually sufficient to make a preliminary diagnosis, stool bioassay remains the gold standard for diagnosis.[10] Unfortunately, botulism testing is a send out test at almost every institution and can take several days to result. As such, treatment should be initiated prior to confirmatory testing if clinical suspicion is high. Stool samples may also be difficult to obtain given that constipation is frequently seen in infantile botulism. If necessary, sterile water enemas may be used to obtain stool samples. Serum testing is rarely available, poorly sensitive, and of little utility.[10] EMG is of varying utility, thought to depend largely on timing of clinical course

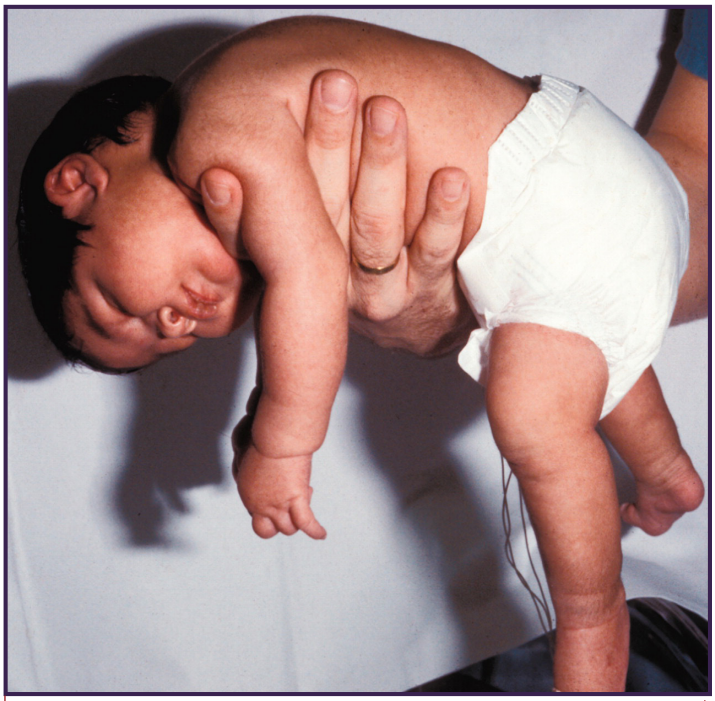

Image 1: Representative image of infantile hypotonia. Image courtesy of: Peredo DE, Hannibal MC. The Floppy Infant: Evaluation of Hypotonia. Pediatrics in Review. 2009;30(9). doi:10.1542/pir.30-9-e66.

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WISTING IN THE WIND:
A GYNECOLOGIC EMERGENCY

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History of Present Illness

The patient is a G1P1001 female in her 20s who presents to the emergency department (ED) with a several week history of right-sided flank pain with radiation to the suprapubic region. She describes the pain as intermittent and crampy. Over the past one-to-two days, the pain has acutely worsened and is now associated with multiple episodes of non-bloody, nonbilious emesis. Her last menstrual period was approximately one month ago. She is not currently sexually active and does not use contraceptives. Five days prior to presentation, she was seen in another facility where a urinalysis was notable for hematuria and she had a negative beta-hCG. No imaging was completed at that time, and she was diagnosed with presumptive nephrolithiasis and treated with naproxen, tamsulosin, and tramadol. She reports her pain has acutely worsened despite adherence to the above therapies. She denies any associated chest pain, shortness of breath, fever, chills, vaginal discharge, vaginal bleeding, diarrhea, and constipation.

Past Medical History
None

Past Surgical History
None

Medications
Naproxen
Tamsulosin
Tramadol

Allergies
No known drug allergies

Social history
No alcohol, tobacco, or illicit drug use

Physical Exam

T	36.7 °C
HR	71
BP	122/71
RR	14
SpO2	100% on RA

The patient is a young Hispanic female who appears uncomfortable but in no acute distress. She is well-developed with no evidence of external trauma. Her abdomen is soft, non-distended with marked tenderness to palpation in the right flank and suprapubic regions. Psoas and obturator tests are negative, and she has no McBurney's point tenderness to palpation. She has normoactive bowel sounds. Cardiac, pulmonary, and neurologic exams are normal. Musculoskeletal and skin exam demonstrate appropriate range of motion and no rashes, ecchymosis, or lesions.

Diagnostic Tests

14.3		146	117	16	
16	169				223
45.1		4.4	10	1.2	

Urine hCG: neg
Urinalysis – blood trace, protein trace, nitrite negative, leukocyte esterase negative

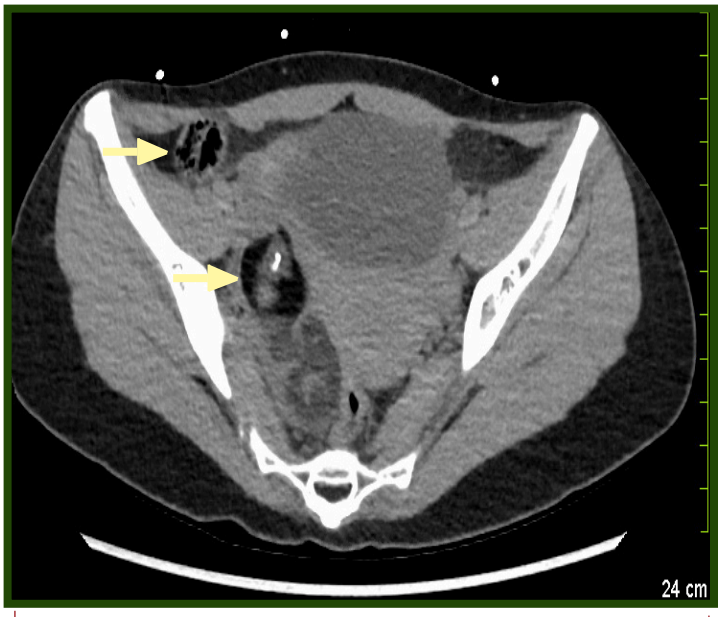

Image 2: Representative image of patient's CT abdomen and pelvis. There is a 13 x 6 cm fat, soft tissue, and calcium-containing mass within the right adnexa, consistent with teratoma. An additioal 10 x 7cm cystic mass within the pelvis may be ap ortion of the teratoma versus separate ovarian cyst.

Hospital Course

The patient was given ondansetron, morphine, and ketorolac for symptom control. Differential diagnosis included ectopic pregnancy, ruptured ovarian cyst, tubo-ovarian abscess, pelvic inflammatory disease, ovarian torsion, uterine leiomyoma, urinary tract infection, nephrolithiasis, pyelonephritis, and appendicitis, among others. The providers obtained CT imaging, which revealed an intraabdominal mass suggestive of a possible ovarian teratoma. Gynecology was emergently involved given the patient's persistent pain and concern for torsion of the right adnexa. The patient had an uncomplicated surgical resection of a large germ cell tumor as well as a right salpingo-oophorectomy and removal of a large ovarian cyst on hospital day one. She tolerated the procedure well and was discharged that same day. The patient has since followed up with gynecology and has noted no significant changes in her health related to this procedure. Pathology showed no evidence of malignancy. The two resected masses were confirmed as a mature cystic

teratoma and serous cystadenoma.

Discussion

Pathophysiology

Ovarian torsion is a feared and difficult to diagnose emergency due to its relatively nonspecific presenting symptoms.[1] Ovarian torsion is the partial or complete rotation of the ovary on the axis between the utero-ovarian and infundibulopelvic ligaments. Often, both the ovary and fallopian tube are involved in this process, though isolated torsion of either structure individually may occur. Initially, ovarian torsion causes venous and lymphatic obstruction, which can then progress to congestion, edema, and eventually ischemia and necrosis if not surgically addressed. Complete arterial obstruction is rare due to the ovaries' dual blood supply from the uterine and ovarian arteries. Additional sequelae from missed or advanced torsion besides damage to the ovary itself include intraperitoneal hemorrhage or infection with development of peritonitis.

Torsion can occur in females of all ages, but it is most common during the reproductive years due to the increased frequency of functional cysts and physiologic changes that occur during the menstrual cycle and pregnancy. The vast majority of torsion is thought to be induced by an ovarian mass, with only ten percent of cases estimated to occur in patients with ovaries without masses.[1,2] Most masses which cause torsion are benign in nature. Malignant neoplasms, by contrast, are often fixed in place by local adhesions and less likely to torse as a result.[3-6] A significant, but lesser-known, risk factor for torsion is pregnancy, which accounts for at least ten percent of all torsion cases[1,2]. This most often occurs in patients with a preexisting ovarian cyst during the second trimester of pregnancy.[7] Additional predisposing characteristics include recent infertility treatment, which can cause ovulation induction and hyperstimulation syndrome or polycystic ovary syndrome (PCOS). Finally, studies show that more than 80% of ovarian torsion cases had an ovarian mass greater than 5cm in diameter, and that torsion is more common on the right as opposed to the left, where the ovary tends to be comparatively confined due to the sigmoid colon and a shorter utero-ovarian ligament.[8,9]

Clinical Presentation

Classically, patients with ovarian torsion will report acute onset of severe, sharp, unilateral lower abdominal pain with associated nausea. However, as with many intraabdominal pathologies, these symptoms are relatively nonspecific and therefore require a high index of suspicion to ensure that the appropriate diagnostic studies are obtained.[5,6,10] Most patients will present within one to three days of symptom onset and may report a history of recent strenuous or vigorous activity. The younger the patient, the longer the symptoms are likely to occur prior to presentation, most likely due to intermittent torsion.[11,13] Known risk factors and a palpable adnexal mass should trigger providers to consider the diagnosis.[6] The differential diagnosis for acute lower abdominal pain in women includes gynecological, gastrointestinal and genitourinarl, as mentioned above. However, unlike the other gynecologic and obstetric pathologies listed, vaginal discharge and bleeding is not common in ovarian torsion, thus this diagnosis can oftentimes be overlooked.

Diagnosis

A high index of suspicion is the greatest contributing factor in making the appropriate diagnosis of ovarian torsion. Laboratory evaluation is not often helpful apart from diagnosing pregnancy. Leukocytosis is uncommon unless the ovary has already become necrotic, thus a normal white blood cell count may increase suspicion for ovarian torsion over appendicitis,[13] however this is not reliable. Instead, one must rely on imaging to identify possible pathology. While CT and MRI can identify the presence of ovarian cysts or masses, and may suggest torsion through visualization of contrast impedance, ovarian edema, or fallopian tube thickening, ultrasound with doppler is considered the test of choice.[14] Both transvaginal and transabdominal studies are recommended in the evaluation of acute pelvic pathology. While most emergency departments still require consultative ultrasonography for formal diagnosis of ovarian pathologies, it is important to note what might be seen on point-of-care ultrasound to raise your clinical suspicion.[15, 16]

Ultrasound findings suggestive of ovarian torsion

Finding	Sensitivity (%)	Specficity (%)	Positive Predictive Value - PPV (%)
Asymmetric ovarian enlargement[□]	85	18	75
Heterogenous ovarian stoma, edema[Δ]	21	100	100
Anterior ovarian location (lateral is normal)[□]	36	87	90
Decreased, absent ovarian arterial doppler flow[□Δ◊]	76-85	37.5-99	80-100
"Whirlpool" sign[□]	90	0	90

References:
[□]Mashiach R, Melamed N, Gilad N, et al. Sonographic diagnosis of ovarian torsion: accuracy and predictive factors. Journal of Ultrasound in Medicine. 2011: 30 (9): 1205-1210.
[Δ]Nizar K, Deutsch M, Filmer S, et al. Dopper studies of the ovarian venous blood flow in the diagnosis of adnexal torsion. Journal of Clinical Ultrasound. 2009: 37 (8): 436-439.
[◊] Pour, TR and Tibbles CD. Selected Gynecologic Disorders. In: R.M. Walls, ed. Rosen's Emergency Medicine: Concepts and Clinical Practice. 9th ed. Philadelphia, PA: Elsevier, 2018. 1232-1239.
[□]Valsky DV, Esh-Broder E, Cohen SM, et al. Added value of the gray-scale whirlpool sign in the diagnosis of adnexal torsion. Ultrasound in Obstetrics & Gynecology. 2010: 36 (5): 630-634.

Table 2: Sensitivities, specificities, and positive predictive values of the most common ultrasound findings suggestive of ovarian torsion. References listed in table.

Asymmetric enlargement of the ovary is the most common finding. Classically, ultrasound will reveal an enlarged ovary with heterogenous stroma and small, peripherally displaced follicles, but these findings are often absent, especially with long standing ischemia. Ultrasound may also demonstrate evidence of ovarian masses, hemorrhage, or pelvic free fluid. Doppler ultrasound

Ovarian Torsion
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NEURLISTERIOSIS

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History of Present Illness

The patient is a Swahili-speaking female in her 40s with a past medical history of HIV on HAART who presents to the emergency department (ED) after being found unresponsive. Family reports that the patient was last seen well approximately 14 hours prior to presentation. The patient is minimally responsive and unable to provide any further history.

Chart review reveals a recent admission five days prior for psychosis and visual hallucinations for which outpatient risperidone was initiated. The patient was seen at that time for dizziness and palpitations. During admission, serum and urine labs, and non-contrast head CT, were within normal limits, and blood and urine cultures had been sent. She was noted to be slightly confused, but this was thought to be secondary to dehydration. She was discharge home in stable condition after improvement in symptoms.

Past Medical History

HIV
Psychosis with delusions

Past Surgical History

None

Medications

Risperidone
Bictegrav-emtricit-tenofov alafenamide
Folic acid

Allergies

No known drug allergies

Physical Exam

T	HR	BP	RR	SpO2
40.0 °C	125	119/47	29	98% on RA

The patient is lethargic, does not attend or regard, and is nonverbal and minimally responsive to painful stimuli. Her pupils are equal, round, and reactive to light, and a disconjugate gaze is present. The patient blinks to confrontation in all visual fields and her face is grossly symmetric. She is noted to have rigidity in all four extremities, left greater than right. She favors the flexed position of extremities, but allows for passive extension. She demonstrates areflexia in biceps, triceps, patellar and Achilles tendons bilaterally with a negative Babinski bilaterally. She is noted to be tachycardic, otherwise cardiopulmonary exam is unremarkable. There are no external signs of trauma, and the patient is incontinent of stool and urine.

Diagnostic Tests

10	13.3 / 204	39.4
141	105	21
3.6	21	1.56

360

ALT 87 / AST 109 / Tbili 0.4 / Alk phos 54 / Albumin 3.6
Lactate 3.4 / Troponin: 0.06 / CK 11,839
VBG: pH 7.4 / pCO2 37 / base excess -1.4
TSH 0.8 / fT4 1.17
EtOH negative / Salicylate negative / Tylenol negative
UDS: negative
Upreg: negative

CT head: negative for acute intracranial process
EKG: T wave inversions in V3-V6, no prior to compare

Lumbar Puncture: opening pressure 29 cm H20
Tube 1 WBCs: 4534
RBCs: 1024
Tube 4 WBCs: 1560
RBCs: 5996
Glucose: 90
Protein: 259

Hospital Course

Given the patient's fever, tachycardia and altered mental status, a broad work up was initiated to include intracranial, infectious, metabolic, and toxidrome-related etiologies. She was started on vancomycin, ceftriaxone, and acyclovir for empiric antimicrobial coverage of encephalitis or meningitis. She was given acetaminophen for her fever, resuscitated with intravenous fluid, and started on external cooling measures. Due to concern for possible neuroleptic malignant syndrome given the recent initiation of risperidone, the patient was empirically given dantrolene. Her mental status did not improve while in the ED and she was admitted to the neurosciences intensive care unit (NSICU).

In the NSICU, providers added voriconazole and ampicillin to cover for fungal and additional bacterial pathogens due to the patient's history of HIV. Infectious disease was consulted, along with psychiatry to rule out malignant catatonia as a possible etiology of her symptoms. Continuous video electroencephalography (EEG) showed no seizure activity and magnetic resonance imaging (MRI) found no focal abnormalities.

During hospitalization, the patient's blood cultures grew *Staphylococcus epidermidis* and *Listeria monocytogenes*. Cerebrospinal fluid (CSF) cultures also grew *L. monocytogenes*. Records from the prior outside hospital visit were later obtained and revealed positive blood cultures for *L. monocytogenes*. Antibiotic therapy was narrowed to vancomycin and ampicillin based on these culture

results. The patient's mental status improved dramatically throughout her hospitalization, and she was able to be discharged to inpatient rehabilitation on hospital day 10. The patient was discharged with a three-week course of ampicillin and a two-week course of vancomycin. The patient was neurologically intact at her infectious disease appointment several months later.

Discussion

Epidemiology and Pathophysiology

L. monocytogenes is an aerobic and facultatively anaerobic, motile, fastidious gram-positive rod that is naturally occurring in soil, water, and flora. Exposure is most often from ingestion of unpasteurized milk, soft cheeses, deli meats, and smoked seafood.[1] After ingestion, bacteria invade the intestinal mucosa and spread systemically. *L. monocytogenes*' ability to grow at refrigerated temperatures contributes significantly to its ability to cause foodborne illness in the developed world .

Infection with *L. monocytogenes* is relatively rare, especially in immunocompetent patients, and commonly presents as a self-limited disease of the gastrointestinal tract. However, *L. monocytogenes* has demonstrated a particular predilection for the central nervous system (CNS), thus has significant potential as an invasive pathogen, especially in neonatal and elderly populations. Primary immunity against *L. monocytogenes* is from T-cell lymphocytic activation of macrophages, thus immunosuppressed and immunocompromised patients are at higher risk of infection.[2] Interestingly, the use of stomach acid suppressants has also been described as a risk factor for infection.[1] Incubation period ranges from several days to up to four weeks depending upon an individual's risk factors.

Pregnant women are another population with increased susceptibility to listeriosis. One in seven cases of listeriosis occurs in pregnant women, attributed to the suppressed cell-mediated immunity of pregnancy. Maternal infection is associated with increased rates of miscarriage, preterm labor, stillbirth, and fetal demise;[3] one study demonstrated major fetal and neonatal complications in greater than 80% of pregnant women infected prior to 29 weeks of gestation.[2] Additionally, infection can be vertically transmitted from mother to the fetus and can, very rarely, lead to granulomatosis infantiseptica, a severe form of fetal infection leading to pyogenic granuloma formations in all internal fetal organs.[4] This may occur with relatively little symptomology of the mother and usually goes undiagnosed until birth. Pregnant women are not at increased risk of neuro-invasive listeriosis, suggesting that placental and CNS infection mechanisms differ.[5]

Regardless of risk factors, invasive listeriosis confers a mortality rate estimated at 20%.[6] In the United States, an estimated 1,600 people contract invasive listeriosis each year, of which an estimated 260 die from infection.[6]

Clinical Presentation

L. monocytogenes has well-described neuro-invasive potential, also known as neurolisteriosis, most commonly presenting as meningitis.[2] While *L. monocytogenes* accounts for only four percent of bacterial meningitis cases in patients aged two to 60, it is responsible 25% of cases in patients younger than two and older than 60 years.[7] Thus, both neonatal and elderly patients with a high clinical suspicion for meningitis are empirically treated for *L. monocytogenes*. Unlike meningitis, encephalitis is relatively rare; it is estimated that anywhere from 6-24% of patients with neurolisteriosis exhibit signs of encephalitis presenting as focal neurologic deficits or seizures.[8]

Another presentation of neurolisteriosis is rhomboencephalitis, a focal encephalitis involving the brainstem and/or cerebellum. *L. monocytogenes* rhomboencephalitis has a characteristic biphasic disease course. Typically, it begins with a prodrome of headache, nausea, and fever which lasts for several days. The second phase then develops abruptly with the onset of asymmetric or unilateral cranial nerve deficits, cerebellar signs, and hemiparesis or hemisensory deficits.[5,8] In contrast to other presentations of neurolisterosis, rhomboencephalitis occurs primarily in otherwise healthy individuals.[5] While the mechanism is unclear, one study posited that *L. monocytogenes* may access the brainstem directly via cranial nerves, thus bypassing the body's immune defenses. In some animal models, conjunctival or buccal inoculation with *L. monocytogenes* has resulted in rhomboencephalitis.[9] Rhomboencephalitis is not unique to *L. monocytogenes*; it has also been described with Epstein-Barr virus, tuberculosis, JC virus, multiple sclerosis, and Behcet's disease.[10]

Respiratory complications are commonly associated with neurolisteriosis as well. Pneumonia affects an estimated 17% of patients with *L. monocytogenes* meningoencephalitis, which is significantly higher than rates observed in meningitis alone.[8] In cases of rhomboencephalitis, respiratory failure occurs in an approximately 41% of patients. Case studies cite impingement of abscesses on the medullary respiratory center or the development of obstructive hydrocephalus as possible etiologies.[9]

In pregnancy, *L. monocytogenes* infection can present with a broad range of symptoms. Many patients will present with fever and nonspecific flu-like symptoms while having disseminated infection and bacteremia. Some may present with primary gastrointestinal symptoms. Others may be completely asymptomatic. Thus, providers must remain vigilant during the course of a patient's pregnancy, especially in those with risk factors for *L. monocytogenes*, as both maternal and fetal morbidity and mortality rates are high.

Evaluation of *Listeria monocytogenes*	
Populations at risk	Neonates Elderly Immunocompromised Pregnant women
Clinical Presentation	gastrointestinal symptoms meningitis/rhomboencephalitis pneumonia
Diagnosis	CSF culture blood culture
Treatment	ampicillin OR penicillin G + aminoglycoside (neurolisteria)

Table 3: Clinical considerations for *Listeria monocytogenes* infection.

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Acyclovir Toxicity

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History of Present Illness

The patient is a female in her 70s with a history of end stage renal disease (ESRD) who is brought to the emergency department (ED) with a chief complaint of altered mental status and a rash on her neck. The patient is unable to provide history due to her altered mental state, therefore history is obtained from her daughter who brought her in for evaluation. The patient's symptoms started approximately one week prior to presentation with a painful, non-pruritic rash on the left side of her neck. Five days prior to today's presentation, the patient was seen at an urgent care for the rash and was prescribed valacyclovir for suspected herpes zoster infection. The following day, her mental status precipitously declined and she was noted to be somnolent, developed incomprehensible slurred speech, and was no longer able to ambulate with her walker. She also began to have auditory and visual hallucinations of deceased relatives. Despite her daughter ensuring compliance with all of her medications, and notable rapid progression of the rash to crusted lesions, the patient's condition continued to deteriorate.

Past Medical History

ESRD on hemodialysis
Hypertension
Polycystic kidney disease
Coronary artery disease
Cerebrovascular accident

Past Surgical History

Appendectomy
Cholecystectomy

Medications

Aspirin
Sertraline
Valacyclovir 1g Q8H x7 days

Allergies

No known drug allergies

Social History

30 pack-year smoker,
uses marijuana, past alcohol abuse

Physical Exam

T	HR	BP	RR	SpO2
36.5 °C	114	124/78	18	100% on RA

The patient is ill-appearing and lethargic. She is alert and oriented to self only. She is able to answer yes and no in response to questions, but cannot provide any information beyond verbalizing her name. Speech is noted to be dysarthric, however no receptive or expressive aphasia. Pupils are equal and reactive to light with intact extraocular movements. Visual fields are full to confrontation. There is no evidence of facial droop and cranial nerves are grossly intact. She has 4/5 strength in the right upper and lower extremities, and 5/5 strength in the left upper and lower extremities. There is no pronator drift in the bilateral upper extremities. Sensation is grossly intact in all four extremities to light touch. Skin exam is notable for a crusting rash to the left neck with healing vesicles, with no additional lesions noted elsewhere. She has a fistula in the right upper extremity with an audible bruit. Cardiopulmonary exam is otherwise unremarkable.

Diagnostic Tests

Lactate 0.9 / VBG 7.36/53/39/30
Troponin <0.04 / BNP 197
AST 30 / ALT 14 / Tbili 0.6 / Ammonia 90
Acetaminophen <10 / Salicylate <3 / Ethanol <10
TSH 1.7 / T4 0.66
Syphilis screen: negative
Peripheral blood cultures x2: no growth to date

CXR: Demonstrates pulmonary edema. Asymmetric opacity in the left upper lobe.
Non-contrast head CT: No acute intracranial hemorrhage or mass effect. Chronic left frontal lobe infarct. Unchanged atrophy and chronic microvascular disease.

Hospital Course

Given the patient's history of dialysis-dependent ESRD, and the acute development of neuropsychiatric symptoms with recent initiation of valacyclovir therapy, the emergency providers astutely had a high clinical suspicion for valacyclovir toxicity. They also assessed her for a superimposed bacterial infection, and chest X-ray noted focal opacities concerning for pneumonia. She was provided with empiric broad spectrum antibiotics, including vancomycin, ceftriaxone, and azithromycin. The patient was admitted to the nephrology service for urgent hemodialysis later that morning, and the infectious disease consultation team discontinued valacyclovir given the patient already had crusting of her lesions without new eruptions. Several hours after hemodialysis, the patient had significant improvement in her mental status with increased alertness and resolution of her dysarthria. She was dialyzed again on hospital day three and subsequently returned to her neurologic baseline. Repeat chest X-ray at that time showed resolution of her prior infiltrates. Antibiotics were de-escalated to azithromycin with plans to finish the course as an outpatient. She was then discharged home on hospital day four under the care of her daughter.

Discussion

Pharmacology

Valacyclovir is an antiviral drug frequently used in the clinical treatment of leukemia, acute encephalitis, herpes simplex virus (HSV), and varicella zoster virus (VZV). It is a prodrug, rapidly converted by hepatic first-pass metabolism to acyclovir, which is then able to penetrate the central nervous system (CNS).[1] In its active form, acyclovir competitively inhibits viral DNA polymerase by acting as an analog to deoxyguanosine triphosphate (dGTP), with activity against HSV-1, HSV-2, VZV and Epstein-Barr virus (EBV).[2] Valacyclovir confers oral bioavailability three to five times that of acyclovir, allowing for less frequent dosing than that of acyclovir, which requires dosing five times daily . Oftentimes, howev-

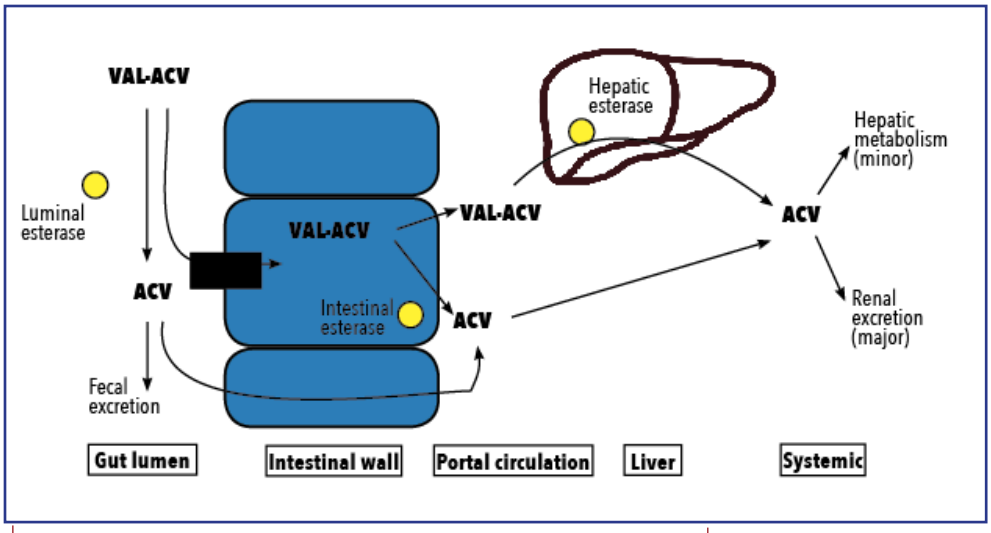

Figure 2: Pathway demonstrating valacyclovir and acyclovir metabolism and excretion.

er, acyclovir is several folds cheaper than valacyclovir, rendering it a more accessible therapy for most patients. It is important to note that the elimination of acyclovir is predominantly renal. The half-life of acyclovir ranges from two to three hours in healthy patients, but may extend up to fourteen hours in patients with ESRD.[3] As such, doses should be reduced according to creatinine clearance in those with renal disease, and may be as low as 500 mg every 24 hours in hemodialysis patients, compared to dosages of up to 1 gram three times daily in patients without renal impairment.

Clinical Presentation

Adverse effects of acyclovir vary greatly in severity, and can include nausea, vomiting, headache, renal failure, and neurotoxicity. In addition to the dosing adjustments that are required in patients with underlying renal impairments, acyclovir itself may also cause acute renal damage. Acyclovir-induced renal failure is caused by precipitation of acyclovir crystals within the renal tubules, leading to obstructive nephropathy, acute interstitial nephritis, and acute tubular necrosis.[4] Undiagnosed, this can create a self-perpetuating cycle as the damaged kidneys fail to filter and excrete circulating acyclovir, and toxic metabolites accumulate. Renal impairment typically begins within 24-48 hours in toxic patients, and may present with nausea and flank pain secondary to obstruction from crystal deposition. Bolus intravenous dosing, dehydration, and underlying chronic renal failure place patients at higher risk of developing acyclovir-induced renal failure.

The first reported case of acyclovir-associated neurotoxicity was in 1998 by Linssen-Schuurmans et al, with multiple subsequent cases since.[5,6] Notable risk factors include chronic renal dysfunction, concomitant neurotoxic drugs, and advanced age.[7] Acyclovir neurotoxicity frequently presents as altered consciousness but may also include myoclonus, dysarthria, photophobia, ataxia, and seizures. Furthermore, acyclovir neurotoxicity has also been shown to manifest with psychiatric components including auditory and visual hallucinations, depression, and suicidality. Multiple case reports have described the association of acyclovir toxicity with Cotard's syndrome or 'death delusion.' This syndrome is characterized by strong delusions of being dead, or convinced that others around the patient are dead.[8] When present, the neurotoxic effects of acyclovir typically manifest within 24 to 72 hours, and can resolve completely within four days, after cessation of the culprit drug.[6]

Diagnosis

The diagnosis of acyclovir toxicity is clinical, and should be suspected in patients with acute renal failure or new neuropsychiatric symptoms in the setting of the aforementioned risk factors. While acyclovir levels can be obtained from the blood, serum, cerebrospinal fluid (CSF), and urine, levels have not been found to correlate with clinical symptoms of toxicity. Further, the development of neurotoxic symptoms has been found to be delayed up to 48 hours after serum concentrations peak.[9] Notably, a downstream metabolite of acyclovir, 9-carboxymethoxymethylguanine (CMMG), has been identified in both serum and CSF of patients with acyclovir toxicity, with detection in the CSF only occurring in patients exhibiting neuropsychiatric symptoms.[10] While this is an interesting finding, testing for CMMG is not widely available and only facilitates, rather than confirms, the diagnosis. Urinalysis may demonstrate positively birefringent, needle-shaped crystals and pyuria, however this is again supportive rather than confirmatory, and absence of such findings does not reliably negate the diagnosis of acyclovir toxicity.[11] In all suspected cases, a basic metabolic panel is crucial, as chronic or acute renal failure precedes the onset of neurotoxicity.

When evaluating a patient with suspected acyclovir toxicity, it is also important to consider other organic mimics including meningitis, HSV encephalitis, herpes zoster associated encephalitis (HZAE), and stroke. Lumbar puncture is imperative, specifically to evaluate for HZAE, as well as other infectious etiologies. It was considered in our case above, however given rapid improvement in our patient's mental status with dialysis, and the sheer availability of urgent dialysis in our case, her symptoms were thought to be more likely secondary to acyclovir toxicity, and thus further diagnostic work up was deferred. Clinically, the differentiation between such etiologies can prove difficult, as HZAE and acyclovir toxicity can both present with somnolence and confusion after the onset of a vesicular skin eruption. Expedient CSF analysis can prompt either continuation of acyclovir for HZAE, or cessation to prevent further toxicity. In the setting of the acutely altered patient with neurologic findings, cranial computed tomography is indicated to rule out space-occupying lesions, and vessel imaging may be considered in the appropriate patients to rule out acute vascular diseaseas needed. Electroencephalogram (EEG) may also be useful if there is concern for non-convulsive status epilepticus.

Treatment

The first step in the treatment of suspected acyclovir toxicity involves the assessment of whether the patient's current dosage is appropriate for their level of underlying kidney function, and whether there are indications for its continuation. For those with chronic kidney disease, dosages often need to be reduced, and in other cases, complete cessation is indicated. Patients exhibiting mild toxicity can generally be treated symptomatically. Nausea and vomiting may be treated with antiemetics; headache with stan

Acyclovir Toxicity
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dard migraine therapies. Acyclovir-induced renal failure may be treated with volume repletion withintravenous fluid therapy and loop diuretics in an attempt to flush out obstructing crystal depositions . Though the use of these therapies are more theoretical in nature given the lack of robust literature on the topic, they have generally been well-tolerated. Patients with CNS depression should have an airway assessment performed early on during their course. Seizures should be aborted with standard antiepileptics. For those with significant neurotoxic symptoms, hemodialysis is indicated and has been shown to be highly effective in returning patients back to their neurologic baseline. Some reports describe removal of 30-60% of the drug after a single four-hour hemodialysis session. Although this may have a profound effect on neurotoxic symptoms, hemodialysis has not been shown to alter outcomes of acyclovir renal toxicity.[12] Additionally, peritoneal dialysis is not an effective means for removing acyclovir from the blood and has no role in management of acyclovir toxicity.

Summary

Patients undergoing acyclovir or valacyclovir therapy with underlying chronic kidney disease are particularly at risk for developing acyclovir-induced neurotoxicity. Symptoms of toxicity can develop precipitously and may provide difficult to differentiate from viral encephalitis. Despite recent advances in biomarkers associated with acyclovir-associated neurotoxicity, the diagnosis remains clinical. Discontinuation of acyclovir, coupled with hemodialysis when indicated, has been shown to significantly improve symptoms and outcomes. This case highlights the caution needed in both prescribing and dosing acyclovir in patients with underlying renal impairment.

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elevated liver enzymes, a uric acid and lactate dehydrogenase to assess for hemolysis, and a chest X-ray or ultrasound to assess for pulmonary edema in the appropriate clinical settings.[2] An electroencephalogram can also be used if presentation is ambiguous for neurologic versus non-neurologic etiology. The combination of blood pressure measurement and the diagnostic evaluation can help determine the severity of the patient's condition and the necessary treatment steps to follow.

Treatment

Delivery is the only curative therapy for severe preeclampsia and eclampsia, but neonatal viability must be weighed into this decision in concert with an obstetric specialist.[7] Additionally, the mother must be stabilized first and foremost prior to consideration for delivery and transport to a facility with appropriate resources. Thus, as with all other emergency management, assessing maternal airway, breathing, and circulation is paramount, along with limiting maternal trauma sustained from the seizure episode. Placing the mother in the left lateral decubitus position will assist in relieve pressure off of the inferior vena cava, and thus improve venous return and maternal circulation.

Next, prioritization of treatment of recurrent seizures needs to occur. Magnesium sulfate is the treatment for preventing recurrent eclamptic seizures and has been used since the early 1900s. While not traditionally considered an anticonvulsant, magnesium sulfate is effective due to the calcium channel antagonism, leading to smooth muscle relaxation and reversal of cerebral arterial vasospasm.[8] It also corrects the underlying endothelial injury that is characteristic of this disease state by releasing endothelial prostacyclin and simultaneously inhibiting platelet aggregation.[9] Magnesium has been shown to be more effective than phenytoin and diazepam for the treatment of seizures in patients with eclampsia, and often can be used successfully as a single agent therapy in this patient population.[10] A loading dose of 4-6 grams of IV magnesium should be administered over thirty minutes, followed by a continuous infusion of 1-2 grams of IV magnesium per hour.[10] Only if the patient continues to have refractory seizures should other antiepileptic medications be considered. Patients with renal dysfunction may have an increased risk for supratherapeutic magnesium levels, and therefore increased monitoring may be warranted targeting a goal of goal of greater than 2-4 mg/dL.[11] Patients should also be

Medication	Mechanism of Action	Dosing	Adverse Effects
Labetalol *1st line*	a,B1,B2-adrenergic receptor antagonist	10-20mg IVP every 20-30 mins (max total daily dose: 300mg)	Possible negative iontropic effects from beta blockade
Hydralazine	Direct vasodilation of arterioles	5-10 mg IVP every 20-40 mins (If blood pressure not at goal after 20-30mg total, then switch to a different agent)	Delayed onset leading to hypotension with repeated doses Higher rates of maternal hypotension compared to nifedipine or labetalol
Nifedipine	Dihydropyridine calcium channel blocker	10-20mg PO every 30 mins PRN (If blood pressure not at goal after 3 doses then switch to a different agent) then 10-20mg every 2-6 hours PRN	No IV formulation Sublingual not recommended

Table 4: Antihypertensive Therapy for Hypertension in Pregnancy

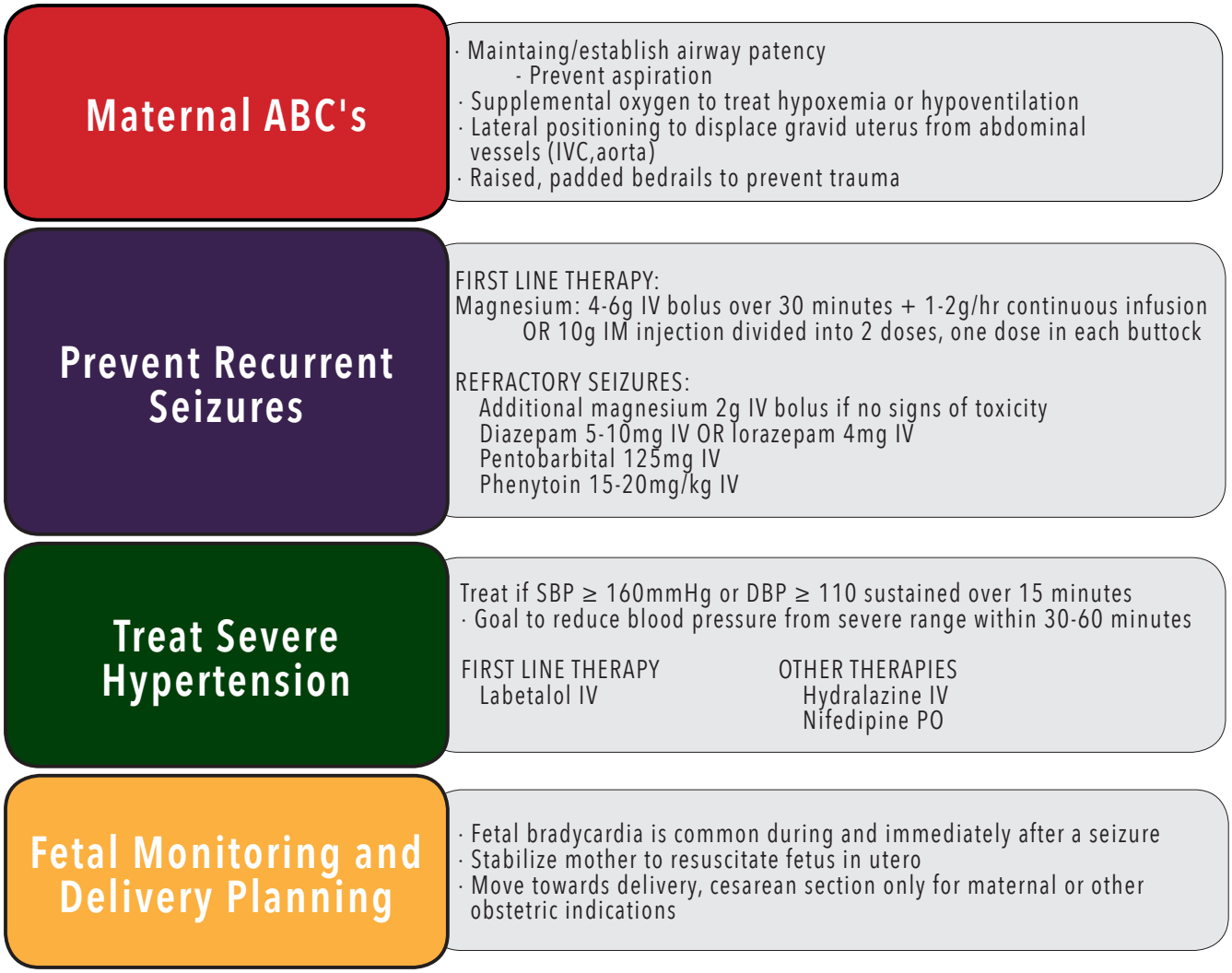

Figure 3: Summative approach to hypertension in pregnancy

monitored for signs or symptoms of toxicity, such as increased hypotension and respiratory depression. Calcium gluconate may be used as an antidote for magnesium toxicity.

In conjunction with seizure management, severe hypertension must also be emergently controlled to prevent risk of stroke and intracranial hemorrhage. The first line agents for blood pressure control are IV labetalol, IV hydralazine, or PO immediate release nifedipine.[10,12] The goal is not to normalize blood pressure, but to prevent prolonged exposure to severe systolic hypertension; thus, an initial goal range of 140–150mmHg systolic pressure and 90–100 mmHg diastolic pressure is reasonable.[7]

Prognosis

Maternal mortality rates of up to 14% have been documented in eclampsia, with up to 15% to 20% of deaths attributable to stroke secondary to severe, uncontrolled hypertension.[13] If the mother survives, there are future consequences to both maternal health and complications with future pregnancies. Women with a history of eclampsia have demonstrated to be at an increased risk for cardiovascular and cerebral disease lateral in life, with chronic hypertension being a commonly developed co-morbidity.[14] Furthermore, recurrent eclampsia occurs in about 2% of subsequent pregnancies.[14] Even if maternal hypertension is closely monitored and managed in future pregnancies, there continues to be an elevated risk for placental abruption, preterm delivery, fetal growth restriction, and perinatal mortality.[14] Thus, all future pregnancies should be monitored with a maternal-fetal medicine specialist as they are considered to be high-risk.

Summary

In conclusion, preeclampsia and eclampsia hold high maternal and neonatal morbidity and mortality rates, and require prompt recognition. A high degree of suspicion must be held in any critically ill pregnant patient more than twenty weeks of gestation, and quick initiation of appropriate management, including maternal stabilization, management of recurrent seizures, and adequate control of hypertension, is vital in reducing risk for complications.

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Neurolisteriosis

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Diagnosis

Suspicion of neurolisteriosis should be based on clinical presentation and risk factors. However, there is no particular historical factor or physical exam finding that will differentiate between *L. monocytogenes* infection and other etiologies of meningoencephalitis disease. Thus, diagnosis largely depends on isolation of the organism via cerebrospinal fluid (CSF) or blood cultures.[1,10] In regards to CSF results, *L. monocytogenes* is unique that it is one of the only nontuberculous bacteria that will have lymphocytosis in addition to increased protein and decreased glucose on CSF analysis.[4] However, providers must be aware that CSF culture sensitivity may be reduced when encountering more focal CNS infections. In regard to blood cultures, *L. monocytogenes* is a fastidious organism which requires Meuller-Hinton agar for growth, and as such, many patients with neurolisteriosis will not develop positive blood cultures.[1] It is estimated that positive blood cultures occur in only 61-63% of cases of *L. monocytogenes* encephalitis.[2,8] Blood cultures may be of limited utility due to two reasons: *L. monocytogenes* is an intracellular parasite and may not be detectable; and it is oftentimes mistaken for diplococci or diphtheroids, therefore it may be named a contaminant if providers are not aware of the clinical suspicion for *L. monocytogenes* infection.[11] Mortality rates are higher in patients with positive blood cultures, suggesting patients with concomitant bacteremia and neurolisteriosis may have a more severe disease profile.[2]

Stool cultures do not typically play a role in diagnosis of *L. monocytogenes*, even during pregnancy. The bacterium is commonly present in the environment, and has been isolated from the gut of asymptomatic humans in several studies, therefore intermittent carriage and shedding may occur that does not always indicate active infection.[12] Furthermore, most gastrointestinal illnesses self-resolve and do not require antibiotic therapy.

Cross-sectional imaging of the brain is recommended in cases of suspected or confirmed neurolisteriosis, as brain abscesses and obstructive hydrocephalus are well described complications.[1,9] MRI should be strongly considered in cases of *L. monocytogenes* encephalitis or rhomboencephalitis if there is any clinical uncertainty or suspicion for intraparenchymal involvement. In a case series of nine patients with confirmed *L. monocytogenes* rhomboencephalitis, only one patient had a normal MRI, indicating that detection of neurosurgically-intervenable lesions are commonly identified.[9]

Treatment

Ampicillin or penicillin G are recommended as first-line agents for *L. monocytogenes* infections. Although aminoglycosides have poor CNS penetration, a 2017 large prospective observational study demonstrated possible mortality benefit when used in conjunction with beta lactam antibiotics in patients with neurolisteriosis or bacteremia that portends a higher risk for CNS infection.[2] Bactrim is an acceptable second-line therapy for those patients with a penicillin or beta lactam allergy.[1] *L. monocytogenes* is resistant to all cephalosporins, and some strains have developed complete resistance to vancomycin as well.[13] Less commonly used antibiotics, such as meropenem and linezolid, have efficacy against *L. monocytogenes* , however these are primarily anecdotally used and only in severe circumstances. Duration of antibiotic therapy largely depends on degree of dissemination, however neurolisteriosis requires at least six weeks of antibiotic therapy.[14]

One study found that neurolisteriosis treated with dexamethasone in addition to antibiotics significantly increased mortality.[2] Thus, steroids are not recommended in the treatment of Listeria encephalitis and rhomboencephalitis, and if initiated empirically at patient presentation, use should be discontinued as soon as *L. monocytogenes* infection is confirmed.[2]

Reported mortality rates differ widely, as *L. monocytogenes* encephalitis and rhomboencephalitis are overall uncommon entities. In one case review, 100% of untreated patients died; of those treated early with ampicillin or penicillin, mortality rates were less than 30%.[8] Mortality rates were higher in patients with underlying malignancies, diabetes, poorly controlled co-morbidities, and those who developed multi-organ failure,[2] whereas otherwise healthy patients had lower mortality rates. CNS infection and bacteremia have 30% and 45% mortality rates, respectively.[2] These reviews suggest that early detection and early institution of antibiotic therapy can be very effective in treating life-threatening *L. monocytogenes* infection, thus empiric coverage should be considered in patients with suspected exposure.[2,3,15] Of those that develop neurolisteriosis and survive, permanent neurologic sequelae remained in 61% of survivors.[8]

Summary

In summary, neurolisteriosis is a rare disease process with a high morbidity and mortality that can affect both immunocompetent and immunocompromised individuals, particularly those at extremes of age and during pregnancy. Early recognition is critical in order to ensure appropriate treatment and improve survival rates.

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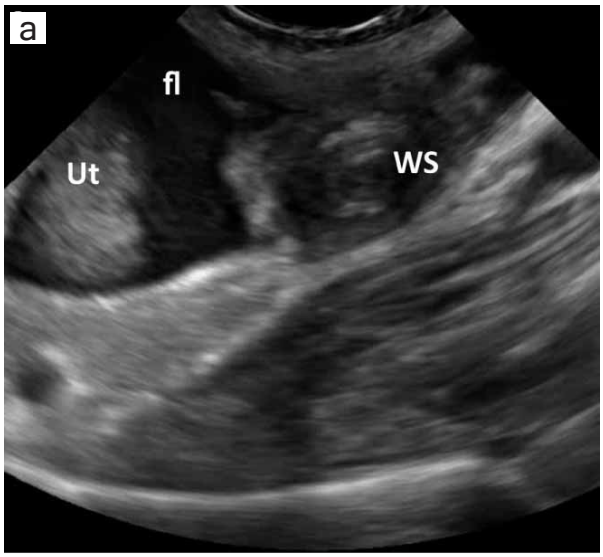

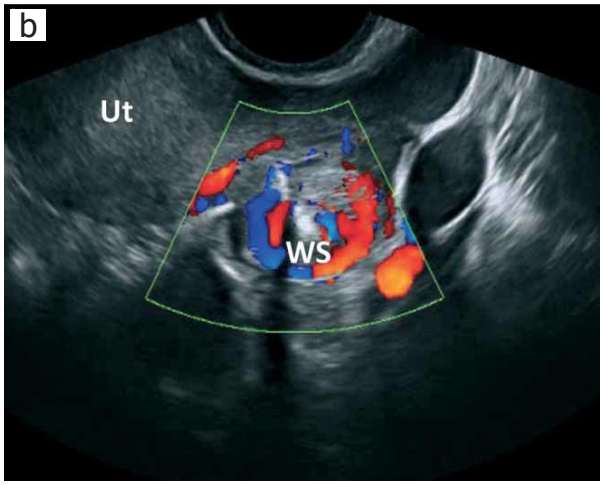

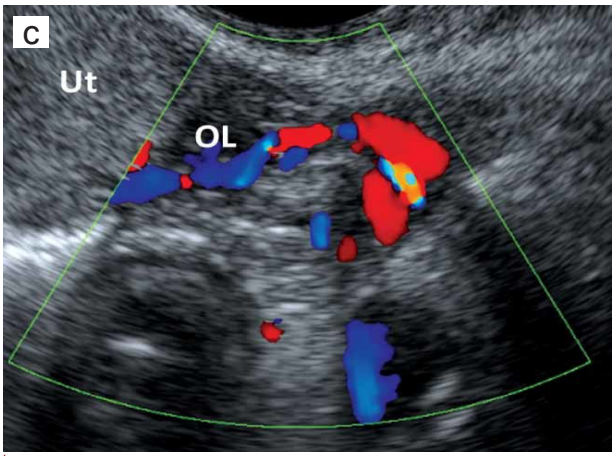

Images 3-5 : (a) gray-scale and (b) color doppler ultrasound images of torsed ovarian ligament demonstrating the classic "whirlpool" sign. In comparison, (c) color doppler ultrasound image showing absence of the whirlpool sign.
fl, fluid; Ut, uterus; WS, whirlpool sign; OL, ovarian ligament
Images courtesy of: Valsky DV, Esh-Broder E, Cohen SM, et al. Added value of the gray-scale whirlpool sign in the diagnosis of adnexal torsion. Ultrasound of Obstet Gynecol 2010; 36: 630.

findings are inconsistent depending on time of evaluation, as torsion can occur intermittently. The most specific ultrasound

finding is decreased or absent arterial doppler flow to the ovaries, which has between 92-97% specificity and a 94-100% positive predictive value for torsion. The whirlpool sign refers to visualization of a twisted pedicle and coiled vessels and also has a 90% positive predictive value for torsion. Ultrasound becomes increasingly sensitive and specific when there are at least two or more sonographic findings present. [13, 17-20]

While confirmation of torsion on imaging is valuable in the clinical setting, it is critically important to maintain focus on the patient's symptomology. Even in the absence of ultrasonographic signs of torsion, if ovarian torsion remains the leading diagnosis based on equivocal lab testing and imaging, there is still a role for emergent gynecologic consultation and laparoscopic evaluation if deemed necessary. Diagnostic laparoscopy remains the gold standard for patients in whom clinical suspicion remains high despite negative imaging results.

Treatment

Once ovarian torsion has been diagnosed, gynecology consultation is paramount. All torsed ovaries require urgent de-torsion and assessment of viability. This can only be accomplished by direct visualization in an operating suite and therefore the mainstays of emergency management are pain control and coordination of gynecologic or surgical evaluation. There is no definitive window after which an ovary is guaranteed to be non-viable, however some studies quote better outcomes if identified and treated within eight hours.[21] Thus, timely identification and involvement of consulting services is of the essence.

Summary

Ovarian torsion remains a highly morbid disease process that is difficult to diagnose. Emergency physicians need to have a high clinical suspicion of ovarian torsion in women of reproductive age. Appropriate use of imaging will lead to an expedited diagnosis and subsequently decrease the risk of infectious and fertility complications.

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and amount of nerve stimulation that is occurring,[11] with patterns resembling a few other neuromuscular disorders, including Lambert-Eaton syndrome. Studies have shown that single fiber EMGs are more sensitive and specific,[12] and given this diagnostic test is usually readily available, it may support the diagnosis while awaiting stool confirmation.[13]

As infantile botulism is a relatively rare diagnosis, it may be missed on initial presentation, and clinical mimics do exist. A 2007 study found that from 1992 to 2005, five percent of patients treated with baby BIG were later found to have alternative diagnoses.[14] The most common final diagnoses were spinal muscular atrophy, metabolic disorders, and infectious diseases such as meningoencephalitis.[14] Viral encephalitis was chief among the missed infectious conditions. Many of the infants ultimately diagnosed with metabolic disorders would likely have been diagnosed at birth with the modern newborn screening implemented today, however the differential should remain broad when encountering an infant with change in muscle tone.[14]

Treatment

Supportive care is still a mainstay of ED and ICU management, and maintaining a broad differential diagnosis with a high suspicion for infantile botulism in the appropriate settings is vital to ensure that this diagnosis is not missed by emergency providers. If clinical suspicion is high, initiating diagnostic testing and therapy in concert with pediatric specialists is crucial as baby BIG remains the only curative therapy available for the treatment of botulism.

Baby BIG irreversibly binds to BT, thus preventing BT from exerting its effects at the neuromuscular junction.[15] In 2006, a landmark randomized-control study randomized 122 patients to receive baby BIG versus supportive care alone.[15] Baby BIG was found to reduce mean hospital length of stay by fifty-four percent, and similar decreases were seen in ICU length of stay, duration of mechanical ventilation, and duration of tube feeding.[15] Subsequent investigations have confirmed the efficacy of baby BIG, however note that the clinical effects are diminished if not administered within the first seven days of hospitalization. Therefore, empiric administration of baby BIG is recommended if clinical suspicion is high while awaiting stool studies.[16]

Baby BIG has a 28-day half-life and can usually be administered as a single dose. The drug is generally well tolerated, with the most common adverse effect being a transient erythematous rash. Serious immune reactions are very rare. Baby BIG is an orphan drug produced exclusively by the California Department of Public Health through their Infantile Botulism Treatment and Prevention Program (IBTPP). The on-call IBTPP physician must be contacted in order to obtain the drug. Many patients will receive antibiotics during initial presentation out of concern for SBI. While it makes intuitive sense to administer antibiotics to patients with infantile botulism given that it is caused by a bacterium, antibiotics are not recommended in confirmed cases of infantile botulism. Gastrointestinal colonization is typically self-limited, and antibiotics theoretically increase the risk of cell death and lysis, resulting in increased toxoid release and worsening paralysis.[15]

Prior to modern intensive care and the invention of baby BIG, mortality from botulism was estimated to be as high as sixty percent.[17] Infantile botulism mortality is difficult to fully characterize as it was only fully recognized as a disease entity in the 1970s, and for many years, had a purported association with sudden infant death syndrome (SIDS), both of which skew much of the data.[17] Thankfully, in the modern era, mortality is as low as two percent, and most patients make a full recovery with complete return of motor function.[18]

Summary

While quite rare, infantile botulism should remain on the differential for any infant presenting with hypotonia. The classic presentation will be symmetric, descending flaccid paralysis. Although stool assays remain the gold standard for diagnosis, recovery time is markedly hastened with early initiation of baby BIG, and treatment should be implemented prior to receiving confirmatory testing. Morbidity and mortality are markedly reduced with current therapies, with full recovery of neurologic function with early treatment.

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Ovarian Torsion	Laurence/Benoit
Conversion Disorder	Liebman/Knight
Meningitis	Habib/Campbell