In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

(Filed: March 31, 2017)

No. 14-741V

SARA ELIZABETH SAJBEL, *as Representative of the Estate of B.B.T., Deceased,*	*	To Be Published
Petitioner,	*	Ruling on Entitlement; Hepatitis B ("Hep B") Vaccine; Hemophagocytic Lymphohistiocytosis ("HLH"); Death.
v.	*	
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	
Respondent.	*	

Richard Gage, Richard Gage, P.C., Cheyenne, WY, for petitioner.
Lisa Watts, U.S. Department of Justice, Washington, D.C., for respondent.

RULING ON ENTITLEMENT[1]

Roth, Special Master:

On August 15, 2014, Sara Sajbel ("Ms. Sajbel," or "petitioner") filed a petition as representative for the estate of her deceased son, B.B.T., for compensation under the National Vaccine Injury Compensation Program, 42 U.S.C. §300aa-10, et seq.[2] (the "Vaccine Act" or "Program"). The petition alleged that the hepatitis B vaccination that B.B.T. received on March 28, 2013 caused him to suffer from hemophagocytic lymphohistiocytosis ("HLH"). Petition at 1.

[1] Because this published decision contains a reasoned explanation for the action in this case, I intend to post this decision on the United States Court of Federal Claims' website, in accordance with the E-Government Act of 2002, Pub. L. No. 107-347, § 205, 116 Stat. 2899, 2913 (codified as amended at 44 U.S.C. § 3501 note (2012)). In accordance with Vaccine Rule 18(b), a party has 14 days to identify and move to delete medical or other information that satisfies the criteria in § 300aa-12(d)(4)(B). Further, consistent with the rule requirement, a motion for redaction must include a proposed redacted decision. If, upon review, I agree that the identified material fits within the requirements of that provision, I will delete such material from public access.

[2] National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755. Hereinafter, for ease of citation, all "§" references to the Vaccine Act will be to the pertinent subparagraph of 42 U.S.C. § 300aa (2012).

I conducted an entitlement hearing in this case on April 14, 2016, in Denver, Colorado. For the reasons stated herein, I find that petitioner has proffered sufficient evidence to demonstrate that the hepatitis B vaccine that B.B.T. received at 32 minutes of age more likely than not caused his development of acquired hemophagocytic lymphohistiocytosis. Accordingly, I find that petitioner is entitled to compensation.

I. Procedural History

Contemporaneously with filing the petition, petitioner also filed her affidavit ("Pet. Aff."). ECF No. 1. Petitioner filed medical records, Petitioner's Exhibits ("Pet. Ex.") 1-13 on September 9, 2014. ECF No. 7. On December 17, 2014, respondent filed a Rule 4(c) Report ("Rule 4") which stated that compensation was not appropriate, along with an expert report from Dr. Kenneth McClain and supporting medical literature, Respondent's Exhibits ("Res. Ex.") A-E. ECF No. 13. Petitioner filed an expert report from Dr. Vera Byers on June 1, 2015, and supporting medical literature on June 12, 2015. Pet. Ex. 14, 15-21, ECF Nos. 21, 22. Petitioner filed additional medical literature on July 6, 2015. Pet. Ex. 22, ECF No. 23. Petitioner filed a supplemental expert report from Dr. Byers on September 10, 2015. Pet Ex. 23, ECF No. 25. That same day, respondent filed a supplemental expert report from Dr. McClain. Res. Ex. F, ECF No. 26. Respondent filed supporting medical literature via compact disc on September 21, 2015. Res. Ex. G-P, ECF No. 28.

This case was reassigned to me on October 22, 2015. ECF No. 31. After conducting a status conference on December 3, 2015, I ordered the parties to submit a joint status report identifying potential hearing dates. *See* Order, issued Dec. 3, 2015, ECF No. 32. On December 14, 2015, I issued a prehearing order, setting an entitlement hearing for March 24 and 25, 2016, in Denver, Colorado. Prehearing Order, ECF No. 34. Petitioner filed her pre-hearing brief on January 28, 2016. ECF No. 39. Respondent filed his pre-hearing brief on February 18, 2016. Due to inclement weather in Colorado forcing an adjournment of the initial hearing, this case ultimately went to hearing on April 14, 2016. Post-hearing briefs were filed by both parties on November 7, 2016.

This matter is now ripe for decision.

II. Summary of Relevant Medical Records

A. Prenatal Development

Petitioner, B.B.T.'s mother, was 24 years old when she became pregnant with B.B.T. Petitioner had a history of asthma, fibroids, and ovarian cysts. Pet. Ex. 1 at 23. Shortly after undergoing bilateral ovarian cystectomies on August 1, 2012, petitioner had several positive pregnancy tests. *Id.* at 25. Petitioner presented to Dr. Berryman on August 6, 2012, where petitioner had a positive urine pregnancy test. *Id*. Dr. Berryman prescribed 200mg of Prometrium,[3]

[3] Prometrium is a brand name for progestin, a hormone. Prometrium can be prescribed to help maintain a pregnancy when not enough progestin is being made by the body. "Progestin," Mayo Clinic, mayoclinic.org.

and ordered an hCG test.[4] *Id*. Petitioner presented to Dr. Berryman on August 16, 2012 after a positive hCG test. *Id*. at 32. An ultrasound showed a "gestational sac with yolk sac." *Id.* Dr. Berryman discontinued the Prometrium capsules, and substituted "Crinone Gel, 8%." *Id*. Petitioner presented on August 28, 2012, with complaints of increased nausea and vomiting; 25 mg of promethazine HCl was prescribed. *Id*. at 30.

On January 16, 2013, an ultrasound revealed that petitioner had polyhydramnios, or excess amniotic fluid. The fetal anatomy, including the stomach, bowel, right kidney, left kidney, and bladder, was noted as normal. Pet. Ex. 1 at 54. On January 30, 2013, petitioner saw Dr. Gene LaMonica and Jenna Cedar, a genetic counselor, at Colorado Health Medical Group, for a detailed ultrasound. A transabdominal ultrasound revealed a normal head, brain, face, spine, chest, abdominal wall, gastrointestinal tract, kidneys, bladder, extremities, skeleton, and four chamber heart. *Id.* at 39. Following the ultrasound, Dr. LaMonica concluded "…we were able to confirm significant polyhydramnios (AFI of 33 cm) with near fetal macrosomia (large baby). Together, these findings strongly suggest the development of gestational diabetes…." *Id*. at 39. Petitioner was prescribed betamethasone steroid injections to treat the polyhydramnios. *Id*. at 28. One injection was administered in January, and the second injection on February 26, 2013. *Id*. at 28. An ultrasound performed on February 27, 2013 revealed the fetal abdomen, including the stomach, bowel, right and left kidneys, and bladder, to be normal. *Id*. at 66. On March 6, 2013, an ultrasound showed normal amniotic fluid and normal fetal abdomen, including the stomach, bowel, right and left kidneys, and bladder. *Id*. at 57, 59. An ultrasound performed on March 13, 2013 revealed right pyelectasis[5] and "fluid improved." *Id*. at 61. On March 20, 2013, examination showed that the polyhydramnios was improved/resolved. Petitioner expressed concern about excessive fetal growth and requested an amniocentesis. A three hour glucose testing was refused. Petitioner advised that she was checking her blood sugar via finger prick and that all numbers were normal. Pet. Ex. 1 at 27; 63.

On March 27, 2013, petitioner was admitted to Parkview Hospital for ultrasound guided amniocentesis. She was noted to have A1 gestational diabetes, resolved polyhydramnios, and excessive fetal growth. Amniotic fluid was sent for a fetal lung maturity profile. Pet. Ex. 3 at 1. The amniocentesis reported positive lung profile, and petitioner was admitted for induction of labor. Pet. Ex. 2 at 9. Upon admission to labor and delivery, petitioner was noted to have A1 diabetes, resolved polyhydramnios, and excessive fetal growth. Her glucose level that morning was 151. *Id*. at 9.

B. Birth and Hepatitis B Vaccination

B.B.T. was born via vaginal delivery on March 28, 2013, at 37 weeks and 4 days, at Parkview Medical Center. Pet. Ex. 2 at 16. He was 9 pounds, 3 ounces, and 21.5 inches long. Pet.

[4] "HCG" stands for "human chorionic gonadotropin." HCG is a hormone produced during pregnancy. An hCG test measures the amount of hCG in a person's body and is used to detect pregnancy. "HCG in Blood Serum Qualitative," UCSF Medical Center, ucsfhealth.org.

[5] Pyelectasis is dilation of the pelvis of the kidney. STEDMAN'S POCKET MEDICAL DICTIONARY (1st ed. 1987) at 628, hereinafter "Stedman's."

Ex. 4 at 6. He scored an 8 on his one-minute Apgar and a 9 on his five-minute Apgar.[6] *Id*. Doctors detected a heart murmur during B.B.T.'s newborn exam, but the murmur was no longer present upon his discharge. *Id*. At 32 minutes of age, B.B.T. received the pediatric hepatitis B vaccination, Recombivax. *Id*. at 14. At 25 hours of age B.B.T. developed jaundice, with a bilirubin level of 8.8. Thereafter at 30 hours, his bilirubin was 9.8 and at 49 hours, it was 8.2. *Id*. at 11. B.B.T. received phototherapy. *Id*. at 56. His records state that at 4:21 am and 6:30 am on March 28, 2013, nurses had described B.B.T.'s skin as "bruising, intact" and pink, but at 6:41 pm that same day, he was noted to be "rashy." *Id*. at 29, 32, 45. Nurses continued to describe B.B.T.'s skin as "rashy" for the remainder of his stay through discharge. *Id*. at 47, 51, 63, 71. B.B.T. was discharged from Parkview Medical Center as a healthy baby on March 30, 2013. *Id*. at 8.

C. Emergency Care

On the morning of March 31, 2013, petitioner "returned B.B.T. to the hospital for bilirubin[7] testing." Pet. Aff. at 1. Later that day, petitioner noted that B.B.T. had been feeding but seemed somewhat lethargic most of the afternoon. Pet. Ex. 7 at 6. After a visit with his grandmother, B.B.T. was placed in his car seat for the 10 minute car ride home. Petitioner stated that when they took him out of the car seat, he was limp and apneic. *Id*. Petitioner called 911; EMS responded. *Id*. B.B.T. "had restored pulse after application of O2." *Id*. He was taken to St. Mary-Corwin Hospital Emergency Room, where doctors inserted an endotracheal tube and a nasogastric tube; they also ran hematology and chemistry labs, an EKG, and a head CT. *Id*. at 8-10, 32-33. A urinary catheter was inserted with "approximately one drop of DK amber clear urine noted." *Id*. at 20. B.B.T. was administered oxygen, IV fluids, antibiotics, and transferred to the Neonatal Intensive Care Unit (NICU) at The Children's Hospital in Denver. *Id*. at 7-10.

D. Transfer to TCH and Diagnosis of HLH

B.B.T. was admitted to The Children's Hospital ["TCH"] on April 1, 2013, at 2:15 am. Pet. Ex. 8 at 1. Upon admission, the neonatologist diagnosed B.B.T. with "severe metabolic acidosis,[8]

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[6] The Apgar score is a numerical expression of the condition of a newborn infant, usually determined at 60 seconds after birth, being the sum of points gained on the assessment of the heart rate, respiratory effort, muscle tone, reflex irritability, and color. DORLAND'S ILLUSTRATED MEDICAL DICTIONARY (32nd ed. 2012) at 1707, hereinafter "Dorland's."

[7] Bilirubin is a product formed during the normal breakdown of red blood cells. It passes through the liver, and is then excreted from the body. Higher than normal levels of bilirubin may indicate liver problems or an increased rate of destruction of red blood cells. "Bilirubin test," Mayo Clinic, mayoclinic.org. High levels of bilirubin can build up and cause jaundice. "Jaundice in Healthy Newborns," Kids Health, kidshealth.org.

[8] Acidosis is when the body fluids contain too much acid; metabolic acidosis can occur when the body produces too much acid, or the kidneys are not removing enough acid from the body. Severe metabolic acidosis can lead to shock or death. Causes of metabolic acidosis include liver failure, kidney disease, and certain medications. "Metabolic Acidosis," Penn Medicine, pennmedicine.org.

encephalopathy, respiratory failure/apnea, hypoglycemia,[9] and hypocalcemia."[10] *Id*. at 10.

B.B.T. was treated by specialists from the metabolic, liver, neurology, oncology/hematology, cardiology, and infectious disease services. *Id*. at 11, 25, 30, 38, 45, 52. On April 3, 2013, an oncologist examined B.B.T. and expressed concerns that B.B.T. may have HLH.[11]

The oncologist suggested that a bone marrow biopsy be performed on B.B.T. if he was stable. Tests were ordered to check for possible viral causes which could trigger HLH. *Id*. at 38. On April 3, 2013, it was noted "[O]ur suspicion is now that he either has primary or secondary HLH." *Id.* at 84. That same day, a sample of B.B.T.'s DNA was sent to Cincinnati Children's Hospital Medical Center to be tested for genetic mutations which could cause familial HLH. At this point in time, B.B.T. had developed liver failure, kidney failure, and cardiomyopathy. *Id*. at 84.

B.B.T. was tested for mutations in the PRF1, MUNC 13-4, and STX11 genes. *Id*. at 450. A mutation in the PRF1 gene causes about 50% of familial HLH cases, while a mutation in the MUNC13-4 gene causes about 30% of cases of familial HLH. Pet. Ex. 9 at 1, 4. The testing revealed no mutations of the tested genes. *Id*. at 1, 4, 5. On April 25, 2013, additional genetic testing was ordered for mutations in RAB27A, STXBP2, SH2D1A, and BIRC4. Pet. Ex. 8 at 584. RAB27A and STXBP2 can be associated with familial HLH, while SH2D1A and BIRC4 are associated with X-linked lymphoproliferative disease. Pet. Ex. 9 at 9, 12, 15, 18. B.B.T. tested negatively for mutations in those genes. Pet. Ex. 8 at 782. By April 11, 2013, B.B.T. had developed five out of the eight diagnostic criteria for HLH, including cytopenia[12] of two cell lines,

[9] Hypoglycemia is an abnormally low concentration of glucose in the blood. Stedman's at 361.

[10] Hypocalcemia is abnormally low levels of calcium in the blood. Stedman's at 360. Neonatal hypocalcemia can occur in the first 10 days of life; symptoms include lethargy, poor feeding, and seizures. Neonatal hypocalcemia is usually treated with IV fluids and electrolytes. "Hypocalcemia in Children," Boston Children's Hospital, childrenshospital.org

[11] Hemophagocytic lymphohistiocytosis ("HLH") occurs when the immune system attacks the body; it can be genetic, or it can be brought on by virus, chemotherapy, or bone marrow transplant. It is a dysregulation of the immune system which results in hyperproduction of cytokines, leading to multi-organ dysfunction and death. HLH is classified into two types: familial, which is an inherited condition passed down from either parent who is a genetic carrier of the condition, and acquired, which is caused by other health problems such as cancer, an already weakened immune system, and infections. Epstein Barr virus is the most prevalent cause. "Hemophagocytic Lymphohistiocytosis," Johns Hopkins Medicine, hopkinsmedicine.org.

[12] Cytopenia is a condition in which there is a lower-than-normal number of blood cells. "Cytopenia," NCI Dictionary of Cancer Terms, National Cancer Institute, cancer.gov.

hypertriglyceridemia,[13] low or absent NK cell activity,[14] hyperferritinemia,[15] and elevated sIL-2r.[16] *Id*. at 507. By April 30, 2013, he also had pulmonary hypertension and hypertrophic cardiomyopathy. *Id*. at 46, 168. Campath, the medication used to treat HLH, had "caused significant cardiovascular collapse." *Id*. at 66. B.B.T. "also experienced a spontaneous intestinal perforation" which required surgery. *Id*. On June 22, 2013, B.B.T.'s medical team met with his parents to discuss B.B.T.'s "recent deterioration, frailty and…clinical instability," and "what is ethically reasonable to consider in light of the futility of his situation." *Id*. at 418. A Do Not Resuscitate Order was put into place on June 25, 2013. *Id*. at 818. On June 26, 2013, B.B.T. was taken off of ventilator support; he died shortly thereafter. *Id*. at 823.

In a letter dated July 10, 2014, Tom Garrington, M.D., one of B.B.T.'s treating physicians, stated:

> Cases of HLH in general can either be primary or familial due to a mutation in one or a number of genes important in regulating immune function; or secondary, due to exposure to some trigger which is usually an infection or malignancy, though other triggers that can stimulate the immune system, such as vaccinations, have been rarely reported to cause HLH in some individuals…[A]n extensive genetic valuation, however, failed to identify a mutation in any of the genes known to be associated with HLH. Regarding potential triggers before – because no infections or malignant disease processes were found, the most likely trigger was felt to be the hepatitis B vaccine he received in the newborn nursery.

Pet. Ex. 13 at 1.

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[13] Hypertriglyceridemia is "an abnormal concentration of triglyceride in the blood." It can occur as the result of certain medications or nephrotic syndrome (kidney problems). Rade N. Pejic and Daniel T. Lee, *Hypertriglyceridemia*, J AM BOARD FAM MED, 19 (3): 310-16 (2006).

[14] "NK cells" are natural killer cells, a type of white blood cell that contains enzymes that can kill tumor cells or cells infected with a virus. NCI Dictionary of Cancer Terms, National Cancer Institute, cancer.gov. NK cells identify and destroy cancer cells or infected cells. NK cells "secrete cytokines…that stimulate and guide the response of other agents of innate immunity and lymphocytes of the adaptive immune system." "Natural Killer cells and Innate Immunity," Ciml Immunology, Centre d'Immunologie de Marseille-Luminy, ciml.univ-mrs.fr.

[15] Hyperferritinemia is an excess of ferritin, an iron storage protein, in the blood and tissues of the body. "Hyperferritinemia-cataract syndrome," Genetics Home Reference, US National Library of Medicine, ghr.nlm.nih.gov.

[16] "sIL-2r," or "soluble interleukin-2 receptor" binds to interleukin-2, a group of cytokines that "stimulates the proliferation of T cells," as well as "the growth and cytolytic function of NK cells." Dorland's at 962-63.

III. The Experts

A. Petitioner's Expert: Vera Byers, M.D.

Dr. Vera Byers has a Ph.D. in immunology, a master's degree in microbiology, and a medical degree. Pet. Ex. 15 at 1. She is board-certified in internal medicine and board-eligible in allergy and immunology. Pet. Ex. 14 at 1. Additionally, she has fellowships in protein chemistry and clinical immunology. *Id*. Dr. Byers is the president of Immunology, Inc., a pharmaceutical consulting business. Pet. Ex. 15 at 2. She was a practicing clinical immunologist in San Francisco, CA. Tr. 8. Additionally, Dr. Byers sits on the National Institutes of Health (NIH) advisory board, where she is involved in determining the feasibility of submitted projects by biotechnology companies. Tr. 10-11. She is also involved in publications on immunology and oncology with a strong emphasis on vaccines. Tr. 12.

B. Respondent's Expert: Kenneth McClain, M.D.

Dr. Kenneth McClain has a Ph.D in virology and pathology and a medical degree. Res. Ex. B. He is board-certified in pediatrics and pediatric hematology and oncology. Tr. 171; *Id*. Dr. McClain is a professor in the Department of Pediatrics at Baylor College of Medicine and an attending physician at Texas Children's Cancer Center. Tr. 174. Dr. McClain has extensive clinical experience in diagnosing and treating HLH. In 2006, he started the Texas Children's Histiocytosis Center, an organization of clinicians and researchers which focuses on histiocytic diseases; it is supported by grants from the National Institutes of Health as well as foundations and family philanthropies. Tr. 173. Additionally, Dr. McClain has written 22 papers on HLH in peer-reviewed journals as well as chapters in medical textbooks. Tr. 173-74. He was the president of the Histiocyte Society from 1998 to 2001, an international group of physicians and scientists who have focused their efforts on improving the diagnosis of HLH and other histiocytic diseases. Tr. 174. Dr. McClain has treated over 400 patients in his career with HLH or variations thereof, and is consulted over 1500 times a year by physicians and families around the world asking for help in treating HLH and other histiocytic diseases. Tr. 170, 172.

IV. Issues to be Determined and Facts in Dispute

The issue to be determined is whether the hepatitis B vaccination that B.B.T. received at 32 minutes of life was the cause in fact and/or the trigger of HLH which led to B.B.T.'s death.

In determining that issue, there are several factual disputes between the experts that must be addressed. First, Dr. Byers opined that petitioner's polyhydramnios was caused by her gestational diabetes, whereas Dr. McClain disputes petitioner's diagnosis of gestational diabetes and believes that the polyhydramnios was an early manifestation of HLH in utero. Second, Dr. Byers opined that the rash that B.B.T. developed as a newborn was a reaction to the hepatitis B vaccine. Dr. McClain disputes whether B.B.T. had a rash as well as the significance of any rash that he may have had. Third, Dr. McClain believes that B.B.T.'s low albumin level when he presented to the emergency department at St. Mary-Corwin was an indication of liver failure and HLH in utero. Dr. Byers pointed to other potential causes of a low albumin level. Finally, Dr. McClain opined that B.B.T.'s bilirubin levels and jaundice after birth and upon presentation to the

emergency department at St. Mary-Corwin were indicators of HLH in utero. Dr. Byers opined that B.B.T.'s bilirubin levels were normal at birth and that the jaundice he developed, which resolved in less than 24 hours with phototherapy, was unrelated. Dr. Byers also pointed out that B.B.T.'s bilirubin level upon presentation to the emergency room at St. Mary-Corwin was normal.

V. The Experts' Opinions and Findings of Fact

A. Polyhydramnios

The experts' agree on the following: (1) polyhydramnios is excess amniotic fluid; (2) the most common cause of polyhydramnios is gestational diabetes; (3) polyhydramnios may also be caused by gestational tract problems in the baby or idiopathic issues like Down syndrome; (4) petitioner developed polyhydramnios in her third trimester; (5) the use of steroids was the appropriate course of treatment; (6) petitioner's polyhydramnios resolved by March of 2013; and (7) polyhydramnios has been reported with children who develop HLH in utero. Tr. 13-16; 26-28; 192-93; Pet. Ex.1 at 28; Pet. Ex. 14 at 2.

Dr. Byers opined that petitioner's polyhydramnios was caused by gestational diabetes. Tr. 13. According to Dr. Byers, petitioner was predisposed to develop gestational diabetes due to her weight, and was noted to be high risk for polyhydramnios in her medical record. Tr. 19-20. Dr. Byers explained that a heavier person needs more insulin, which puts a greater strain on the pancreas. *Id*. Pregnancy increases the requirement for the pancreas to support the extra weight and increases the likelihood that an overweight mother will develop gestational diabetes. *Id*. at 20.

According to Dr. Byers, on January 2, 2013, petitioner's glucose level was 106 mg/L. The baby was noted to be large and polyhydramnios was identified. Pet. Ex. 14 at 2. Based upon the ultrasound and petitioner's result on the first glucose screening, there was a strong suggestion that petitioner had developed gestational diabetes. Tr. 17, 140-41. Petitioner was given two steroid injections, one in January of 2013[17] and the second on February 26, 2013. Tr. 26-27; Pet. Ex. 1 at 28; Pet. Ex. 14 at 2. Dr. Byers clarified that the steroids would resolve only the polyhydramnios, not the gestational diabetes; gestational diabetes only resolves once the baby has been delivered. Tr. 28.

On March 6, 2013, petitioner's glucose level was 151, which was noted to be "HH" (extremely high). Tr. 23; Pet. Ex. 1 at 6. Dr. Byers pointed out that petitioner had "elevated blood glucose immediately after [B.B.T.'s] birth." Pet. Ex. 14 at 7. Combined with an unusually large baby, it is more likely than not that the polyhydramnios was caused by gestational diabetes. *Id*. Dr. Byers noted that three of petitioner's doctors attributed petitioner's polyhydramnios to gestational diabetes. Tr. 16-18, 32; Pet. Ex. 1 at 1; Pet. Ex. 2 at 8; Pet. Ex. 3 at 1.

Dr. McClain agreed that gestational diabetes is a much more frequent cause of polyhydramnios, but pointed out that the literature supports an association between polyhydramnios and HLH, citing to G. Balta, et al., *Association of Nonimmune Hydrops Fetalis With Familial Hemophagocytic Lymphohistiocytosis in Identical Twin Neonates With Perforin*

[17] There is no record of the first injection, only a reference to the administration of a "second injection" in February. Pet. Ex. 1 at 28.

His222Arg (c665A>G) Mutation, J. PEDIATR. HEMATOL. ONCOL., 35(8): 332-34 (2013), filed as Resp. Ex. K ["Association of Nonimmune Hydrops Fetalis with Familial HLH"] and C. Malloy, et al., *Hemophagocytic Lymphohistiocytosis Presenting with Nonimmune Hydrops Fetalis*, J. PERINATOL., 24: 458-60 (2004), filed as Resp. Ex. L ["Perinatal Neonatal Case Presentation HLH presenting with nonimmune hydrops fetalis"]. Resp. Ex. F at 3, 6.

Unconvinced that the petitioner had gestational diabetes, Dr. McClain stated that the data in the medical record was insufficient to diagnosis petitioner with gestational diabetes because she refused a three hour glucose test even though her glucose screening was at 151 in March of 2013. Tr. 194. In his report, Dr. McClain opined that polyhydramnios was the first sign that B.B.T. had HLH in utero and that the steroid injections given to treat the polyhydramnios blunted the progression of the disease. Tr. 194; Resp. Ex. F at 3.

At hearing, however, Dr. McClain stated that HLH presents in various ways and admitted that it may or may not have been part of the polyhydramnios. Tr. 193. He furthermore stated that the steroids that made the polyhydramnios resolve may or may not have affected the early stages of HLH intrauterinely. *Id*. He stated that it was a possibility, but not all patients with HLH have an excess of fluid around them. *Id*. When asked what he believed caused the petitioner's polyhydramnios, Dr. McClain conceded that he did not really know: "…HLH could have been part of that. Probably not…it's out there as one of the possibilities." Tr. 207.

When asked on cross examination if it was still his opinion that petitioner's polyhydramnios was caused by B.B.T. having HLH in utero, Dr. McClain responded "I think it's less likely than positive." Tr. 207.

Petitioner's treating physicians diagnosed her with gestational diabetes. The experts agree that gestational diabetes is the most common cause of polyhydramnios. At hearing, Dr. McClain was no longer convinced that petitioner's polyhydramnios was caused by B.B.T. having HLH in utero. Accordingly, I find that it is more likely that petitioner's polyhydramnios was a result of gestational diabetes and not HLH in utero.

B. Hepatitis B vaccine and Rash

When B.B.T. was born, he had no skin conditions, and was noted to be pink with some bruising. Pet. Ex. 4 at 29. B.B.T. received the hepatitis B vaccination at 4:33 a.m. *Id*. At 6:30 a.m., he was noted to have a soft, round abdomen, and pink skin. *Id*. at 32. At 6 p.m., about 14 hours after the hepatitis B vaccination, his skin was described as "rashy." *Id*. at 45. At 6:55 a.m. on March 29, 2013, his skin was again described as "rashy." *Id.* at 51. At 6 p.m. on March 29, 2013 and again twelve hours later at 6 a.m. on March 30, 2013, the date of discharge, B.B.T.'s skin was described as intact but "rashy." *Id*. at 63, 71.

Dr. Byers opined that the rash "was most probably due to antigen-antibody complexes against the Hepatitis B virus." Pet. Ex. 14 at 8. Dr. Byers pointed out that according to the package insert, which is approved by the Food and Drug Administration, rash is listed as a possible "adverse event." Tr. 67. About ten percent of clinical trial patients receiving the hepatitis B vaccine over a five year period reported rashes. Tr. 67-68.

Petitioner was tested for anti-IgG hepatitis B antibodies on August 28, 2012 with a result of 71.22 (index value is 0.00-0.99) which was noted to be "H" (high). Pet. Ex. 1 at 43.

Dr. Byers explained that IgG antibodies, which a newborn gets from their mother, is a subclass of the immunoglobulins, which is a mature antibody. Tr. 69. The first time that the body interacts with a certain antigen, it will usually develop an IgM, which is essentially five star-like IgG molecules. *Id*. The second time, if the molecule stays around a long time in the body, it will convert to the IgG, which is generally much higher in titer than the IgM and "…grabs onto the protein harder." *Id*. The hepatitis B vaccine is a very strong immunogen that activates the immune system, including B cells, which make antibodies, and T cells, which produce cytotoxic reactions. Tr. 68. Either B cells or T cells can cause the immune system to produce antigen-antibody complexes. *Id*. B.B.T. would have received antibodies against the hepatitis B virus from his mother. Tr. 72. When he received the hepatitis B vaccination, he developed an antigen-antibody complex, causing him to develop a rash. Tr. 68-69, 72-73. Dr. Byers maintained that, had the rash been biopsied, it would have showed inflammatory cells which go into the hair follicles and produce a little maculopapular rash. Tr. 68-69.

When asked if the hepatitis B vaccine would act as a rechallenge under these circumstances, Dr. Byers responded that rechallenge means that a person has educated, mature, antigen-specific cells, which upon a second exposure to the antigen, respond by making a higher concentration of antibodies. Tr. 73. B.B.T. was too young to make those high titers of antibodies himself; however, because he would have received hepatitis B antibodies from his mother, the immunological response would be similar to a rechallenge. *Id*.

On cross examination, Dr. Byers was presented with an article entitled "The persistence of anti-HBs antibody and anamnestic response 20 years after primary vaccination," Resp. Ex. Q, which showed that 20 years after primary vaccination, 37 percent of participants had protective levels of antibodies with geometric mean titer of 55.44 to 77.01. Dr. Byers agreed that those levels were protective under the standards, but were still "quite high." Tr. 127-28. Respondent's counsel pointed out that those participants were revaccinated to increase their protective antibody level to 176.28. Dr. Byers responded that the authors were trying to study the effect of the booster and clarified that she never said petitioner's titers were "bad," only that they were high. Tr. 128-29.

Dr. Byers was also presented with page 3 of Dr. McClain's supplemental expert report, Resp. Ex. F, which describes various rashes found in infants. Dr. Byers discussed the various rashes and why she would rule each of them out, concluding that the use of the term "rashy" in the medical record indicated to her that B.B.T. had a maculopapular rash over much of his body; otherwise the location of the rash would have been specified. Tr. 75. Dr. Byers agreed that the notations in the record were made by nurses and that no doctor had diagnosed the rash, nor was B.B.T. treated for the rash. She further pointed out that no blood was drawn from B.B.T. to measure for antigen-antibody complexes. Tr. 135-37.

According to Dr. McClain, there was nothing in the records to support a hepatitis B reaction. Tr. 194. He agreed that B.B.T. was "rashy," but stated that there was no objective evidence to say that it was caused by the vaccine. Tr. 195. According to Dr. McClain, if the rash

were significant, B.B.T.'s medical record would have had more detail. Tr. 196. Furthermore, B.B.T. was not treated for a rash. Dr. McClain stated that babies have a lot of skin abnormalities and there were no pictures of the rash to know what it really looked like. Tr. 195. According to Dr. McClain, B.B.T. had a normal skin examination upon discharge. Tr. 196.

B.B.T. was noted to be "rashy" fourteen hours after receiving the hepatitis B vaccination and was still "rashy" on the day of discharge. Pet. Ex. 4 at 71. Since there are neither photographs nor a more definitive description of the rash, there is no way of knowing if the rash was a maculopapular rash as described by Dr. Byers. However, it was significant enough for a notation of "rashy" to be documented throughout the record once it occurred. Dr. Byers' explanation for how the hepatitis B vaccine could cause the rash was plausible, and notably, neither objected to nor disagreed with by Dr. McClain. Nor did Dr. McClain disagree that B.B.T. would have received antibodies against hepatitis B virus from his mother, whose antibodies were noted to be high. It is therefore probable that B.B.T.'s immunological response was similar to rechallenge, causing him to develop a rash.

C. ALT, AST, Albumin and Bilirubin Levels

On March 31, 2013, day four of life, B.B.T. was brought to the emergency room at St. Mary-Corwin Hospital after being found limp and apneic in his car seat following a brief car ride. Pet. Ex. 7 at 6.

According to Dr. Byers, upon B.B.T.'s arrival at St. Mary-Corwin, he was in cardiac failure with a temperature of 92 degrees. Tr. 42-43. His abdomen was noted to be soft, with no masses or hepatomegaly (enlarged liver). Tr. 37; Pet. Ex. 7 at 7. His bilirubin level was normal at four. Tr. 43. The normal bilirubin level indicated that B.B.T.'s liver was functioning correctly and excreting bilirubin properly; otherwise, he would have had an increased bilirubin level due to buildup in the bloodstream. Tr. 42-45; Pet. Ex. 7 at 9.

Dr. Byers explained the results of the blood work performed upon B.B.T.'s arrival to the emergency room, and more specifically, the significance of the AST, ALT, and albumin results. AST is an enzyme which indicates liver health. Tr. 45. If there is liver damage, the AST level will increase. *Id*. The test is very sensitive; even the mildest liver damage will be picked up. *Id*. Dr. Byers noted that "a good night of martinis" would cause an elevated AST the next day; however, in that case, AST levels would quickly return to normal. Tr. 47. Upon arrival at St. Mary-Corwin, B.B.T.'s AST level was slightly elevated at 70; the top of normal range is 40. *Id*. Dr. Byers explained that a slightly elevated AST is not typically cause for alarm: "…you worry…about it being five times the top normal." Tr. 46-47.

ALT is an enzyme found in the walls of the bile ducts. Tr. 48. Dr. Byers explained that the liver has two functions; one is to detoxify the bile and put it into the stool, and the second is to synthesize albumin. Tr. 48-49. If the ability to make albumin or detoxify bile is defective, the ALT will be elevated. *Id*. When B.B.T. arrived at St. Mary-Corwin, his ALT level was normal. Tr. 50. Dr. Byers stated that, while AST levels can change quickly, ALT levels are more stable. *Id*. Serious liver damage, whether to the biliary tract or liver cells, will cause the levels of ALT and AST to increase. *Id*., Pet. Ex. 7 at 9.

Albumin is a protein made by liver cells. Tr. 51. Its main clinical function is to hold fluid in blood vessels. *Id*. If the albumin level decreases, the vessels will start to leak, and albumin will leak out. *Id*. According to Dr. Byers, a normal child has about four grams of albumin. Tr. 58. B.B.T.'s albumin level at birth is unknown because he was a healthy newborn and no blood tests were done; however, upon arrival at St. Mary-Corwin, his albumin level was 1.6. Tr. 52, 58. Dr. Byers stated that if the liver were not functioning correctly, the albumin would decrease, causing edema, or swelling. Tr. 52. There was no evidence of edema during B.B.T.'s first three days of life. *Id*. Furthermore, B.B.T. was not deemed to be in liver failure until April 3 – four days after he presented to the emergency room at St. Mary-Corwin; additionally, he was not assessed as having hepatomegaly until he was being treated at Denver Children's Hospital. Pet. Ex. 7 at 84; Pet. Ex. 8 at 11. There was nothing in B.B.T.'s records that would indicate that he was born with either acute or chronic liver failure. Therefore, it is unlikely that the drop in B.B.T.'s albumin level was caused by his liver. Tr. 57-58.

According to Dr. Byers, albumin can also decrease as a result of acute or chronic renal failure. Tr. 214. Albumin is filtered by the kidneys; patients with renal disease can lose up to 3.5 grams or more of albumin in 24 hours.[18] Tr. 58. Dr. Byers pointed out that, when B.B.T. was brought to St. Mary-Corwin, a urinary catheter was inserted and approximately one drop of dark amber clear urine was noted. Tr. 56. Dr. Byers stated that the dark amber drop was either denatured red blood cells or bilirubin. Tr. 56-57. Dr. Byers explained that the dark amber in the urine, in conjunction with acute renal failure, was an indication "that the child was peeing out a lot of components, including the albumin." Tr. 57; Pet. Ex. 7 at 8. Upon his admission to Denver Children's Hospital, B.B.T. was noted to be in kidney failure. Tr. 57-61, Pet. Ex. 7 at 8, *see generally* Pet. Ex. 27. It was Dr. Byers' opinion that B.B.T.'s albumin level of 1.6 was caused by developing kidney failure and it dropped quickly because he was urinating albumin.

Dr. McClain initially opined that B.B.T.'s low albumin level was strong evidence that B.B.T. developed HLH in utero, and that the steroids given to petitioner to control her polyhydramnios controlled the HLH as well. Resp. Ex. A at 4. B.B.T.'s albumin level on day four of life was 1.6, less than half of the median normal level of 3.6. *Id*. Dr. McClain explained that albumin is a critical protein for keeping fluid in vessels. When the albumin level is low, there will be edema, like the facial edema noted when B.B.T. was brought to the emergency room on day four of life. *Id*. In furtherance of his initial opinion that B.B.T. developed HLH in utero, Dr. McClain stated that fetal liver disease, as evidenced by low albumin and liver function enzymes, contributes to polyhydramnios, which occurs in HLH. *Id.* Dr. McClain opined that HLH was affecting the liver and bone marrow during the last two months of intrauterine life; petitioner developed polyhydramnios as a result of fetal anemia and liver dysfunction. *Id.*

Dr. McClain explained the "half-life" of albumin, or the amount of time for albumin to decrease from its expected level by 50 percent. Resp. Ex. T. According to Dr. McClain, albumin has a range of 2.8 to 5; the median normal level at birth is 3.9. Tr. 178. For albumin to decrease to 1.6, B.B.T.'s liver would have to have stopped producing albumin more than 20 days before his birth. *Id*. An albumin level of 3.9 reduced by one half life is 1.95; B.B.T. had an albumin level of 1.6 on day four of life. Tr. 178-79. Dr. McClain stated that B.B.T. had an intrauterine albumin

[18] Ruben Peralta, "Hypoalbuminemia: Clinical Presentation," Medscape Reference (2011), filed as Pet. Ex. 26 ["Peralta, R., 'Hypoalbuminemia Clinical Presentation'"].

level of approximately four; therefore, the onset of the decreased albumin synthesis would have to have occurred much earlier in gestation to produce a level of 1.6 on day four of life. Resp. Ex. A at 4. Albumin is a stable protein; it does not go up or down quickly. Therefore, the low albumin level at birth means something must have been happening in utero. Tr. 179.

Dr. McClain agreed that B.B.T.'s albumin level at birth is unknown since there was no blood work done at birth, but stated that knowing the half-life of the protein and that it decreases at a fixed rate makes it more likely than not that something was wrong 20 plus days before birth. Tr. 180.

Dr. McClain was asked if B.B.T.'s 12 percent loss of body weight upon discharge from the hospital and his feeding poorly on day four of life contributed to his decreased albumin level. Tr. 179-80. Dr. McClain responded that such a drop in albumin level would require extraordinary starvation over a long term, not four days. Tr. 180. He reiterated that albumin decreases at a fixed rate, and poor feeding would not allow it to decrease from 3.9 to 1.6 in the first four days of life. *Id*.

Dr. McClain was asked if B.B.T. being born at 37 weeks would have put him on the lower end of the normal range of 2.8 to 5. Tr. 182. Dr. McClain stated that B.B.T. was a big baby; the lower end of the range is for small and premature babies. *Id*. Being born at 37 weeks would not have affected his albumin level. Tr. 183.

Dr. McClain maintained at hearing that the low albumin level in this case was a measurement of B.B.T.'s liver function. According to Dr. McClain, the enzyme levels provide a view of what is happening in the liver. Depending on the extent of liver damage, those levels may range from moderate to very elevated. Tr. 181. However, Dr. McClain conceded that when B.B.T. was brought to St. Mary-Corwin on day four of life, his ALT of 24 and AST of 70 were essentially normal. Resp. Ex. F at 4. Hours later at Denver's Children's Hospital, his ALT was 511 and AST was 2206. *Id*. Dr. McClain was unclear whether the rise occurred naturally or was due to the "fresh frozen plasma, cryoprecipitate and red blood cell transfusions" that B.B.T. received. *Id*.

When presented with an article entitled "Hypoalbuminemia: Clinical Presentation," Pet. Ex. 27, Dr. McClain agreed that, in addition to liver failure, acute and chronic inflammation can be responsible for low albumin levels, and that HLH is inflammation. Tr. 184; Pet. Ex. 27. When questioned about the article's discussion of albumin loss as a result of kidney failure, Dr. McClain responded that the article refers to massive protein loss, 3.5 grams or more within 24 hours, associated with nephrotic syndrome, a condition that B.B.T. did not have. *Id*. He stated that the article is completely irrelevant to how B.B.T. had low albumin in this case. *Id*. However, Dr. McClain stated that when B.B.T. was brought into the emergency room, his creatinine was initially normal at 1.06, but 45 minutes later it was high at 1.3. Tr. 185. Dr. McClain conceded that there was "…evidence that he did have some renal disease that wasn't present at the very moment he came in." Tr. 184-85; 220-21; Pet. Ex. 7 at 8. When asked about the dark amber noted in the emergency room record following insertion of the catheter, Dr. McClain admitted that he was trying to find the report referred to by Dr. Byers during her testimony, because he had not seen it, adding that it could have been hemolyzed blood, bilirubin, or concentrated urine. Tr. 209.

Though Dr. McClain initially opined that B.B.T.'s jaundice was further evidence of abnormal liver function in utero, at hearing, he noted that the bilirubin levels at 25 hours of age were "not terribly important." Tr. 193. He conceded that there was no objective data to suggest that it was not just neonatal hemolysis or bilirubin metabolism problems. Tr. 192-93. He further noted that, when B.B.T. was brought into the emergency room on day four of life, the bilirubin was not markedly elevated at first. Tr. 192-93. Dr. McClain added that besides making albumin, the liver makes proteins that help the coagulation system. Tr. 192. Blood coagulation proteins and albumin are part of what are called the synthetic properties of the liver; if you are lacking in these proteins, you bleed more easily. *Id*. Dr. McClain stated that B.B.T. was found to have low platelets and "probably was in coagulopathy early on." *Id*. This was the cause of B.B.T.'s oozing heel stick noted on April 1, 2013. *Id*. It is notable that the record refers to a circumcision with no bleeding noted as well as numerous attempts to draw blood from B.B.T.'s heel during this time, which may have contributed to his "oozing" of the heel. Pet. Ex. 4 at 65, 69-70.

There was significant testimony from both experts about liver function, AST, and ALT, but most significantly about albumin levels. Dr. McClain attributed B.B.T.'s low albumin level at day four of life to liver failure beginning 20 to 30 days before birth. Tr. 177. Dr. Byers' testimony was more credible, given that B.B.T. had normal AST, ALT, and bilirubin levels on day four of life, with no hepatomegaly – all signs of a healthy, functioning liver. Pet. Ex. 7 at 9. Dr. Byers' explanation of kidney failure as the cause of B.B.T.'s low albumin level was more plausible. B.B.T. was diagnosed with kidney failure upon his arrival at Denver Children's Hospital. Pet. Ex. 8 at 38. This was further apparent from the amber drop seen in the urine upon insertion of the catheter in the emergency room at St. Mary-Corwin. Pet. Ex. 14 at 8. This finding was significant enough that the doctor inserting the catheter found it to be noteworthy. Furthermore, Dr. Byers explained, and Dr. McClain agreed, that albumin can be lost rapidly in the event of kidney failure. Dr. McClain admitted that he had not seen the notation regarding the amber in the urine, but believed it could have been hemolyzed blood, bilirubin, or concentrated urine. Tr. 209.

Therefore, it is more likely that B.B.T.'s low albumin level was the result of kidney failure, causing B.B.T. to urinate albumin and resulting in a rapid decrease in albumin level, rather than liver failure, which would result in a much slower loss of albumin.

D. HLH in Utero vs. HLH Developing After the Hepatitis B Vaccine

B.B.T. was tested for all known genetic mutations responsible for familial HLH and for X-linked lymphoproliferative disease. He tested negative for all of the mutations. Pet. Ex. 8 at 782; Pet. Ex. 9 at 1, 4, 5, 9, 12, 15 and 18.

In a letter dated July 10, 2014, Tom Garrington, M.D., one of B.B.T.'s treating physicians, stated:

> Cases of HLH in general can either be primary or familial due to a mutation in one or a number of genes important in regulating immune function; or secondary, due to exposure to some trigger which is usually an infection or malignancy, though other triggers that can stimulate the immune system, such as vaccinations, have been rarely reported to cause HLH in some individuals…[A]n extensive genetic

> valuation, however, failed to identify a mutation in any of the genes known to be associated with HLH. Regarding potential triggers before – because no infections or malignant disease processes were found, the most likely trigger was felt to be the hepatitis B vaccine he received in the newborn nursery.

Pet. Ex. 13 at 1.

Dr. Byers was asked, if B.B.T. had HLH in utero, would the steroid injections received by petitioner in January and February of 2013 have controlled the HLH? She responded that the half-life of steroids is days, "maybe three days, something like that." Tr. 98. "[T]he literature will tell you that the babies with in utero HLH are born very compromised, with fluid where it shouldn't be and with large spleens, large livers, [and] possibly capillary leak syndrome." Tr. 99. B.B.T. was not born with any of these symptoms.

Dr. Byers was asked, if B.B.T. had HLH in utero, would the HLH have been evident on the ultrasounds and the amniocentesis? Her response was "yes." Tr. 99-100. Petitioner had multiple ultrasounds showing normal fetal anatomy, including head, brain, face, spine, chest, abdominal wall, gastrointestinal tract, kidneys, bladder, extremities, and skeleton; all of the ultrasounds were normal through the end of the pregnancy. Tr. 76-77, 78-79; Pet. Ex. 1 at 38-39. The amniocentesis was normal as well. Pet. Ex. 14 at 3. Dr. Byers further pointed out that the pathology results of petitioner's placenta showed a mature placenta with a three vessel umbilical cord; there were no significant pathologic changes. Tr. 88; Pet. Ex. 2 at 165. Dr. Byers described petitioner's placenta as "perfectly normal." Tr. 88. Had B.B.T. had HLH in utero, the pathology of the placenta would have provided evidence of lymphocytic phagocytosis, one of the criteria for diagnosing HLH. Tr. 86-87; Pet. Ex. 28.

Dr. Byers addressed the articles submitted by respondent in support of his position that B.B.T. had HLH in utero. She discussed the Shah article referenced by Dr. McClain (Resp. Ex. M[19]), which addressed a 24 week fetus in a woman who had previously had two children who died of HLH after birth. Tr. 81. The ultrasound showed that the fetus had massive hepatosplenomegaly (enlarged liver and spleen), as well as ascites[20] and hydrocephalus.[21] *Id*. Steroids were administered via umbilical vein. The hydrocephalus and ascites resolved, and the hepatosplenomegaly improved. *Id*. However, two weeks later, the hepatosplenomegaly worsened. Another round of treatment was given, and the fetus was delivered early with massive hepatosplenomegaly and ascites. *Id*. At birth, the baby had low hematocrit, high AST and ALT levels, and no NK (natural killer) cell function, which is one of the eight criteria for diagnosing HLH. Tr. 82. Dr. Byers explained that this is how a child with HLH in utero presents. *See*

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[19] Ami J. Shah et al, *Pre- and Post-Natal Treatment of Hemophagocytic Lymphohistiocytosis*, PEDIATR. BLOOD CANCER, 52 (1): 139-42 (2009), filed as Resp. Ex. M ["Pre and Post Natal Treatment of HLH"].

[20] Ascites is an accumulation of fluid in the abdominal cavity. Dorland's at 164.

[21] Hydrocephalus is an accumulation of cerebrospinal fluid within the skull; the fluid is usually under increased pressure. In children it can be characterized by brain atrophy, mental deterioration, and convulsions. Dorland's at 890.

generally, Resp. Ex. M. Dr. Byers pointed out that, despite the combination of etoposide and dexamethasone (steroids) in utero, it was ineffective in halting or controlling the HLH for more than two weeks. Tr. 84. The child was born with ascites and an enlarged liver and spleen. Dr. Byers explained that the spleen is the home of the immune cells that produce cytokines; with HLH, the spleen swells because it is overproducing cytokines, resulting in the cytokine storm. Tr. 85-86. B.B.T. did not have a swollen spleen in utero.

Dr. Byers discussed Resp. Ex. J, "Case 28-2004: Newborn Twins with Thrombocytopenia, Coagulation Defects and Hepatosplenomegaly,"[22] and the findings of arteritis with elevated levels of interleukin-6, one of the cytokines associated with hemophagocytic lymphohistiocytosis, in the umbilical cord plasma, which suggested that some event resulting in the overexpression of cytokines occurred in utero. Resp. Ex. J at 1123-24. Dr. Byers reiterated that a baby with HLH in utero would have cytokines present in the placenta and umbilical cord. Tr. 89-90. B.B.T.'s placenta and umbilical cord were normal. Tr. 88. Dr. Byers also noted that the child in the article was started on phototherapy for jaundice on the second day of life, but the bilirubin level continued to rise, and phototherapy was discontinued due to ineffectiveness. Tr. 90. In contrast, B.B.T.'s phototherapy was "quite efficacious." Tr. 90; *see generally*, Resp. Ex. J.

Dr. Byers then discussed respondent's articles on hydrops fetalis, explaining that hydrops fetalis is fluid accumulation in two compartments of the fetus,[23] and results from an RH incompatibility, which can be immune or non-immune, but has now been eliminated by RhoGAM. Tr. 90-91. According to Dr. Byers, the majority of hydrops fetalis cases indicates that either the fetus has anemia or there is something wrong with the heart or lungs, forcing the babies to be born early via C-section or die in utero. Tr. 91-92. B.B.T. did not have hydrops fetalis. Tr. 92.

Dr. McClain testified that he has been studying HLH for 27 years and it has been a major part of his career, "taking care of patients and finding new therapies and being part of international study groups to define how these patients can be better treated." Tr. 170. He has seen over 400 patients in his career and many variations "on the theme" of HLH.

He described HLH as "… a disease where the immune system has gone very, very far off-kilter, and there is an inflammatory response to one of many possible triggers, sometimes unknown triggers. And without a check in the immune system, the inflammatory response continues elaborating multiple cytokines, especially interferon gamma, which causes damage to the bone marrow, the liver, the spleen, the kidneys, the brain, the heart and the lungs." Tr. 171.

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[22] Jeffrey M. Lipton, et al., *Case 28-2004: Newborn Twins with Thrombocytopenia, Coagulation Defects and Hepatosplenomegaly*, N ENGL J MED, 351 (11): 1120-30 (2004), filed as Resp. Ex. J. ["Case 28-2004 Newborn Twins with Thrombocytopenia Coagulation Defects and Hepatosplenomegaly"].

[23] For respondent's articles on hydrops fetalis, *see* G. Balta, et al., *Association of Nonimmune Hydrops Fetalis With Familial Hemophagocytic Lymphohistiocytosis in Identical Twin Neonates With Perforin His222Arg (c665A>G) Mutation*, J. PEDIATR. HEMOTOL. ONCOL., 35(8): 332-34 (2013), filed as Resp. Ex. K ["Association of Nonimmune Hydrops Fetalis with Familial HLH"] and C. Malloy, et al., *Hemophagocytic Lymphohistiocytosis Presenting with Nonimmune Hydrops Fetalis*, J. PERINATOL., 24: 458-60 (2004), filed as Resp. Ex. L ["Perinatal Neonatal Case Presentation HLH presenting with nonimmune hydrops fetalis"].

According to Dr. McClain, HLH has a staccato presentation, and patients do not present with all the symptoms simultaneously, especially babies; some can have hydrops and hepatomegaly, and some do not. Tr. 186. Therefore, it is not surprising that B.B.T. did not have hepatomegaly or ascites in the first days of life. Tr. 185.

According to Dr. McClain, B.B.T. could have had HLH at birth and still had a normal placenta. Tr. 197. Hemophagocytosis is not necessary or sufficient for a diagnosis; it may not be present in the placenta at all, depending "on how far along in the process the child is." Tr. 198. According to Dr. McClain, in an extreme presentation of HLH, the blood filters through the placenta and picks up macrophages with the hemophagocytosis; then, the cytokine storm in the baby can cross over to the mother, and cause the placenta to be abnormal. Tr. 198.

When asked about Dr. Byers' discussion of the Balta article,[24] Dr. McClain conceded that all the children had mutations with more dramatic and early presentations. He further stated that HLH is so variable, it is not uniform in all patients. Tr. 186; Resp. Ex. K. Dr. McClain stated that he has seen several cases in his hospital where one child with a mutation presented with a dramatic presentation and ultimately died and the other with the same mutation did not present with dramatic problems for years. "So it's not just the mutation. Its other things in the environment or secondary mutations that we haven't identified. So there is really more than one element to this genetic trigger…." Tr. 187-88.

To demonstrate the variability of presentation of HLH, Dr. McClain referenced the case report of twins (Resp. Ex. J),[25] which discusses the perforin mutation and dramatic presentations; both died. Dr. McClain explained that the mutations that have been identified are often associated with dramatic presentation and poor outcome. Tr. 188-89. However, he pointed to Table 1 of the article, which shows that some patients do not present with ascites or hydrops. Tr. 189; *see* Resp. Ex. J. Additionally, Resp. Ex. M[26] shows another case study of HLH associated with the perforin mutation where three brothers with the perforin mutation all had HLH in utero with dramatic presentations. Two of the brothers died; the third survived via extraordinary measures, but is severely damaged. Tr. 190; *see generally*, Resp. Ex. M.

Dr. McClain further discussed Resp. Ex. N, "An animal model of hemophagocytic lymphohistiocytosis (HLH): CD8 T cells and interferon gamma are essential for the disorder,"[27] in which mice were infected with lymphocytic choriomeningitic virus, causing perforin-deficient mice to experience HLH-like symptoms. Like the neonates with perforin mutations, the mice

[24] Filed as Resp. Ex. K, *infra* note 23.

[25] Lipton, *Case 28-2004: Newborn Twins with Thrombocytopenia, Coagulation Defects and Hepatosplenomegaly, supra* note 24.

[26] Shah, *Pre- and Post-Natal Treatment of Hemophagocytic Lymphohistiocytosis, infra* note 19.

[27] Michael B. Jordan, et al, *An animal model of hemophagocytic lymphohistiocytosis (HLH): CD8$^+$ T cells and interferon gamma are essential for the disorder*, BLOOD, 104 (3): 735-43 (2004), filed as Resp. Ex. N ["An animal model of hemophagocytic lymphohistiocytosis (HLH) CD8 T cells and interferon gamma"].

developed severe symptoms. The mice were cured of the HLH after interferon gamma was eliminated from the plasma; however, when interferon alpha was eliminated instead of interferon gamma, many of the mice died. Tr. 188. The study concluded that, without the presence of interferon gamma, the perforin-deficient mice would not have developed HLH-like symptoms. Tr. 188; *see generally*, Resp. Ex. N. Dr. McClain noted that genetic testing indicated that B.B.T. did not have a perforin mutation.

The articles filed by respondent portray the gravity of HLH in utero and how severely affected the fetuses can be. Resp. Exs. J, K, L, and M. Even those treated with chemotherapy medication or combinations of steroids administered through the umbilical vein showed recurrence of symptoms within two weeks of administration of treatment. *See* Resp. Ex. J.

Dr. Byers pointed out that B.B.T. was a healthy baby at birth. Examination showed a round, soft belly, with no enlarged liver or spleen. Pet. Ex. 4 at 29. Ultrasounds throughout petitioner's pregnancy and up to the date of delivery, when the amniocentesis was performed, showed normal anatomy. Pet. Ex. 1 at 39, 57, 59, 61, 66. The placenta was likewise normal. Pet. Ex. 2 at 165. Even upon presentation to the emergency room on day four of life, B.B.T. did not have any organ swelling. Pet. Ex. 7 at 7. Dr. Byers maintained that the steroid injections administered, in January and February of 2013, would not have controlled HLH in utero, as the half-life of steroids is approximately three days. Tr. 98.

Dr. McClain stated that HLH can present very quickly or gradually over time, and that the disease does not have a steady trajectory; it can improve or worsen before "it goes kaboom." Tr. 181-82.

I am unconvinced that B.B.T. had HLH in utero or that a disease so virulent could have been kept under control by two steroid injections administered 8 and 4 weeks before birth, or that ultrasounds, amniocentesis and placental pathology could all be normal when the literature relied upon by respondent suggests otherwise. To that end, there is no convincing evidence that B.B.T. had HLH in utero.

E. Can the Hepatitis B Vaccine Trigger HLH?

Dr. Byers opined that the hepatitis B vaccine triggered B.B.T.'s HLH. Pet. Ex. 14 at 5. She explained:

> Cytokines are essential for normal immune function…Cytokines recruit additional inflammatory cells which, in the case of HLH, worsens the disease…[I]n this case where the baby has pre-existing antibodies acquired from his mother, the hepatitis vaccine can cause antigen/antibody complexes. These complexes then can produce a rash and vasculitis, damaging tissue. The damaged tissue, in turn, produces previously hidden antigens, "cryptotopes." These cryptotopes are antigenic in and of themselves and activate B and T cells. The activated cells can then produce more inflammation and further tissue damage. A phenomenon called epitope spreading then causes the activation of immune cells which are programmed to react to other antigens. This then results in an autoimmune reaction. A phenomenon called

> bystander activation then enhances cytokine production and activates more auto reactive immune cells.

Id. at 6.

According to Dr. Byers, it is not only the cytotoxic T cells which are affected; very low levels of Natural Killer (NK) cells and elevated levels of sIL-2r (indicating hyperactivity of the T lymphocytes) are two of the key parameters for making the diagnosis of HLH.[28] Pet. Ex. 14 at 5. Dr. Byers explained that this is called a "cytokine storm." The term was coined following a study in which all of the participants in a clinical trial wound up in the ICU.[29] The term has subsequently been used to characterize diseases such as HLH that produce such devastating consequences. *Id*.

Dr. McClain similarly described HLH as a syndrome of an excessive inflammatory response by the immune system to any one of a large number of stimuli. According to Dr. McClain, "Literally any infectious agent; bacteria, fungi, protozoans, and viruses have been implicated as well as HLH-associated gene mutations, malignancies, underlying immune deficiencies, and rheumatologic disease." Resp. Ex. A at 3. Dr. McClain explained that in familial HLH, there are mutations in a series of genes responsible for carrying "death inducing" enzymes from the inside of a lymphocyte to the cell surface, where they are injected into the target cell and kill it:

> The packaging and transport of these enzymes and injection into the target cell include the products of 6 different genes associated with HLH. The first of these to be discovered was Perforin, which is responsible for making the hole in target cells. There are 2 other genes which regulate the ability of lymphocytes to control Epstein Barr virus infection. Mutation on both chromosomes of any of these 8 genes not only leads to defective killing of a target, but also causes the lymphocytes to lose the ability to 'turn off' the immune hyperactivity. The lymphocytes which are critical for this activity are called Natural Killer cells and cytotoxic T lymphocytes.[30] When the defective NK cells or cytotoxic T cells identify a target, but can't kill it, these cells start producing interferon gamma and tumor necrosis factor alpha, as well as other immune stimulating proteins known as cytokines. They stimulate the target cell which in response sends signals back to these lymphocytes and a cascade of immune hyperactivity is begun that leads to abnormal collections of macrophages in the bone marrow and other organs leading to 'hemophagocytosis' or eating of other blood cells.

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[28] *See* S. Chandrakasan and A. Filipovich, *Hemophagocytic Lymphohistiocytosis: Advances in Pathophysiology, Diagnosis, and Treatment*, J. PEDIATR., 163 (5): 1253-59 (2013), filed as Pet. Ex. 17 ["Chandrakasan, Hemophagocytic lymphohistiocytosis"]; G. Janka and K. Lehmberg, *Hemophagocytic syndromes – An update*, BLOOD REVIEWS, 28: 135-42 (2014), filed as Pet. Ex. 19 ["Janka, Hemophagocytic syndromes"].

[29] G. Suntharalingam et al., *Cytokine Storm in a Phase 1 Trial of the Anti-CD28 Monoclonal Antibody TGN1412*, N. ENGL. J. MED., 355: 1018-28 (2006), filed as Pet. Ex. 20 ["Suntharalingam, Cytokine Storm in a Phase 1 Trial of the Anti-CD28 Monoclonal Antibody"].

[30] B.B.T. had no NK cell function, which is one of the key findings in HLH.

Id. at 3-4.

Dr. McClain further explained that the "cytokines from the macrophages and lymphocytes are toxic to the lungs, kidneys, liver, brain, heart, and other organs leading to the dramatic presentation of HLH patients with sudden collapse of the respiratory, cardiovascular, renal, hepatic, and central nervous system." *Id*. at 4. Therefore it is not uncommon for these patients to appear normal one day and be in intensive care the next. *Id*. Dr. McClain stated that there are genetic mutations associated with HLH that have not yet been identified, and new mutations are being found. Tr. 176-77.

Dr. McClain maintained that the hepatitis B vaccine does not contain interferon gamma and therefore could not trigger HLH. He then stated, "There has been a study published showing that hepatitis B vaccine elicits a very small amount of interferon gamma response in the lymphocytes of children, young children, [and] infants that get this vaccine." Tr. 175. "[I]nterferon gamma is the most important cytokine in causing HLH. If you don't have elevated interferon gamma you don't get HLH…The facts of the literature show there is absolutely no evidence that hepatitis B vaccine can excite the immune system and cause HLH." Tr. 176.

Dr. Byers responded by pointing to an article titled "Hemophagocytic Lymphohistiocytosis: Advances in Pathophysiology, Diagnosis, and Treatment," which states that HLH is characterized by marked elevation in cytokines such as interferon gamma, tumor necrosis factor alpha, IL-6, IL-8, IL-12, IL-18 and macrophage colony stimulating factor. Dr. Byers pointed out that, though interferon gamma plays a critical role in macrophage activation and hemophagocytosis, there are other cytokines that play a role as well. Tr. 211-12; Pet. Ex. 17.

While Dr. Byers agreed with Dr. McClain that HLH can have a rapid onset, she noted that "…the stimuli appears, but then it's going to take some time for the clinical results to occur…." Tr. 104-05. B.B.T. was a normal fetus in utero and a "perfect" baby when born; there was no infectious disease seen, and no other trigger for the HLH but the hepatitis B vaccine. *Id*. Furthermore, B.B.T. did not test positively for any of the genes associated with HLH; therefore, his was classified as an "acquired" case of HLH. Pet. Ex. 14 at 5. "The common pathophysiologic mechanism in all these diverse causes of HLH is the activation of the innate immune system." *Id*.

According to Dr. Byers, hepatitis B vaccine is one of the most powerful vaccines because it has to trigger a fairly weak immune system – that of the neonate. Tr. 103. Dr. Byers stated that infectious agents, infectious disease, and vaccines trigger the immune system by activating the cells of the innate immune system to make a series of cytokines. "The problem is not that you're turning them on, but that you can't turn them off, because they lack the NK cells…and any other cells that can react with the perforin channels to kill the guys that are doing the bad stuff." Tr. 101. If a vaccine didn't trigger the immune system, the vaccine would not work at all. Tr. 102.

With petitioner's high titers of hepatitis B antibodies, the hepatitis B vaccine caused B.B.T. to form antigen-antibody complexes and allowed "the innate immune system to produce cytotoxic agents, the cytotoxic cytokines." Tr. 103. The rash was a footprint. *Id*.

Based upon my review of all of the literature filed by both sides in this matter, I asked Dr. Byers if I was correct in my understanding that HLH must be triggered by something. Her response was, that is what the literature would tell you. She agreed with Dr. McClain that there are genetic conditions that are associated with HLH, primarily producing abnormalities in the perforin family. But clinical genetics is a relatively new science, and it is not known if, in the absence of stressors, somebody with only the genetic abnormalities could spontaneously develop HLH. It would be unusual for a child to grow to adulthood without suffering one of the infections linked to HLH. Tr. 108. Dr. Byers added that she agrees with Dr. McClain that there may be other genetic mutations associated with HLH that have not yet been identified and that new mutations are being found. Tr. 162; 168.

I asked Dr. Byers, if B.B.T. had HLH in utero, whether something would have to have triggered the HLH after his birth, or whether he could have developed it without having received the hepatitis B vaccine. Dr. Byers candidly responded, "We don't know." Tr. 109.

Dr. McClain stated that there is no literature to associate hepatitis B vaccine with HLH. The VAERS reports relied upon by Dr. Byers to provide an association is "without substance." Tr. 196. If hepatitis B vaccine was a trigger for HLH, he would expect it to be in the literature. Tr. 198.

Dr. McClain further testified that, in his practice, he has seen instances where other doctors at his hospital thought that numerous vaccinations given at one time triggered HLH on temporal relationship alone. Dr. McClain did not recall any cases where a single vaccine was associated with HLH. Tr. 199. Similarly, it is not unusual to be unable to determine what caused HLH, as there is no general course for HLH; it is variable. Tr. 199-200. According to Dr. McClain, there are no data to support an association between the hepatitis B vaccine and HLH. Tr. 201.

According to Dr. McClain, B.B.T. had a very terrible form of HLH, and even without the vaccine, he would have suffered that same outcome. Tr. 201.

Dr. McClain stated that the triggers of HLH are a mystery and often there is no absolute trigger: "… [T]here are many things in the immune system that we don't understand. And why some genetic causes or non-genetic causes suddenly flip over into an extreme form, as it was, is completely unknown." Tr. 207.

I asked Dr. McClain if the HLH process was already happening and the cytokines were in active motion and then another attack on the immune system is introduced, whether via adjuvant or a vaccine, would that not make the child worse? Dr. McClain responded: "I see your point. There is (sic) no data to support or refute what you just said. I don't know." Tr. 204.

Based upon the reports, medical literature, and testimony, I find that the hepatitis B vaccine more likely than not triggered HLH in B.B.T.

VI. Conclusions of Law and Decision on Entitlement

A. Petitioner Has Met Her Burden of Showing by Preponderant Evidence that the Hepatitis B Vaccine Triggered B.B.T.'s HLH.

Under the Vaccine Act, petitioner may prevail on her claim by proving a "Table" injury, in which causation is presumed, or alternatively, by proving an "off-Table" injury, in which she identifies a causal link between the vaccine and the injury alleged.[31] Because HLH is not listed as a Table injury, petitioner must produce preponderant evidence that the hepatitis B vaccine is responsible for B.B.T.'s injuries.

An "off-Table" claim requires that petitioner establish by preponderant evidence that a covered vaccine caused or significantly aggravated the injury claimed. § 11(c)(1)(C)(ii)(II). Petitioner need not show that the vaccination was the sole cause, or even the predominant cause, of B.B.T.'s condition; showing that the vaccination was a "substantial factor" and a "but for" cause of B.B.T.'s injury is sufficient for recovery. *Shyface v. Sec'y of Health and Human Servs.*, 165 F.3d 1344, 1352 (Fed. Cir. 1999); *see also Pafford v. Sec'y of Health and Human Servs.*, 451 F.3d 1352, 1355 (Fed. Cir. 2006) (petitioner must establish that a vaccination was a substantial factor and that harm would not have occurred in the absence of the vaccination).

Although a petitioner cannot be required to show "epidemiologic studies, rechallenge, the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect," when petitioner files medical literature, a special master may weigh and evaluate that medical literature. *Capizzano v. Sec'y of Health and Human Servs*., 440 F.3d 1317, 1325 (Fed. Cir. 2006). Causation is determined on a case by case basis, with "no hard and fast *per se* scientific or medical rules." *Knudsen v. Sec'y of Health and Human Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994). Close calls regarding causation must be resolved in favor of the petitioner. *Althen v. Sec'y of Health and Human Servs.*, 418 F.3d 1274, 1280 (Fed. Cir. 2005).

The Federal Circuit has set forth three factors petitioner must satisfy to prove causation in off-Table cases. *Althen* requires that petitioners provide: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." *Althen*, 418 F.3d at 1274, 1278. All three *Althen* factors must be satisfied to prevail on an off-Table claim.

The medical theory must be a reputable one, although it need only be "legally probable, not medically or scientifically certain." *Knudsen*, 35 F.3d at 548-49. The Supreme Court's opinion in *Daubert v. Merrill Dow Pharmaceuticals, Inc.*, likewise requires that courts determine expert opinions to be reliable before they may be considered as evidence. "In short, the requirement that an expert's testimony pertain to 'scientific knowledge' establishes a standard of evidentiary reliability." *Daubert*, 509 U.S. 579, 590 (1993) (citation omitted). The Federal Circuit has stated that a "special master is entitled to require some indicia of reliability to support the assertion of

[31] "Table" injuries are injuries listed on the Vaccine Injury Table, 42 C.F.R. § 100.3 (2009), which develop within a given time frame after receiving a specific vaccine.

the expert witness." *Moberly ex rel. Moberly v. Sec'y of Health and Human Servs.*, 592 F.3d 1315, 1324 (Fed. Cir. 2010).

The experts agree that B.B.T. was diagnosed with HLH. The experts also agree that B.B.T. suffered from the cascading list of physical damage caused by HLH between March 31, 2013 and the time of his death. At first blush, it appeared that the experts disagreed as to what triggered B.B.T.'s HLH. However, at hearing, the experts ultimately were not as far apart as they initially appeared.

1. *Althen* Prong One: Can the Hepatitis B Vaccine Cause HLH?

The first prong of *Althen*'s three part causation test has been characterized as the equivalent of the "Can it cause?" inquiry used in toxic tort litigation. *See Pafford v. Sec'y of Health and Human Servs.*, No. 01-165V, 2004 WL 1717359, at *4 (Fed. Cl. Spec. Mstr. July 16, 2004), *aff'd*, 64 Fed. Cl. 19 (2005), *aff'd*, 451 F.3d 1352 (Fed. Cir. 2006). In other words, has petitioner demonstrated that the vaccination in question is capable of causing the alleged injury?

Dr. McClain maintains that there is no evidence that the hepatitis B vaccine can excite the immune system and cause HLH. Tr. 176; 204. However, Dr. McClain agrees that HLH is a syndrome of excessive inflammatory response by the immune system to any one of a large number of stimuli. "Literally any infectious agent; bacteria, fungi, protozoans, and viruses have been implicated as well as HLH-associated gene mutations, malignancies, underlying immune deficiencies, and rheumatologic disease." Resp. Ex. A at 3.

Both experts agree, as does the supporting medical literature proffered by both parties, that HLH requires a trigger which activates the innate immune system, whether the triggering mechanism comes in the form of a virus, infection, cancer, or autoimmune disease. Furthermore, both experts agree that proinflammatory cytokines are released when the immune system is activated, and that in the event of HLH, the cytokines fail to shut down, resulting in a "cytokine storm" which damages the bone marrow, liver, spleen, kidneys, brain , heart and lungs.

Dr. McClain explained it well when he stated:

> [T]he normal immune response is that the injected vaccine protein is taken up by macrophages which deliver it to T lymphocytes in lymph nodes. These T lymphocytes then present the antigenic proteins of the vaccine partnered with immune stimulating antigens of the T Cell receptors to B lymphocytes which make the protective antibodies. The normal immune response is highly regulated and goes from activated to quiet in a few days. In HLH, the defective NK and cytotoxic T lymphocytes have either been alerted to a danger by macrophages trying to present an antigen, or the lymphocytes have decided the macrophage is a danger and are trying to destroy it. However, they can't destroy the macrophage and their activity can't be stopped, so the hyper-immune stimulation begins with both types of cells sending signals to the other leading to a "snow ball effect" that lasts until etoposide and dexamethasone are given to quiet the hyperactive response.

Resp. Ex. A at 6.

While there is not a great deal of literature available, the literature filed for both petitioner and respondent is persuasive for petitioner's expert's theory. Other special masters have in the past found that HLH and other similar conditions can be triggered by a vaccination. *See Brown v. Sec'y of Health & Human Servs.*, No. 99-044V, 2000 WL 1207255 (Fed. Cl. Spec. Mstr. Aug. 3, 2000) (vaccine triggered acute hemolytic anemia though paucity of medical literature existed); *Gall v. Sec'y of Health & Human Servs.*, No. 91-1642V, 1999 WL 1179611 (Fed. Cl. Spec. Mstr. Oct. 31, 1999) (vaccine was triggering agent of familial hemophagocytic lymphohistiocytosis (FHL)); *Ackley v. Sec'y of Health & Human Servs.*, No. 98-122V, 2002 WL 985435 (Fed. Cl. Spec. Mstr. Apr. 29, 2002) (MMR vaccine was the trigger of HLH).

Furthermore, though there are some disagreements on parts of the theory, it appeared to the undersigned both at hearing and upon writing this decision that the two experts agreed more than they disagreed in this case. Based on the medical records, reports, medical literature, and testimony submitted, I find that petitioner has satisfied Prong I that it is more likely than not that a hepatitis B vaccine could activate the innate immune system, causing a release of pro-inflammatory cytokines, triggering a cytokine storm and resulting in the development and/or triggering of HLH.

2. *Althen* Prong Two: Did the Hepatitis B Vaccine Trigger B.B.T.'s Development of HLH?

The second prong of *Althen*, the requirement for a logical sequence of cause and effect between the vaccine and the injury, has been characterized as addressing the "Did it cause?" or specific causation query. *See Pafford*, 2004 WL 1717359, at *4. In other words, even if a vaccine can cause the injury alleged, petitioner must show that it did so in her case.

Dr. McClain stated that, because the hepatitis B vaccine does not contain interferon gamma or contains only small amounts of interferon gamma, it could not have caused HLH in B.B.T. Dr. Byers refuted that by highlighting an article on advancements in pathophysiology, diagnosis, and treatment of HLH which acknowledged the role of interferon gamma, but added that there are other cytokines at play, confirming that interferon gamma is not the sole cause of the extremely heterogeneous group of manifestations of a cytokine storm. Hepatitis B vaccine as well as other vaccines can activate some or all of the cytokines. Tr. 211-12.

Dr. McClain was candid in admitting that the triggers of HLH are a mystery and often there is no absolute trigger. "… [T]here are many things in the immune system that we don't understand. And why some genetic causes or non-genetic causes suddenly flip over into an extreme form, as it was, is completely unknown." Tr. 207.

I asked him, if the HLH process was already happening and the cytokines were in active motion and then another attack on the immune system is introduced, whether via adjuvant or the vaccine itself, would that make the child worse? Dr. McClain responded: "I see your point. There is (sic) no data to support or refute what you just said. I don't know." Tr. 204.

Moreover, the Federal Circuit has instructed special masters to consider carefully the views of treating doctors. *Capizzano*, 440 F.3d 1317, 1326. Dr. Garrington, one of B.B.T.'s physicians, concluded that, because B.B.T. did not have any of the genes associated with HLH, and no infections or malignant disease process were found, "the most likely trigger was felt to be the hepatitis B vaccine he received in the newborn nursery."
Pet. Ex. 13 at 1.

The statements of treating physicians are probative, and Dr. Garrington's opinion that the vaccine caused B.B.T.'s development of HLH is significant. This factor weighs heavily in petitioner's favor. Petitioner has satisfied Prong II, that the hepatitis B vaccine did in fact cause and/or trigger B.B.T.'s HLH.

3. *Althen* Prong Three: Timing

The third *Althen* factor requires that petitioner establish that her injury occurred within a time frame that is medically appropriate for the alleged mechanism of harm. *See Pafford*, 451 F.3d at 1358. However, a mere showing of a proximate temporal connection between a vaccination and an injury is insufficient, standing alone, to establish causation. *Grant v. Sec'y of Health and Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992). A proximate temporal relationship, even when coupled with the absence of any other identified cause for the injury, is not enough to demonstrate probable cause under the Vaccine Act's preponderance standard. *Moberly*, 592 F.3d at 1323 (citing *Althen*, 418 F.3d at 1278).

There is a question as to whether B.B.T. had HLH in utero, raising the question of whether the hepatitis B vaccine significantly aggravated the HLH or "triggered" B.B.T.'s HLH. Section 300aa-33(4) defines "significant aggravation" as "…any change for the worse in a preexisting condition which results in markedly greater disability, pain or illness accompanied by substantial deterioration of health."

It is notable that on January 30, 2012, an ultrasound showed normal anatomy. Pet. Ex. 1 at 39. An ultrasound that accompanied the amniocentesis the day before B.B.T.'s birth was also normal with no abnormalities. Pet. Ex. 1 at 28-29. Additionally, the placenta was normal. Pet. Ex. 2 at 165. This is significant because an overexpression of cytokines would be seen in the placenta and/or umbilical cord of a newborn with HLH. Tr. 88-90; Resp. Ex. J at 1123-24.

B.B.T. was administered a hepatitis B vaccine at 32 minutes of age on March 28, 2013. Fourteen hours later he was noted to be "rashy." Three days later, he was lethargic and not eating and ultimately found to be not breathing. He was brought to the emergency room critically ill. Accordingly, I find that petitioner has shown a "medically appropriate" temporal connection between B.B.T.'s receipt of the hepatitis B vaccine and his development of HLH.

B. Burden Shifting: Respondent Must Show an Alternative Cause of Injury

A petitioner who satisfies all three prongs of the *Althen* test has established a prima facie showing of causation. *Hammitt v. Sec'y of Health & Human Servs*., 98 Fed. Cl. 719 (2011).

Consequently, the burden now shifts to the government to prove that an alternative cause, unrelated to the administration of the vaccine, was the "sole substantial factor" in causing the alleged injury. *De Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1354 (2008). *See also Hammitt*, 98 Fed. Cl. at 726 (explaining that respondent's burden is to show that the "factor unrelated" was the "sole substantial factor" in causing the injury). Additionally, a factor unrelated "may not include 'any idiopathic, unexplained, unknown, hypothetical, or undocumentable cause, factor, injury, illness or condition.'" 42 U.S.C. § 300aa-13(a)(2); *see also Doe/11 v. Sec'y of Health & Human Servs.*, 83 Fed. Cl. 157 (2008) (holding that an idiopathic diagnosis cannot be a "factor unrelated," as it is idiopathic).

Petitioner has met the *Althen* criteria, therefore providing a *prima facie* showing that the hepatitis B vaccine caused B.B.T. to develop HLH. Respondent has put forth the theory that B.B.T. developed HLH in utero, before he received the hepatitis B vaccine. However, respondent has not shown any alternative cause that could have caused or triggered B.B.T.'s HLH. Extensive testing showed no genetic mutations that would lead to familial HLH; therefore, B.B.T. was classified by his treating physicians as having "acquired HLH." Respondent's expert noted in his report that acquired HLH can be triggered by "literally any infectious agent; bacteria, fungi, protozoans, and viruses have been implicated as well as HLH-associated gene mutations, malignancies, underlying immune deficiencies, and rheumatologic disease." Resp. Ex. A at 3. There is no evidence that B.B.T. suffered from any of these conditions in utero or after birth.

Respondent has essentially proffered the theory that B.B.T.'s HLH was idiopathic, or "a disease of unknown cause."[32] Such a theory is insufficient to meet the "factor unrelated" burden. Accordingly, respondent has not met his burden of showing that an alternative cause was the sole substantial factor in causing B.B.T.'s HLH.

VII. Conclusion

Petitioner has put forth preponderant evidence that the hepatitis B vaccine received by B.B.T. either caused or significantly aggravated the development of acquired hemophagocytic lymphohistiocytosis, and has therefore demonstrated entitlement to compensation. This case shall proceed to the damages phase.

IT IS SO ORDERED.

s/ Mindy Michaels Roth
Mindy Michaels Roth
Special Master

[32] Stedman's Medical Pocket Dictionary at 367.