In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Filed: September 5, 2019

G.C. *by her parent* BRYNN CONTINO,	*	PUBLISHED
Petitioner,	*	No. 15-773V
v.	*	Special Master Gowen
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	Entitlement; Influenza ("flu"); Urticarial Vasculitis; Bystander Activation.
Respondent.	*	

Lawrence R. Cohan, Anapol Weiss, Philadelphia, PA, for petitioners.
Darryl R. Wishard, United States Department of Justice, Washington, DC, for respondent.

RULING ON ENTITLEMENT[1]

On July 23, 2015, Brynn Contino ("petitioner"), on behalf of her minor child, G.C., filed a petition in the National Vaccine Injury Compensation Program.[2] Petitioner alleges that G.C. developed urticarial/hypersensitivity vasculitis which was caused in fact by the influenza ("flu") vaccination received on December 3, 2013. Petition at Preamble. Based upon a full review of all of the evidence and testimony presented, I find that petitioner is entitled to compensation.[3]

[1] In accordance with the E-Government Act of 2002, 44 U.S.C. § 3501 (2012), because this opinion contains a reasoned explanation for the action in this case, **this opinion will be posted on the website of the United States Court of Federal Claims**. This means the opinion will be available to anyone with access to the internet. As provided by 42 U.S.C. § 300aa-12(d)(4)B), however, the parties may object to the published Decision's inclusion of certain kinds of confidential information. Specifically, under Vaccine Rule 18(b), each party has 14 days within which to request redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). **If neither party files a motion for redaction within 14 days, the entire opinion will be posted on the website and available to the public in its current form.** *Id.*

[2] The National Vaccine Injury Compensation Program is set forth in Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755, codified as amended, 42 U.S.C. §§ 300aa-10 to 34 (2012) (hereinafter "Vaccine Act" or "the Act"). Hereinafter, individual section references will be to 42 U.S.C. § 300aa of the Act.

[3] Pursuant to Section 300aa-13(a)(1), in order to reach my conclusion, I have considered the entire record including all of the medical records, statements, expert reports, and medical literature submitted by the parties. This opinion discusses the elements of the record I found most relevant to the outcome.

I. BACKGROUND

A. Procedural History

On July 23, 2015, petitioner filed her claim that G.C.'s December 13, 2013 flu vaccination was the cause-in-fact of her development of urticarial/hypersensitivity vasculitis. Petition (ECF No. 1). An initial status conference was held on September 1, 2015. Scheduling Order (ECF No. 7). Respondent indicated that he would like to review an expert report from petitioner prior to determining on how to proceed. *Id.* Petitioner was ordered to file all medical records and an expert report. *Id.*

On October 28, 2015, petitioner filed medical records.[4] Petitioner's ("Pet.") Exhibit ("Ex.") 5 (ECF No. 9). Then on November 18 and 19, 2015, petitioner filed her first expert report from Dr. Vera Byers[5] and supporting medical literature. Pet. Exs. 6-8(1) (ECF Nos. 10-12). On February 5, 2016, respondent filed his first expert report by Dr. Harry Schroeder, Jr.[6] and supporting medical literature. Respondent's ("Resp.") Ex. A (ECF No. 16).

[4] With the petition, petitioner filed a Notice of Intent to File Medical Records via compact disc ("CD"). Exhibits 1-4 were filed via CD. ECF No. 1.

[5] Dr. Vera Byers obtained a bachelor's degree in microbiology in 1965, a M.A. in microbiology in 1967, and a Ph.D in immunology in 1969, all from the University of California-Los Angeles (UCLA) Pet. Ex. 7 at 1; Tr. 54. She completed a fellowship in protein chemistry at Abbott Laboratories from 1969-1971 and a fellowship in clinical immunology and allergy from 1971-1973. Pet. Ex. 7 at 1. She testified that during this fellowship, she saw and treated rheumatology patients as well as those with genetic immunodeficiencies. Tr. 55. She obtained an M.D. in 1981, then completed a three-year residency in internal medicine from 1981-1984, all from the University of California-San Francisco (UCSF). From 1984-1987, Dr. Byers work at Immunology Incorporated Medical Group in California, which was a private medical practice where she saw patients with rheumatology and allergy/immunology issues. Tr. 55; Pet. Ex. 7 at 3. Dr. Byers testified that she has diagnosed and treated patients with chronic urticaria and vasculitis. Tr. 58. Dr. Byers is currently the medical director and a consulting medical toxicologist for pharmaceutical companies at Immunology Inc. Pet. Ex. 7 at 2. She has frequently served as an expert witness in civil litigation and in the Vaccine program, where she has previously been qualified as an expert in immunology. In this case, petitioner proffered and I accepted Dr. Byers as an expert in the area of clinical immunology, particularly as it relates to evaluating and determining whether particular vaccines can trigger autoimmune diseases, including urticarial vasculitis.

[6] Dr. Harry Schroeder obtained a bachelor's degree in chemistry in 1974 from Texas A&M University, a M.D. from Baylor College of Medicine in 1981 and a Ph.D. in cell biology in 1979 from Baylor College of Medicine. Resp. Ex. B. He testified that he did his residency at the University of Kentucky in Lexington, Kentucky. Tr. 204. Dr. Schroeder then went to the University of Washington where he obtained training in medical genetics. *Id.* He is board certified in internal medical and clinical genetics. *Id.* From 1986-1988 he pursued training in immunology, molecular immunology at the Howard Hughes Institute in Seattle, Washington. Resp. Ex. B at 2; Tr. 204. Dr. Schroeder began a teaching career at the University of Alabama at Birmingham in 1988. Tr. 204. Dr. Schroeder spent a sabbatical year at the University of Cologne in Cologne Germany at the Institute of Genetics under the mentorship of Klaus Rajewsky. Tr. 204. He is currently a Director of the University of Alabama at Birmingham ("UAB") in Immunology and Director of the T32 Training Program in Immunologic Diseases and Basic Immunology at UAB. Resp. Ex. A at 1. Dr. Schroeder also serves as an associate editor for the Journal of Immunology, for the Journal of Allergy and Clinical Immunology. Tr. 205; Resp. Ex. A at 1. He is also the editor of the textbook, *Clinical Immunology: Principles and Practices.* Tr. 205. Dr. Schroeder testified that has never testified before the Vaccine Court, but reviewed five cases for the respondent. Tr. 211. Dr. Schroeder also testified that he never treated any children with chronic urticaria. Tr. 219. In this case, respondent proffered and I accepted Dr. Schroeder as an expert in the area of immunology. Tr. 222.

Additionally, the same day, respondent filed his Rule 4(c) report recommending against compensation. Resp. Report ("Rept.") (ECF No. 17). Respondent asserted that G.C.'s "symptom onset began in September 2013, on or about three months before her flu vaccination. G.C.'s symptom recurrence was relatively consistent both before and after vaccination….Thus, G.C.'s urticarial vasculitis has followed the normal course of the disease process, and the flu vaccination neither caused nor aggravated the disease course." Resp. Rept. at 5.

A Rule 5 status conference was held on February 24, 2016. The parties were ordered to submit additional expert reports. Scheduling Order (ECF No. 18). Petitioner submitted a supplemental expert report by Dr. Vera Byers on May 9, 2016. Pet. Ex. 12 (ECF No. 22). Respondent submitted a responsive report by Dr. Harry Schroeder on July 25, 2016. Resp. Ex. J (ECF NO. 24).

After a status conference held on August 9, 2016, where the undersigned reviewed the additional expert reports, the parties agreed to proceed simultaneously with litigative risk settlement discussions and scheduling a date for an entitlement hearing. Scheduling Order (ECF No. 25). The parties engaged in unfruitful settlement discussions until December 16, 2016, at which point they reached an impasse and elected to proceed to an entitlement hearing scheduled for September 13, 2017. Resp. Status Report (ECF No. 32). Both parties briefed the case prior to the hearing. Pet. Prehearing Submissions filed June 1, 2017 (ECF No. 34); Resp. Prehearing Submissions filed June 28, 2017 (ECF No. 35).

An entitlement hearing was held on September 13, 2017 and was continued on November 8, 2017 in Washington, D.C. Petitioner, Ms. Brynn Contino offered fact testimony. Petitioner presented expert testimony from Dr. Vera Byers. Respondent presented expert testimony from Dr. Harry Schroeder via video conference. The parties submitted post hearing-briefs addressing key issues raised during the entitlement hearing and identifying the most relevant medical literature submitted. *See* Pet. Post Hearing Brief ("Pet. Brief") (ECF No. 63); Resp. Post Hearing Brief ("Resp. Brief") (ECF No. 64); and Pet. Post Hearing Rebuttal Brief (ECF No. 65).

This matter is now ripe for adjudication.

B. Summary of Relevant Facts

1. Medical Records from Birth to Influenza Vaccination on December 3, 2013

G.C. was born on November 6, 2010. Pet. Ex. 1 at 5. On December 23, 2010, G.C. presented to the Frederick Memorial Hospital emergency department with three days of coughing and congestion, no fevers, but had vomited twice. Pet. Ex. 5 at 62. She tested negative for the flu virus, but positive for respiratory syncytial virus ("RSV"). *Id.* at 63. A deep nasal suction was performed with little improvement and she was placed on 1 Liter of oxygen, then increased to 2 liters. Pet. Ex. 1 at 175. G.C. was transported via helicopter to Johns Hopkins where she was admitted to the pediatric intensive care unit ("ICU"). *Id.*

G.C. was admitted to Johns Hopkins from December 23-27, 2010. Pet. Ex. 3 at 6-10. Prior to discharge, she was weaned off oxygen support for 24 hours before she was sent home without any signs of respiratory distress. *Id.* at 7.

The following year, G.C. was treated by Dr. James Lee on various occasions for coughs and upper respiratory infections. *See* Pet. Ex. 1(a) at 63, 127, 160. However, she continued receiving her scheduled childhood immunizations. Pet. Ex. 1(a) at 12 & Pet. Ex. 1(b) at 187.

In February 2012, G.C. had a complete blood count test performed. Pet. Ex. 1(a) at 37. The test showed that her IgA, IgM and IgG subclasses were in normal range, but the total IgG was low. Pet. Ex. 5 at 130-135. Then on March 9, 2012, G.C. underwent a bilateral myringotomy and ventilation tube placement.[7] Pet. Ex. 1(a) at 75; Pet. Ex. 5 at 144.

On April 2, 2012, Dr. Samuel Rosenberg assessed G.C. for coughing and recurrent otitis media. Pet. Ex. 1(a) at 81. Her physical exam was normal. *Id.* He noted that "her IgG was slightly reduced but the remainder of her immunoglobulins were normal and pneumococcal antibodies which showed elevation in several serotypes [are] indicative of good antibody response." *Id.* After reviewing her history and performing a physical exam, Dr. Rosenberg recommended G.C. use an inhaler with corticosteroids to treat any asthma component to her cough. *Id.* He stated that "IgG level was slightly reduced, but I do not feel that this is representative of any significant immune system issue." *Id.* Dr. Rosenberg also believed that the PE tubes placed in G.C.'s ears would "dramatically help with her recurrent respiratory symptoms." *Id.*

In the fall of 2012, G.C. has the right ventilation tube removed. Dr. Lee stated that "an underlying acute otitis media with perforation was noted." Pet. Ex. 1(a) at 76. Then in December 2012, a second myringotomy with an adenoidectomy was performed. Pet. Ex. 1(a) at 75.

In April 2013, G.C. was taken to see Dr. Lee twice for a cough without fever. Pet. Ex. 1(a) at 102 & 104. He observed that her left ear tube appeared to be blocked by "opaque effusion," but she did not have any rash or skin lesions. *Id.* at 102. He prescribed a course of amoxicillin twice a day for ten days. *Id.* at 103.

Ms. Contino testified that in late August 2013, G.C. developed a rash. Transcript ("Tr.") 9. Ms. Contino stated that hives were located on G.C.'s armpit, bottom half of her thighs and the back of her knees. *Id.* She described these hives as "raised." Tr. 10. Ms. Contino testified that she treated the hives with Benadryl and the rash went away within an hour. Tr. 12 & 35. She testified that a similar rash re-appeared on G.C. in September 2013. Tr. 9-10. Ms. Contino again gave G.C. Benadryl and the rash resolved within an hour. Tr. 12. She described that G.C. was "uncomfortable because they were itchy," but the rash did not affect G.C's play or eating. Tr. 11 & 35.

[7] A myringotomy and ventilation tube placement is a common procedure that surgically places small tubes in a child's eardrum to help drain fluid out of the middle ear in order to reduce the risk of ear infections. Ear tubes are recommended for children who have persistent fluid buildup behind the eardrum.

On September 13, 2013, G.C. was seen by Dr. Lee for assessment of a rash on her cheek that began two days prior to the office visit. Pet. Ex. 1(a) at 98. Dr. Lee observed "well defined pink patches, only slightly raised mostly along waistband, backs of thighs, ankles but also on abdomen, back of hands and cheek." *Id.* He stated that "[G.C.] seems unaffected-well appearing/acting, not itching, rash is nontender, she was very cooperative with exam….seems to be more of an irritant dermatitis." *Id.* Dr. Lee recommended Ms. Contino treat with Benadryl as necessary. *Id.*

The next month, on October 3, 2013, G.C. was seen by allergist, Dr. Monika Korff, for hives. *Id.* at 69-70. Ms. Contino reported that 2-3 weeks ago G.C. "woke up one morning and was covered in hives….After taking the Benadryl for a day, the rash resolved." *Id.* at 69. The rash reappeared three days later and was resolved by Benadryl. *Id.* Then, G.C. had another episode of rashes that resolved with Benadryl within 24 hours. *Id.* Dr. Korff performed a physical exam of G.C. and found that her conjunctivae were clear, allergic shiners absent and her lungs have good breath sounds without wheezing or rhonchi. *Id.* at 70. Dr. Korff assessed G.C. with dermatographic urticaria that "certainly explained the hives" and recommended treating the symptoms with Benadryl during episodes versus daily use of a long acting antihistamine as prophylaxis. *Id.*

On October 21, 2013, G.C. saw Dr. Lee for constipation and difficult voiding. Pet. Ex. 1(a) at 96. Dr. Lee observed G.C.'s skin as "pink, warm and dry." *Id.* A urine sample was negative for protein. *Id.* Dr. Lee assessed G.C. with an abnormality of urination, noting G.C. was resistant on the toilet and opined that her voiding and constipation was attributable to toddler independence, rather than a medical issue. *Id.* at 97. A urinalysis was negative for protein in G.C.'s urine. *Id.*

Dr. Lee saw G.C. on November 11, 2013 for complaints of an ongoing wet cough and congestion. Pet. Ex. 1(a) at 94. Upon physical exam, G.C. appeared "unhappy, but non-ill acting." *Id.* Most notably, no skin rashes or lesions were observed. *Id.* Dr. Lee diagnosed G.C. with an acute upper respiratory infection of unspecified site and was given a ten-day course of amoxicillin. *Id* at 95.

On December 3, 2013, G.C. received her third flu vaccine. Pet. Ex. 1(a) at 12.

2. Medical History Post Flu Vaccination to Present

The family travelled from Maryland to Florida for a trip to Disney World on Saturday, December 7, 2013. Tr. 14. During the car trip, Ms. Contino noticed "smaller red blotchy rashes" on G.C. that "started on her stomach area." *Id.* On December 9, 2013, while in the amusement park, G.C. refused to walk and complained that her legs really hurt. Tr. 15. Ms. Contino testified that G.C.'s hands, feet and lips began to swell. *Id.* She further testified that G.C. had between 60 to 80 bruises all over her body, including on her thighs, backside and stomach. That same night, Ms. Contino took G.C. to the emergency room of Florida Hospital. Tr. 21 & Pet. Ex. 5.

G.C. was treated at the emergency department of Florida Hospital for hives, a fever of 101 degrees Fahrenheit, bruising and swelling. Pet. Ex. 5 at 12, 16 & Pet. Ex. 2(a) at 7. The clinical impression of G.C. at the emergency room was G.C.'s symptoms were "most consistent with a viral exanthem" and she was given a steroid injection. Pet. Ex. 4 at 18. Upon discharge, she was given a prescription of prednisolone and Benadryl. *Id.* Ms. Contino testified that G.C.'s swelling went down after the steroid treatment at Florida Hospital, but the bruising remained. Tr. 25.

Ms. Contino testified that this was the first time that G.C. had developed bruising associated with a rash. Tr. 23. She explained that G.C. experienced episodes of recurrent bruising and swelling in January 2014. Tr. 27.

On February 3, 2014, G.C. was seen by pediatric allergist, Dr. Glenn Silber. Pet. Ex. 1(a) at 60. During that visit, Ms. Contino reported that G.C. continued to have rashes around three times a week that lasted about six hours and some swelling occured with cold exposure. *Id.* A physical exam revealed that G.C. had no rash and no dermatographism.[8] *Id.* Ms. Contino testified that she showed Dr. Silber pictures she had taken of G.C. in Florida. Tr. 27. Dr. Silber assessed G.C. with "probable vasculitis-doubt allergy with no pruritus" and recommended G.C. seek treatment from a pediatric rheumatologist. *Id;* Tr. 27.

Ms. Contino testified that due to a four week wait for an appointment with a rheumatologist at Johns Hopkins, she drove G.C. to the Cleveland Clinic. Tr. 28. G.C. was seen by pediatric rheumatologist, Dr. Andrew Zeft, on February 12, 2014. Pet. Ex. 9 at 4. His physical exam of G.C. was relatively normal, but he ordered a complete blood count and immunoglobulin test. *Id.* Dr. Zeft opined that G.C.'s diagnosis was "most consistent with hemorrhagic edema of infancy triggered by influenza vaccination. Preceding urticaria may be idiopathic or potentially part of illness spectrum. No biopsy has been done on skin lesions to clarify leukocytoclastic vasculitis pathology. Presentation is not consistent with urticarial vasculitis." *Id.* G.C.'s blood IgG, IgA and IgM levels were within normal limits.[9] *Id.* at 13. When Dr. Zeft spoke to G.C.'s mother on February 13, 2014 to relay the test results, G.C. had apparently developed "new dependant bruises." Pet. Ex. 9 at 16. Dr. Zeft recommended to recheck G.C.'s blood count and to consider dapsone.[10]

On February 20, 2014, G.C. was evaluated by rheumatologist, Dr. Sangeela Sule, at Johns Hopkins Division of Rheumatology. Pet. Ex. 2(a) at 4. Dr. Sule noted that two days after

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[8] Dermatographism (also spelled, "dermagraphism") is a type of physical urticaria in which moderately firm stroking or scratching of the skin with a dull instrument produces a wheal with a red flare on each side. *Dorland's Illustrated Medical Dictionary* 32nd ed. (2012) (hereinafter "*Dorland's"*) at 499.

[9] Petitioner's Pre-Hearing Brief states that G.C.'s IgG level was below normal and cites to Petitioner's Exhibit 1(a) at 37. However, this reference is to an immunoglobulin test result from 2012.

[10] Dapsone is an antibacterial and antifungal medication administered orally for the treatment of dermatologic noninfectious inflammatory diseases. It was also used to treat leprosy and malaria. Golusin, Z. et al., *What do we know about diaminodiphenylsulfone?* 53 Med. Pregl. 369-72 (2000). Available at https://www.ncbi.nlm.nih.gov/pubmed/11214480 (accessed on August 22, 2019).

G.C. received the flu vaccine, she had hives, her legs and feet were swollen, and bruising appeared.[11] *Id.* at 4. Dr. Sule developed a working diagnosis of "urticarial vasculitis" and referred G.C. to dermatology for a biopsy to confirm the tentative diagnosis of urticarial vasculitis. *Id.* at 6. Additionally, Dr. Sule wanted a repeat urinalysis and recommended a renal ultrasound because of the two prior urine samples with elevated protein/creatinine ("pr/cr") ratios. *Id.* at 6.

G.C. returned to Johns Hopkins on March 19, 2014 for an evaluation by pediatric nephrologist, Dr. Cozumel Pruette. *Id.* at 7. Dr. Pruette noted that the working diagnosis is "urticarial vasculitis" and there was concern that the proteinuria noted on previous urine samples may indicate possible renal involvement. *Id.* at 8. Dr. Pruette requested an additional first morning urine sample and a skin biopsy. *Id.* at 8.

G.C. had a skin biopsy performed on her left arm on March 27, 2014 that confirmed the diagnosis of urticarial vasculitis. *Id.* at 9-10. The biopsy was positive for granular deposition of IgM and C3 in superficial derma blood vessels. Pet. Ex. 3 at 4. The test was negative for IgA, IgG and Fibrin. *Id.* Dr. Grant Anhalt noted that the "findings are seen in vasculitis." *Id.* Dr. Max Fischer reviewed the biopsy results and changed G.C.'s diagnosis from "consistent with urticaria; negative for vasculitis" to "urticaria-like reaction pattern." *Id.* at 5.

On April 3, 2014, Dr. Sule called G.C.'s mother to confirm the biopsy findings and recommended G.C. begin 10 mg of prednisone and 15 mg Azathioprine[12] daily. *Id.* at 10. On April 14, 2014, Dr. Puttgen saw G.C. to remove the suture. Dr. Puttgen stated that the differential diagnosis confirms vasculitis "which in the setting of the clinical presentation is consistent with urticarial vasculitis. The presentation in G.C. is somewhat unusual as the lesions come and go in less than 24 hours often, more typical of standard urticaria." She continued by stating, "However, coupled with the complaints of leg pain and proteinuria, a more systemic process does fit." Pet. Ex. 2(a) at 10.

On April 25, 2014, Ms. Contino reported to Dr. Sule that G.C. was still experiencing intermittent hives associated with itching and pain. Pet. Ex. 2(a) at 11. Dr. Sule requested that the pharmacy at Johns Hopkins compound Azathioprine to a form that G.C. would be able to take, instead of tablets. *Id.*

Drs. Sule, Puttgen and Pruette continued to manage and follow G.C.'s health between April and February 2015. *See* Pet. Ex. 2(a) at 9-18. G.C. continued to provide urine samples that showed abnormal urine pr/cr ratios, with individual numbers being within normal ranges. *Id.* at 12.

[11] Dr. Sule incorrectly states that G.C. received flu vaccine on December 5, 2015. G.C. received a flu vaccine on December 3, 2013. *See* Pet. Ex. 1(a) at 12.

[12] Azathioprine is an immunosuppressant drug that is used to treat dermatomyositis, systemic lupus erythematosus, inflammatory bowel disease, vasculitis and rheumatoid arthritis. Accessed at: https://www rheumatology.org/I-Am-A/Patient-Caregiver/Treatments/Azathioprine-Imuran

On August 11, 2014, Dr. Pruette spoke with Ms. Contino regarding G.C.'s recent urine results showing increased pr/cr ratio. *Id.* at 13. Dr. Pruette recommended that G.C. remain on Imuran and prednisolone given that G.C.'s proteinuria is "relatively stable, kidney function remains stable and she is clinically doing well." *Id.* Ms. Contino informed Dr. Pruttgen that G.C. was still experiencing leg pain and wanted to speak with Dr. Sule about decreasing the dose of prednisolone. *Id.*

Ms. Contino testified that throughout the spring of 2014 and into the fall of 2014 G.C. was in constant pain. Tr. 37. G.C. would have pain primarily in her hip and legs, but occasionally in her arms. Tr. 38. G.C.'s rash symptoms were more intermittent, but would appear if she got very hot, however, G.C.'s pain was constant. Tr. 37.

In September 2014, G.C. was seen by Dr. Jillian Kaskavage at Johns Hopkins Pediatric Rheumatology. Pet. Ex. 1(a) at 53. Ms. Contino reported that G.C. did not have any rash over the summer, but as the weather got cooler, G.C. had a rash appear at night, but was gone by the morning. *Id.* Additionally, G.C. was not complaining of any itchiness or pain. *Id.* Ms. Contino stated that G.C. experienced some pain in her lower extremities and observed G.C. grabbing her shins, however, no joint swelling was observed. *Id.* Dr. Kaskavage recommended G.C. continue on Azathioprine for at least one year at 2 mg daily due to the likely "renal involvement" and her continued abnormal urine pr/cr ratio. *Id* at 54.

On December 17, 2014, Dr. Pruette saw G.C. for a follow-up appointment. Pet. Ex. 1(a) at 46. Dr. Pruette reported that G.C.'s proteinuria trend had been improving since the steroids were initiated. *Id.* Ms. Contino reported that G.C. still experienced leg pain, but no recent rash. *Id.* Dr. Pruette again assessed G.C. with proteinuria associated with underlying urticarial vasculitis. *Id.* She stated that G.C. responded favorably to the regimen of Azathioprine and steroids and that there was no need for a kidney biopsy at that time. *Id.* at 49. Dr. Pruette recommended that G.C. continue weaning her steroid dose and take MiraLAX to reduce her constipation. *Id.*

From December 2014 through January 2015, G.C.'s doctors continued to wean her from prednisone and continued the course of Azathioprine at the current dose. Pet. Ex. 2(a) at 17. Then on February 16, 2015, G.C. experienced a recurrence of her urticarial vasculitis with multiple hives observed all over her body when she missed a dose of prednisone. *Id.* at 18. Dr. Sule recommended G.C. be treated with rituximab, 375 mg/m2 once a week for four weeks. Pet. Exs. 1(b) at 10 & Pet. Ex. 2 at 22-24.

On March 25, 2015, G.C. was brought into the Johns Hopkins clinic presenting with a red rash on her face and abdomen but was alert and playful. Pet. Ex. 2 at 24. It was reported that again G.C. had missed a dose of prednisone. *Id.* Dr. Sule advised Ms. Contino to continue to give G.C. prednisone and to make a follow up appointment in a few weeks. *Id.*

Dr. Mark Gorelik, pediatric rheumatologist, attended to G.C. on April 16, 2015. Pet. Ex. 2(b) at 25. Ms. Contino reported that as G.C. was weaning from the steroids, a rash reappeared on her face, but no other symptoms returned. *Id.* Ms. Contino also reported that G.C. was slightly more tired lately and irritable since the wean. *Id.* Upon physical exam, Dr. Gorelik

observed a small 1 cm erythematous rash over the left check. *Id.* at 26. He noted that G.C.'s symptoms are improving on Azathioprine, but she had a borderline abnormal urine pr/cr ratio and suggested a follow up appointment in two months. *Id.* at 26. Ms. Contino called the clinic four days later, requesting to speak to the doctor and that G.C. was experiencing back pain over the past month. *Id.* at 26. Dr. Pruette followed up with Ms. Contino the following day, reporting that G.C.'s lab results were "good/stable," and indicated that continuing the steroid wean would be appropriate. *Id.* at 27.

On May 20, 2015, Dr. Pruette reported to Ms. Contino that G.C.'s lab results showed an increase in her pr/cr ratio from the previous month. Pet. Ex. 2(b) at 9. Ms. Contino reported that G.C. has "significant sun sensitivity from the steroids," but informed Dr. Pruette there were "no other skin complaints." *Id.* Dr. Pruette and Ms. Contino agreed to continue G.C. on the current prednisolone dose, check G.C.'s creatinine and CD19/CD20 counts to assess for ongoing effects of recent Rituximab course and follow proteinuria. *Id.* The lab results from May 21, 2015 show that G.C.'s CD19/CD20 lymphocyte levels were at zero. *Id.* at 45.

On August 10, 2015, G.C. was seen by Dr. Lee for a fever of 102 degrees and a sore on her tongue. Pet. Ex. 10 at 6. Upon a physical exam, G.C. was irritable and excessively crying. *Id.* Dr. Lee described G.C. as "uncomfortable and acutely ill." *Id.* at 11. Dr. Lee described a "yellow pustule [on] tip of tongue. Also, more classic cold sores inner mucus membrane and gingiva [is] generally inflamed." *Id.* The next day, August 11, 2015 G.C. was hospitalized at Johns Hopkins for a rash that lasted 10 days, a fever of 102 degrees Fahrenheit and sores in her mouth for seven days. Pet. Ex. 6 at 4. G.C. was diagnosed with a viral exanthema and discharged on August 15, 2015.[13] *Id.*

Ms. Contino testified that G.C.'s mouth ulcers appeared monthly. Tr. 49. G.C. went back to Dr. Lee in October 2015 with sores under her tongue, decreased appetite and difficulty sleeping. Pet. Ex. 10 at 10. G.C. had been prescribed cephalexin on August 12, 2015. *Id.* A physical exam confirmed a single ulcer on G.C.'s inner cheek area. *Id.* at 12. Dr. Lee prescribed lidocaine to apply to the affected area of the mouth three times a day. *Id.*

Ms. Contino described the hives and bruising that appeared on G.C. after she received the flu shot as "smaller" with a "purplish tint to them," in addition to "lots of swelling and pain in her legs." Tr. 33. Petitioner submitted into evidence multiple color photographs of G.C. taken in December 2013 that depicted rashes and extensive bruising. *See* Pet. Ex. 18(a) Further, she testified that G.C.'s condition was much improved after receiving the rituximab treatment in March 2015. Tr. 38. However, G.C. continues to have mouth ulcers and continues to be on steroids because of her kidney involvement. Tr. 49-50; 340. She testified that G.C. is still on steroids and has been consistently since April 2014. Tr. 340. As recently as 2017, doctors at Kentucky Children's Hospital are determining if G.C. can wean from the steroids because of concern that the steroids may be doing more harm to G.C.'s kidneys than the disease. *Id.*

[13] Both Dr. Byers and Dr. Schroeder make reference to G.C. being hospitalized on August 11, 2015, however, those records were never filed with the Court. Petitioner's Exhibit 10 provides the lab results from G.C.'s hospitalization at that time but does not provide any further information.

II. LEGAL STANDARD

The Vaccine Act provides two avenues for petitioners to receive compensation. A petitioner may demonstrate a "Table" injury,[14] or that a vaccine listed on the Vaccine Table was the cause-in-fact of any injury. In the present case, petitioner does not establish that she has suffered a Table injury.

To satisfy the burden of proving causation-in-fact, petitioner must "show by preponderant evidence that the vaccination brought about the injury by providing 1) a medical theory connecting the vaccination and injury; 2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and 3) a showing of proximate temporal relationship between vaccination and injury." *Althen v. Sec'y of Health & Human Servs.,* 418 F. 3d 1274, 1278 (Fed. Cir. 2005). Petitioner's must establish each *Althen* prong by the preponderance of the evidence. *Caves v. Sec'y of Health & Human Servs.,* 100 Fed. Cl. 119, 132 (2011), *aff. per curiam,* 463 Fed. Appx. 932 (Fed. Cir. 2012).

The preponderance of the evidence standard requires a petitioner to demonstrate that it is "more likely than not" that the vaccine caused her injury. *Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010). Proof of medical certainty is not required. *Bunting v. Sec'y of Health & Human Servs.*, 931 F.2d 867, 873 (Fed. Cir. 1991). In particular, a petitioner must demonstrate that the vaccine was "not only [a] but for cause of the injury but also a substantial factor in bringing about the injury." *Moberly*, 592 F.3d at 1321 (quoting *Shyface v. Sec'y of Health & Human Servs.,* 135 F.3d 1344, 1352-53 (Fed. Cir. 1999); *Pafford v. Sec'y of Health and Human Servs.*, 451 F.3d 1352, 1355 (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 & Human Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994). A fact-finder may rely upon "circumstantial evidence" which the court found to be consistent with the "system created by Congress, in which close calls regarding causation are resolved in favor of injured claimants." *Althen*, 418 F. 3d at 1280.

Establishing a sound and reliable medical theory connecting the vaccine to the injury often requires petitioners to present expert testimony in support of his or her claim. *Lampe v. Sec'y of Health & Human Servs.,* 219 F.3d 1357, 1361 (Fed. Cir. 2000). Expert testimony in the Vaccine Program is usually evaluated according to the factors set forth in *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 594-96 (1993); *see also Cedillo,* 617 F.3d at 1339 (citing *Terran v. Sec'y of Health & Human Servs.,* 195 F.3d 1302, 1316 (Fed. Cir. 1999). Thus, for Vaccine Act claims, a "special master is entitled to require some indicia of reliability to support the assertion of the expert witness." *Moberly* at 1324. The *Daubert* factors are used in *weighing* the reliability of scientific evidence proffered. *Davis v. Sec'y of Health & Human Servs.,* 94 Fed. Cl. 53, 66-67 (2010). Where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen v. Sec'y of Health & Human Servs.,* 219 F.3d 1339, 1347 (Fed. Cir. 2010) (citing *Lampe v. Sec'y of Health & Human Servs.*, 219 F.3d 1357, 1362 (Fed. Cir. 2000).

[14] A "Table" injury is an injury listed on the Vaccine Injury Table, 42 U.S.C. § 100.3, corresponding to the vaccine received within the time-frame specified.

Once a petitioner has proven causation by preponderant evidence, the burden shifts to respondent to show by a preponderance of the evidence that the injury is due to factors unrelated to the administration of the vaccine. *Deribeaux ex rel. Deribeaux v. Sec'y of Health & Human Servs.*, 717 F.3d 1363, 1367 (Fed. Cir. 2013) (citing § 13(a)(1)(B)). Respondent has the burden of demonstrating that "a factor unrelated to the vaccination is the more likely or principal cause of injury alleged. Such a showing establishes that the factor unrelated, not the vaccination, was 'principally responsible' for the injury. If the evidence or alternative cause is seen in equipoise, then the government has failed in its burden of persuasion and compensation must be awarded. *Knudsen*, 35 F.3d at 551.

III. DISCUSSION

A. Diagnosis

The medical records establish that G.C. has been diagnosed with urticarial vasculitis. Pet. Ex. 2(a) at 10. The parties do not dispute G.C.'s ultimate diagnosis, but debate when the autoimmune condition began.

Respondent argued that G.C's symptoms of manifested in the late summer or early fall of 2013, three months prior to the vaccination. Resp. Ex. A at 8; Resp. Brief at 8. Petitioner argued that G.C.'s rash and hives that appeared in the late summer/early fall of 2013 were part of a separate allergic response and that she did not develop symptoms associated with her autoimmune urticarial vasculitis until after the December 3, 2013 flu vaccination.

1. Acute Urticaria

Urticaria, better known as "hives," is a common dermatologic condition that typically presents with intensely pruritic, well-circumscribed, raised wheals ranging from several millimeters to several centimeters or larger in size.[15] Urticaria is historically divided into acute and chronic disease, dependent on the disease duration.[16] Pet. Ex. 16(f) at 2. Urticaria that recurs within a period of less than six week is classified as acute; chronic urticaria becomes chronic if disease activity continues for six weeks or longer. *Id.*

According to Nelson's Pediatric Textbook, acute urticaria is often caused by an allergic IgE-mediated reaction.[17] Pet. Ex. 16(t) at 1. However, acute urticaria can also result from non-IgE mediated stimulation of mast cells caused by viral agents including Epstein-Barr and hepatitis B or physical stimuli, such as a change in temperature. *Id.* at 1-2.

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[15] Paul Schaffer, *Acute and Chronic Urticaria: Evaluation and Treatment*, 95 Am. Family Physician 11 (June 1, 2017), https://www.aafp.org/afp/2017/0601/p717.html

[16] Clive Grattan, *The Urticarias: pathophysiology and management*, 12 Clinical Medicine 2, 164-167 (2012). [Pet. Ex. 16(f)].

[17] Donald Y.M. Leung and Stephen C. Dreskin, *Chapter 147: Urticaria (Hives) and Angioedema*, 18th ed. Nelson's Pediatrics Textbook, 979-82 [Pet. Ex. 16(t)].

Allergic acute urticaria is a "self-limited process that occurs when an allergen activates mast cells in the skin." *Id.* As explained in the Grattan article, "the mast cell plays a central role in most patterns of urticaria by releasing histamine which, in turn, acts on capillaries and cutaneous nerve endings to elicit the characteristic itchy red wheals." Pet. Ex. 16(f) at 3. The stimulus for mast cell degranulation may be immunological. *Id;* Pet. Ex. 6 at 5; Pet. Ex. 8(c) at 1[18]; and Pet. Ex. 17(e) at 1.[19] The cross-linking of two or more adjacent allergen-specific immunoglobulin ("IgE") molecules bound to the high affinity IgE receptor ("FcεRI") will initiate a series of calcium-dependent intracellular signaling events leading to incomplete degranulation in allergic urticaria. Pet. Ex. 16(f) at 3. This leads to the release of histamine, leukotrienes, platelet activating factor (PAF), enzymes such as tryptase and chymase, cytokines and chemokines. Pet. Ex. 16(l) at 2.[20]

Acute urticaria typically resolves within twelve hours and responds well to antihistamines. Pet. Ex. 6 at 5; Pet. Ex. 8(c) at 13; Pet. Ex. 16(f) at 1; Pet. Ex. 16(t) at 4.

2. Chronic Urticaria

Chronic urticaria is diagnosed when symptoms have been continuously or intermittently present for six weeks. *See* Pet. Ex 8(j)[21]; Pet. Ex. 16(f); Pet. Ex. 17(e). Critical to the definition of chronic urticaria in the medical articles submitted is the duration of the lesions. Najib and Sheikh define chronic urticaria as "symptoms have been *continuously or intermittently present for at least six weeks."* Pet. Ex. 8(j) at 1 (emphasis added). Chang, et. al, defines chronic spontaneous urticaria as the presentation of itchy wheal-and-flare skin reactions, angioedema or both *for a period of greater than six weeks.*[22] Pet. Ex. 8(f) (emphasis added). Grattan states that urticarial activity may be active for a few weeks, settle for another few weeks or months, then unpredictably return to what it was previously. *Id.*

Causes for chronic urticaria can be physical, allergic, hereditary or autoimmune. *See* Resp. Ex. A at 9; Pet. Ex. 6 at 5; Pet. Ex. 17(e) at 2; and Pet. Ex. 16(f) at 3. Between 30 and 50 percent of cases of chronic urticaria are autoimmune in nature. Pet. Ex. 8(j) at 1.

Both the experts agree that chronic urticaria resulting from an autoimmune disorder are due to the development of autoantibodies directed against either the FcεRI receptor or the IgE on mast cells and basophils. Resp. Ex. A at 9; Pet. Ex. 6 at 6. The autoantibodies directed against

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[18] Katherine Altman and Christopher Chang, *Pathogenic Intracellular and Autoimmune mechanisms in Urticaria and Angioedema,* 45 Clinical Rev. Allerg. Immunol, 47-62 (2013) [Pet. Ex. 8(c)].

[19] Gregory M. Metz and John S. Sundy, *Allergy and immunology problems and musculoskeletal specialists,* Rheumatology Network (May 7, 2009), http://www rheumatologynetwork.com [Pet. Ex. 17(e)].

[20] Allen P. Kaplan, MD, *Urticaria and Angioedema: Synopsis,* World Allergy Organizations (2014) [Pet. Ex. 16(l)].

[21] Umer Najib M.D. and Javed Sheikh, M.D., *The Spectrum of Chronic Urticaria,* 30 Allergy Asthma Proc., 1-10 (2009) [Pet. Ex. 8(j)].

[22] Tse Wen Chang, Ph.D, et.al., *The potential pharmacologic mechanisms of omalizumab in patients with chronic spontaneous urticaria,* 135(2) J. Allergy Clin. Immunol., 337-342 (2014) [Pet. Ex. 8(f)].

the IgE binding site on mast cells cause the mast cells to spontaneously degranulate in absence of allergens. Pet. Ex. 6 at 6; Pet. Ex. 16(f) at 3 & Pet. Ex. 17(e) at 2. According to the Metz article, approximately 40 percent of patients with chronic idiopathic urticaria have autoantibodies directed against a subunit of the FcεRI or to cell-surface IgE that may lead to IgE receptor cross-linking, leading to cell activation. Pet. Ex. 17(e) at 2.

The Altman article also indicates that the dysregulation of intracellular signaling pathways involving Syk, SHIP-1 or SHIP-2 in basophils and mast cells may be another autoimmune mechanism of chronic urticaria. Pet. Ex. 8(c) at 1, 5; Resp. Ex. A at 9. SHIP-1 and SHIP-2 are negative regulatory molecules that can dephosphorylate positive signaling mediators and control the activation and degranulation of mast cells and basophils, ultimately downregulating mast cell and basophil activation. *Id.* Syk on the other hand promotes mast cell degranulation. *Id.* Altman cited a study in which the mast cells from patients with chronic urticaria with an elevated level of histamine release after stimulation were found to have lower levels of SHIP-2 and increased levels of Syk. Pet. Ex. 8(c) at 4-5. Dr. Schroeder also endorsed this mechanism for development of chronic urticaria. Resp. Ex. A at 9.

The first line of treatment for chronic urticaria are first or second generation H1-receptor antagonists (antihistamines). Pet. Ex. 8(j) at 6. These drugs include Benadryl (first generation), Zyrtec (second generation) or Claritin (second generation). *Id.* at 6-7. If the patient's symptoms do not respond to the H1-antagonists alone, then corticosteroids can be considered. *Id.* at 7; Pet. Ex. 16(t) at 4. In autoimmune chronic urticaria that is unresponsive to first-and-second line treatments immunomodulatory drugs may be used, such as cyclosporin, Dapsone, and intravenous immune globulin. Pet. Ex. 8(h) at 2.[23]

3. Urticarial Vasculitis

Urticarial vasculitis is a subgroup of the larger vasculitides disorders characterized by inflammation of blood vessels leading to tissue or end-organ injury.[24] Resp. Ex. I at 2. Vasculitis may be triggered by an infectious agent or may be a complication of primary autoimmune dysregulation and/or immunosuppressive therapy, among other disorders. *Id.* Urticarial vasculitis primarily affects the small vessels of the skin.[25] Pet. Ex. 16(q) at 2. A small number of individuals with chronic urticaria may have urticarial vasculitis.[26] Overall, vasculitis in children is rare. Resp. Ex. I at 2. Patients with vasculitis and urticaria are considered a sub-population of chronic spontaneous urticaria. Pet. Ex. 16(l) at 2. According to the Najib article,

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[23] Marcus Mauer et. al, *Omalizumab for the Treatment of Chronic Idiopathic or Spontaneous Urticaria,* 386 N. Eng. J. Med., 924-35 (2013) [Pet. Ex. 8(h)].

[24] Caterina Bonetto et al., *Vasculitis as an adverse event following immunization-Systemic literature review,* Vaccine 2015 [Resp. Ex. I].

[25] What is Urticarial Vasculitis? Vasculitis Foundation, accessed on August 13, 2019: https://www.vasculitisfoundation.org/education/forms/urticarial-vasculitis/

[26] S. J. Deacock, *An Approach to the patient with urticaria,* Clin. Exp. Immunol (2008); doi: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2492902/#b71

"urticarial vasculitis is considered to be an extreme form of chronic urticaria." Pet. Ex. 8(j) at 4. Non-blanching lesions can last for more than 24 hours and leave residual marks. *Id.* Vasculitic lesions have different features from typical urticaria, including a burning or painful sensation instead of pruritus, abdominal pain and fever. Pet. Ex. 17(e) at 6.

According to the article by Jennette and Falk,[27] "urticaria can be a manifestation of small-vessel vasculitis, especially when there is an immune-complex deposition with extensive complement activation." Pet. Ex. 16(k) at 6. The article also distinguishes urticarial vasculitis from allergic urticaria, stating, "vasculitic urticaria lasts for more than a day, may evolve into purpuric lesions and may be accompanied by hypocomplementemia." *Id.* The article by Russell and Gibson[28] clarifies that hypocomplementemic urticarial vasculitis ("HUV") is frequently associated with systemic lupus erythematosus ("SLE") like systemic findings, often with multiorgan involvement. Pet. Ex. 16(w) at 3.

A skin biopsy is performed to confirm vasculitis. *Id.* A predominantly dermal interstitial neutrophilic infiltrate has been shown to be more frequent in HUV. *Id.* at 5. Skin biopsies from patients with immune-complex mediated vasculitis reveal significant neutrophilic infiltrates.[29] Pet. Ex. 16(q) at 5. Immunofluorescence evaluation may be used because of the difficulty identifying a lesion of the ideal age. *Id.* Russell and Gibson note that "especially in patients with widespread, recurrent crops of palpable purpura, knowledge of the age of lesions can be extremely difficult." *Id.* When evaluating the vasculitic lesion by immunofluorescence, prominent IgM can be suggestive of SLE. *Id.* at 6. Strong deposition of C3 in either blood vessels or the basement membrane zone is more suggestive of HUV. *Id.* at 5.

The treatment for vasculitis depends on the severity of the symptoms of the patient. Pet. Ex. 16(w) at 6. The use of anti-inflammatory drugs and antihistamines are used to treat symptomatic complaints. *Id.* However, for recurrent or chronic symptoms utilizing immune suppressant medication, like azathioprine or cyclosporine may be effective. *Id.* Azathioprine has been shown to be effective in preventing clinical recurrence, either on its own or with low-dose continued prednisone. *Id.* at 7.

In this case, G.C. had a skin biopsy performed on March 27, 2014 that confirmed vasculitis. Pet. Ex. 3 at 2. The biopsy demonstrated "subtle dermal edema with a sparse perivascular and interstitial infiltrate consisting of neutrophils, eosinophils and lymphocytes, with a mild predominance of neutrophils. Pet. Ex. 3 at 5. Direct immunofluorescence revealed granular deposition of IgM and C3 in superficial dermal blood vessels. *Id.* at 4. Dr. Sule began treating G.C. with 10 mg of prednisone and 15 mg of azathioprine on April 3, 3014 after reviewing the pathology report from the biopsy. Pet. Ex. 2 at 10.

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[27] J. Charles Jennette, M.D. and Ronald J. Falk, M.D., *Small-Vessel Vasculitis*, 337 New England Jour. Of Medicine, 1512-1517 (1997) [Pet. Ex. 16(k)].

[28] James P. Russell, M.D. and Lawrence E. Gibson, M.D., *Primary cutaneous small vessel vasculitis: approach to diagnosis and treatment*, 45 International Journal of Dermatology, 3-13 (2006) [Pet. Ex. 16(w)].

[29] Durga P. Misra and Vikas Agarwal, *Innate immune cells in the pathogenesis of primary systemic vasculitis*, 36 Rheumatol Int. 169-182 (2016) [Pet. Ex. 16(q)].

Additionally, G.C. was referred to the Harriet Lane Kidney Center for evaluation of proteinuria.[30] Dr. Pruette stated that there was a concern for possible kidney involvement. Pet. Ex. 3 at 5. Dr. Pruette noted that kidney involvement is rare, but has been "described as more severe when noted in children with urticarial vasculitis." *Id.*

B. Classification of G.C.'s Condition Before and After the Vaccination

The petitioner contended that the hives G.C. experienced in August and September 2013 were "merely allergic in nature." Pet. Brief at 23. Petitioner argued that the symptoms and treatment of G.C.'s hives in the fall of 2013 differed dramatically from the symptoms and treatment of G.C.'s skin condition that began occurring five days after she received the flu vaccination. *Id.* Respondent argued that G.C.'s post-vaccination diagnosis was the natural progression of her pre-vaccination symptomology and disease process. Resp. Brief at 14. Respondent stated that "…it is less important for the Special Master to try to define what type of urticaria G.C. had before the vaccination. The important point is that [G.C] had urticaria before the vaccination, and was later diagnosed with [chronic urticaria] and [urticarial vasculitis] after vaccination." *Id.*

The respondent is asking the Court to simply accept his assertion that G.C.'s pre-vaccination symptoms were the beginning of her urticarial vasculitis without further inquiry as to the differences between the nature, duration and treatment of G.C.'s symptoms before and after the vaccination. Yet, answering the question as to what type of urticaria G.C. had prior to the vaccination is critical to resolving this case, particularly when the difference is distinguishing between a common skin condition, hives, and an autoimmune condition, urticarial vasculitis.

Dr. Byer's opined that the intermittent hives G.C. experienced four months prior to the vaccination were "consistent with an allergic, IgE mediated condition." Dr. Byers stated that the hives were "mild," "only lasted one day at a time," and, "responded to Benadryl." Pet. Ex. 6 at 6; Pet. Ex. 12 at 2.

Dr. Byers testified that in the summer of 2013, G.C.'s urticaria met the classification for acute urticaria. Tr. 75. She stated that the three episodes of hives G.C. had prior to the vaccine were readily treated within hours with Benadryl which resolved the rash. Tr. 78; 136. Dr. Byers explained that hives are "basically limited to the epidermis, which is the top layer of skin…primarily caused by vasodilation." *Id.* G.C.'s hives prior to the vaccine were mild and required no treatment beside Benadryl. Pet. Ex. 12 at 2. There was no edema or bruising. *Id.* Further, Dr. Byers observed that the location of the hives prior to the vaccine was in G.C.'s armpit, back of the legs and the stomach and the rash was not accompanied by edema. Tr. 80 & 135. There are no other medical records that document any skin lesion, rash or hives between mid-September 2013 and the December 9, 2013 emergency room visit at Florida Hospital.

Dr. Schroeder, on the other hand, opined that the hives G.C. experienced in the fall of 2013 was the first appearance of chronic urticaria, G.C.'s autoimmune condition and it naturally progressed after the vaccination. Resp. Ex. A at 8, 10; Resp. Ex. J at 3-4. In responding to Dr.

[30] Proteinuria is excessive serum proteins in the urine, such as in renal disease, after strenuous exercise, and with dehydration. *Dorland's* at 1535.

Byers' opinion that G.C.'s initial hives was acute urticaria cased by allergens, Dr. Schroeder stated, "Most importantly, with the exception of the febrile episode five days post vaccination that resolved within a week and which her physicians judged due to a viral exanthem, the rash which was the most visible manifestation of her vasculitis *was the same prior to and after the administration of the influenza vaccine."* Resp. Ex. A at 11 (emphasis added). After reviewing the medical records, Dr. Schroeder concluded, "The records indicate that the skin manifestations occurred every two to three weeks before the vaccination and every two to three weeks after the vaccination." *Id.* at 12.

A review of the medical records, the expert testimony and medical literature, the persuasive testimony of Ms. Contino, and the photographic evidence petitioner submitted into the record, demonstrates that G.C.'s condition prior to the vaccination and after the vaccination were distinctly different in presentation and symptomology.

When G.C. was evaluated at her pediatrician's office for a rash on September 13, 2013, G.C.'s skin condition was described as "well defined pink patches, only sl (slightly) raised mostly along waistband, backs of both thighs, ankles, but also on abdomen, back of hands and cheek (R)." Pet. Ex. 1(a) at 98. Dr. Lee noted that "G.C. seems unaffected-well appearing/acting, not itching, rash is nontender, she was cooperative with exam." *Id.* Dr. Lee recommended Benadryl and an oatmeal bath as necessary. *Id.* G.C. saw Dr. Lee again on October 21, 2013 for unspecified constipation. *Id.* at 97. Her skin appeared "pink, warm, dry," and there was no mention of a rash. *Id.* In the medical record from the visit with Dr. Korff on October 3, 2014 states, "About 2-3 weeks ago [G.C.] woke up one more morning and was covered in hives. She was seen by the pediatrician and placed on Benadryl. After taking the Benadryl for a day, the rash resolved. Then 3 days later the hives reappeared and Benadryl again helped. She had another episode after that which again resolved with Benadryl." Pet. Ex. 1 at 69-70. Dr. Korff did not report any active hives, lesions or other skin markings on her physical exam of G.C., aside from noting that G.C. is dermatographic. *Id.* at 70. Dr. Korff diagnosed G.C. with dermatographic urticaria and recommended symptomatic treatment with Benadryl during episodes. *Id.* at 70. Ms. Contino testified that G.C. did not experience any additional hives in September, October, November and in December prior to the flu vaccine. Tr. 336.

The medical records are also consistent with Ms. Contino's testimony. She described the hives that appeared in the fall of 2013 as "red and large," and "covered a very large area on [G.C.'s] armpit, on her stomach and the backs of her legs." Tr. 8. Ms. Contino testified that based on the recommendation of the pediatrician, she gave G.C. Benadryl and the hives "went away within an hour." Tr. 12. She testified that between late August and early September 2013, she treated G.C.'s hives with Benadryl and they resolved within an hour each time. *Id.* Ms. Contino also testified that G.C.'s last episode of hives in the fall of 2013 occurred in late September. Tr. 13. She testified that G.C. did not experience another episode of hives from late September to the time of vaccination on December 3, 2013. *Id.*

After the vaccination, Ms. Contino's description of G.C.'s hives changed dramatically. She testified that five days after the flu vaccination small red spots began to appear on G.C. Tr. 14, 337. Then G.C.'s legs began to swell and her feet began to turn purple. Tr. 337. G.C. refused to walk while in Disney World. *Id.* Ms. Contino stated that the rashes began to spread to

her cheeks and up and down her legs. Tr. 15. Additionally, G.C. developed "60-80 bruises all over her body," that appeared purplish. Tr. 16. Ms. Contino rushed G.C. to the emergency room on the evening of December 9th where she was given steroids and Benadryl. Tr. 343.

When the family returned home from Florida, the purplish bruises, swelling in her hands and feet and joint pain would return "a couple of times a week." Tr. 342. Ms. Contino testified that G.C. did not have any symptoms of pain, swelling, or bruising associated with the hives that appeared in September. Tr. 342, 344. She stated that beginning with the event in Florida G.C's leg and joint pain was so bad that she would only lay in bed and cry. Tr. 338. Ms. Contino testified that G.C.'s symptoms of joint pain and swelling were so serious that she drove all the way from Maryland to the Cleveland Clinic to get G.C. seen as soon as possible. *Id.* It was not until a skin biopsy was performed on March 27, 2014 that G.C. was definitively diagnosed with urticarial vasculitis.[31] *See* Pet. Ex. 3 at 1.

Dr. Schroeder was focused solely on the recurrence of G.C.'s hives and did not acknowledge that the post-vaccine hives were accompanied by joint pain, bruising and swelling and kidney issues that began in December and continuing thereafter. His opinion that "the rash which was the most visible manifestation of [G.C.'s] vasculitis *was the same to and after* the administration of influenza vaccine," is contradicted by both the medical evidence and the convincing testimony of Ms. Contino.

When G.C. was treated for hives in the fall of 2013, the medical records did not include any notation that G.C. was experiencing any of the symptoms associated with vasculitis. It was only after the vaccination did G.C. begin to complain about joint pain, experience significant swelling and develop bruises. *See* Pet. Ex. 3 at 4,7; Pet. Ex. 9 at 16. Both the medical records and Mrs. Contino's testimony are clear that the rash G.C. experienced in the fall of 2013 responded almost immediately to Benadryl. *See* Pet. Ex. 1(a) at 69, 98; Tr. 335.

During the hearing, Dr. Schroeder acknowledged that some of the symptoms G.C. experienced in the fall of 2013 were different than the symptoms that presented after the vaccination. He conceded that G.C. did not have any leg or feet swelling in September 2013, as she did experience on December 9, 2013. Tr. 301. Dr. Schroeder also conceded that G.C. did not experience bruising in September or early October, as she did after the vaccination. Tr. 302. In fact, Dr. Schroeder stated, "the symptomatology that [G.C] had in December was different then the symptomatology that she had before and after. *I don't recall there being any reports in the case…when she was having the active vasculitis where she had difficulty walking…general swelling, et cetera, or that she had a fever.* Everything was focused on her skin." Tr. 308 (emphasis added). When questioned whether he agreed if the symptoms of pain, history of bruising, history of swelling was suggestive of something different than urticaria, Dr. Schroeder stated, "Yes. Yes. That's what I said. There's a difference about what happened in December versus what happened before and after. I agree with that." Tr. 311-12. However, Dr. Schroeder attempted to distinguish the symptoms of bruising, joint pain and swelling that G.C. experienced in December as unique, one-time event caused by a virus.

[31] A biopsy for this condition can only be done on an active lesion and because of the episodic nature of the disease and the difficulty in scheduling an immediate appointment at Johns Hopkins when a flare occurred the biopsy was not done until March 27, even though Dr. Sule's working diagnosis was urticarial vasculitis before that time.

As explained above, vasculitis is often accompanied by joint pain or swelling and can have renal involvement. The record well establishes that G.C.'s symptoms of joint swelling, bruising and pain, in addition to the hives, continued regularly until she was diagnosed with urticarial vasculitis and treated accordingly. The newly appearing vasculitic symptoms of bruising, swelling and joint pain was the reason that Ms. Contino drove G.C. from Maryland to the Cleveland Clinic. It was the accompanying symptoms of joint pain, swelling, and bruising that caused Dr. Silber and the doctors at Johns Hopkins to suspect vasculitis and order a biopsy to confirm the diagnosis. *See* Pet. Ex. 1(a) at 60; Pet. Ex. 2(a) at 6.

Based on the medical records, the opinions of the experts and the testimony of Ms. Contino, I conclude that it is more likely than not that the hives G.C. experienced in the fall of 2013 should be classified as an allergic IgE-mediated response and what she experienced five days post-vaccination was the initial presentation of G.C.'s autoimmune urticarial vasculitis which continued thereafter.

A. Althen Prong One: Medical Theory

1. Legal Standard

Under *Althen* prong one, the causation theory must relate to the injury alleged. Thus, a petitioner must provide a "reputable" medical or scientific explanation, demonstrating that the vaccine received *can cause* the type of injury alleged. *Pafford*, 451 F.3d at 1355-56 (Fed. Cir. 2006). The theory need only be "legally probable, not medically or scientifically certain." *Id.* at 1380 (quoting *Knudesn,* 35 F.3d at 548). However, the theory still must be based on a "sound and reliable medical or scientific explanation." *Knudsen* at 548. The Federal Circuit explained in *Althen* that "while [that petitioner's claim] involves the possible link between [tetanus toxoid] vaccination and central nervous system injury, *a sequence hitherto unproven in medicine,* the purpose of the Vaccine Act's preponderance standard is to allow the finding of causation in a field *bereft of complete and direct proof of how vaccines affect the human body." Althen,* 418 F.3d at 1280 (emphasis added).

2. Discussion

The experts agree that the causes of chronic urticaria can be autoimmune. Pet. Ex. 6 at 5; Resp. Ex. A at 9. Petitioner submitted an article by Altman and Chang titled, *Pathogenic Intracellular and Autoimmune Mechanisms in Urticaria and Angioedema,* which Dr. Schroeder stated provided "a good review of our current understanding of the pathogenesis of urticaria." Resp. Ex. A at 9. Additionally, both the experts agree that the G.C.'s underlying urticarial vasculitis is the product of an autoimmune process. Resp. Ex. A at 12; Pet. Ex. 6 at 8; and Pet. Ex. 12 at 2. The main disagreement between the experts is the nature of the urticaria that G.C. experienced prior to the vaccination and the urticaria G.C. experienced post-vaccination.

a. Experts' Opinion on Causation

Dr. Byers opined that through bystander activation the flu vaccine caused G.C.'s urticarial vasculitis which initially appeared after the flu vaccination. Pet. Ex. 6 at 8; Tr. 118-119. The Agmon-Levin[32] article, which Dr. Byers' quoted in her first report and during hearing testimony explains bystander activation:

> "Bystander activation is a situation where enhanced cytokine production promotes the expansion of autoreactive T cells, whose prior number has been insufficient to produce an overt disease. In the case of polyclonal activation of B cells, the increased B cell proliferation, antibody production and the generation of circulating immune complexes may eventually damage self-tissues."

Pet. Ex. 8(b) at 2; Tr. 118-119. Dr. Byers also submitted an article by Fujinami et al[33]., that described the role of bystander activation in the production of autoimmune disease. Pet. Ex. 16(e). The article describes the stimulation of antigen presenting cells that could potentially activate pre-primed autoreactive T-cells which then initiate autoimmune disease by bystander activation. Pet Ex 16(e) at 2.

Dr. Byers testified that every individual is born with dormant autoreactive immune cells. Tr. 123; Pet. Ex. 23 at 4. She testified that the body contains anti-self lymphocytes, including CD4 T cells, CD8 T cells, and B cells that are slowly replicating, but under control of T-regulatory cells. Tr. 119. She explained that these cells can be activated by the innate immune systems response to an antigen. Tr. 122-124. When the cells of the innate immune system are activated they react with the antigen, but also release cytokines. Id. Macrophages and dendritic cells first respond to an incoming antigen and produce a blast of cytokines. Pet. Ex. 23 at 9. The enhanced cytokine production activate the adaptive immune system's B and T cells that are antigen specific. Pet. Ex. 23 at 6, 8; Tr. 124-127. In addition to the antigen-specific T and B cells, the dormant autoreactive T and B cells are also activated and may start to generate autoantibodies. Pet. Ex. 23 at 8; Tr. 126-127.

Dr. Byers referred to an article by van Alst et al.[34] to further explain that in bystander activation, T cells unrelated to an antigen presented can be activated without classical T-cell receptor (TCR) ligation, but rather via cytokines like IL-2 as a result of the excessive activation of cells during the classical response. Pet. Ex. 17(a); Tr. 130-31.

Dr. Byers explained that the third flu vaccine G.C. received on December 3, 3013 caused a sudden inflammatory response in her skin by the release of pro-inflammatory cytokines. Pet. Ex. 6 at 8. She explained the flu vaccination stimulated the innate immune system in G.C.,

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[32] Nancy Agmon-Levin et. al., *Influenza Vaccine and Autoimmunity,* 11 IMAJ 183-185 (2009) [Pet. Ex. 8(b)].

[33] Robert S. Fujinami et al., *Molecular Mimicry, bystander activation, or viral persistence: Infections and autoimmune disease,* 19(1) Clinical Microbiology Reviews, 80-94 (2006) [Pet. Ex. 16(e)].

[34] Susan van Alst et al., *Bystander activation of irrelevant CD4+T cells following antigen-specific vaccination occurs in the presence and absence of adjuvant.* 12(5) PLoS One, e0177365 (2017) [Pet. Ex. 17(a)].

generating pro-inflammatory cytokines which signaled activation and replication of cytotoxic T cells or B cells specific to the flu vaccine, but also of heterologous T or B cells which attacked the cells in the vascular walls. Tr. 130-33. She testified that heterologous T or B cells would be activated to produce anti-IgE receptor antibodies that would bind to the mast cells causing episodic degranulation. Tr. 133. This anti-IgE receptor antibody caused the clinical manifestation observed in G.C. Pet. Ex. 6 at 8. Additionally, antigen-antibody complexes are involved in the vasculitis. *Id.* The antigen-antibody complexes embed themselves in the vessels, fixing complement and produce the vasculitis. *Id.*

The respondent and Dr. Schroeder first argued that there are no epidemiological studies connecting the flu vaccine to vasculitis. Dr. Schroeder referred to the Bonetto et al. article to support the assertion that existing medical literature does not allow establishing a causative link between vaccination and vasculitis. In Bonetto et al., the authors conducted a systemic medical literature review of 75 studies that included case reports, controlled trials and retrospective/observational studies that related to vasculitis following immunization. Resp. Ex. I at 2. However, the article also states that "standard diagnostic criteria for vasculitis are limited and rarely applied; therefore, it is not possible to draw any conclusion on causality based on the current data." *Id.* at 8. The article notes that the vaccine most often reported to precede vasculitis is the influenza vaccine. *Id.* at 9. Further, the article states that the authors of 43 case reports considered that a link between vasculitis and vaccination was possible or likely, hypothesizing that the mechanism may involve immune complex deposition in the blood vessel wall. *Id.*

Furthermore, an editorial by Zafrir et al.[35]observed that the most common autoimmune phenomena described following the flu vaccine were different vasculitic diseases. Pet. Ex. 17(c) at 2. The authors note that the 33 case reports of post-influenza vaccination vasculitides reported are rare compared with the amount of influenza vaccines administered yearly but pose a possible link between the vaccination and autoimmunity. *Id.* Dr. Schroeder argued that the higher case reports involving the flu vaccine and vasculitis was due to the high frequency in which the flu vaccine is administered. Tr. 280; Resp. Ex. J at6.

Dr. Schroeder conceded that bystander activation is a means by which autoantibodies can be produced, leading to an autoimmune disease. Tr. 213-214. He argued that for bystander activation to work, the specific autoimmune antibodies would have had to have been present before hand. Tr. 253. However, the essence of the bystander activation theory is that *non-specific* dormant autoimmune cells can be activated in the lymph nodes by the cytokines stimulated in response to the foreign antigen. Dr. Byers testified that there were likely quiescent B cells present for some time and it was the massive release of cytokines that activated those autoreactive B cells to start spewing out her IgM antibodies which were then seen in the biopsy. Tr. 350. Dr. Byers explained that after G.C. received the flu vaccine, the IgM anti-IgE receptor antibodies produced the rash and also produced the antigen-antibody complexes, that embedded themselves into the vessels, fixing complement, which is what led to the vasculitis. Tr. 351; Pet. Ex. 6 at 8.

[35] Yaron Zafrir et al., *Post-Influenza Vaccination Vasculitides: A Possible New Entity*, 15 Journal of Clinical Rheumatology, 269-270 (2009) [Pet. Ex. 17(c)].

Then Dr. Schroeder argued that bystander activation is a less efficient process for generating B cells. Tr. 253. He testified that "had the reaction occurred a month after the vaccination…there would have been time." Tr. 254. He opined that five days was too fast for a bystander activation to be the mechanism for triggering G.C. urticarial vasculitis. Tr. 256. However, he did not account for the fact that G.C's immune system had likely been primed by prior flu vaccines, as this was her third flu vaccination.

After review of the testimony and the medical literature I conclude that bystander activation is a reasonable and reputable theory that is recognized in the literature and can explain the role of the vaccine in triggering the occurrence of autoimmune vasculitis in this case.

B. *Althen Prong Two:* Logical Sequence of Cause and Effect

1. Legal Standard

To satisfy *Althen* prong two, petitioner must show, by a preponderance of the evidence a "logical sequence of cause and effect showing that the vaccination was the reason for the injury." *Althen* at 1278. Even if the vaccination can cause the injury, petitioner must show "that it did so in [this] particular case." *Hodges v. Sec'y of Health & Human Servs.,* 9 F.3d 958, 962 n.4 (Fed. Cir. 1993).

Proof of *Althen* prong two requires a logical explanation as to how the vaccine did cause the injury in the petitioner. "A logical sequence of cause and effect means what it sounds like- the claimant's theory of cause and effect must be logical." *Capizzano v. Sec'y of Health & Human Servs.,* 440 F.3d at 1326.

2. Discussion & Conclusion

Dr. Byers offered the theory of bystander activation to explain how the third flu vaccine G.C. received can cause urticarial vasculitis. Dr. Byers also opined that this theory fit the present case because the clinical manifestations of the allergic acute urticaria G.C. experienced prior to the vaccination was markedly different from the symptoms she experienced after receiving the vaccination. Pet. Ex. 12 at 2.

Dr. Byers explained that the rash and hives accompanied by bruising and swelling that G.C. experienced after the vaccination was more consistent with a vasculitis. Tr. 349; Pet. Ex. 12 at 2. Dr. Schroeder, on the other hand, argued that there was "no proof that the skin manifestations before and after vaccination were different….there is no documentation in the medical records that distinguishes the rashes before and after vaccination from each other." Resp. Ex. A at 12.

Dr. Schroeder's assessment that G.C.'s skin manifestations" were the same before and after the vaccine was limited to the presentation of the urticaria and failed to consider the ongoing vasculitic symptoms G.C. experienced post-vaccination. The vasculitic symptoms of joint pain, swelling and bruising first manifested five days after the flu vaccine and continued with some regularity. Tr. 338. However, Dr. Schroeder apparently disregarded Ms. Contino's

reports of joint pain, swelling and reoccurring bruises to physicians, leading him to an unduly restrictive description of G.C.'s post-vaccination condition. During cross-examination, Dr. Schroeder acknowledged that the medical records relating to G.C.'s hives from September and October do not indicate that G.C. experienced any swelling, bruising or joint pain in association with presentation of the hives. Tr. 300-02. He testified, "All I have is a description of a rash, and the fact that they were treating her for urticaria. So I presume that she had an urticarial rash, if they were treating her for urticaria. She had an urticarial rash before, she had an urticarial rash after, right? And so it seems to me that it's the same condition." Tr. 313. However, it was evident from the course of treatment and diagnostic assessments of G.C. at the Cleveland Clinic and Johns Hopkins that the physicians were considering something considerably different than Benadryl responsive hives.

In his first report, Dr. Schroeder offered two alternative explanations as to why G.C. experienced markedly different symptoms five days after the vaccine compared to the symptoms she experienced in the fall. First, Dr. Schroeder associated the different symptoms G.C. experienced in December to the change in temperature from Maryland to Florida. He explained that the "…the episode on December 8, 2013 occurred during travel from Maryland to Florida in December, a period where the temperature differential between these two states is exacerbated." Resp. Ex. A at 8-9. Dr. Schroeder then attributed the different symptomology to a viral infection. He stated that "At Florida Hospital, her symptoms were judged by her emergency room physicians to be most consistent with a viral exanthema." *Id.* at 9. He continued by stating, "…these particular symptoms with fever resolved and did not recur. Instead, the patient returned *to the pattern of a rash alone* occurring every two to three weeks that held sway since September of 2013." *Id* (emphasis added). When Dr. Schroeder was asked by the Court if given the knowledge of the full history of the development of this condition, which the emergency room doctor did not have, whether he still attributed the different symptomology that appeared in G.C. in Florida to a viral exanthem, he responded, "I can't say to be frank." Tr. 309.

As described in more detail above, the rashes and hives G.C. experienced in the fall of 2013 were short-lived and resolved quickly when given Benadryl. *See* Pet. Ex. 1(a) at 98; Tr. 9-10. A physical examination of G.C. on September 13, 2013 found her "well appearing/acting, not itching, rash is nontender." Pet. Ex. 1 at 98. It was recommended that the rash be treated with Benadryl and an oatmeal bath. *Id.* When assessed the next month by Dr. Korff, she diagnosed G.C. with dermatographic urticaria and recommended treating the symptoms with Benadryl versus daily use of a long acting antihistamine. Pet. Ex. 1(a) at 70. Ms. Contino testified that the hives in the fall were not accompanied by fever, extreme pain or bruising. Tr. 8; 10-13.

Five days after G.C. received the flu vaccination on December 3, 2013, G.C. began to exhibit hives and rashes across her abdomen and thighs. Pet. Ex. 2 at 7; Tr. 14-5. Six days after receiving the vaccine, G.C,'s hives and rash spread across her body, accompanied by pain, a fever of 101 degrees and bruises accompanying the rash. Pet. Ex. 4 at 16-17; 23-24; Tr. 14-24. At the emergency room in the Florida Hospital, G.C. was treated with steroids that reduced the swelling in G.C.'s legs, but the bruises remained. Tr. 20-21. Ms. Contino explained that G.C.'s symptoms of swelling and joint pain, along with the rashes and bruises reappeared about a month after the flu vaccine and continued a few times a week. Tr. 338-43.

During the hearing, Dr. Byers explained that in the fall of 2013, the medical professionals that treated G.C. for hives did not suspect any systemic involvement. Tr. 136. Instead, G.C. was treated with Benadryl and the urticaria resolved within a few hours. *Id.* However, when G.C. saw Dr. Silber on February 3, 2014 for recurrent rash and joint pain, he suspected a systemic disease, diagnosed G.C. with "probable vasculitis" and recommended G.C. see a pediatric rheumatologist. Pet. Ex. 1 at 60.

At the Cleveland Clinic, based on the reported symptoms by Mrs. Contino and the photographs Ms. Contino presented to Dr. Zeft, G.C. was diagnosed with "hemorrhagic edema of infancy (a form of vasculitis) triggered by influenza vaccination. Preceding urticaria may be idiopathic or potentially part of an illness spectrum." *Id.* at 58. Dr. Byers explained that Dr. Zeft's diagnosis of "hemorrhagic edema of infancy" was the second time in the medical records that a medical professional was considering vasculitis as an explanation for G.C.'s symptoms. Tr. 93-94. She explained that "hemorrhagic edema of infancy," is small vessel vasculitis. *Id.* Dr. Zeft recommended a complete blood count with differential, a urinalysis, complement metabolic panel to test for C3 or C4 and a serum immunoglobulin test, specifically looking for elevated IgA. Pet. Ex. 1 at 58; Tr. 94. At Johns Hopkins, Dr. Sule became concerned with G.C.'s elevated protein/creatine ratio and recommended G.C. undergo a skin biopsy and repeat urinalysis. Pet. Ex. 2 at 3. The skin biopsy performed on March 27, 2014 confirmed the ultimate diagnosis of urticarial vasculitis. *Id.* at 10.

From then on, G.C. has been treated with steroids and immunosuppressive drugs. Tr. 41; *see also* Pet. Ex. 2 at 10-18. G.C. continues to experience leg and joint pain, along with rash flare-ups and mouth ulcers. Pet. Ex. 15 at 4; Tr. 49-50, 343.

While the "history of present illness," in the medical records from the Cleveland Clinic and the first two appointments from Johns Hopkins somewhat confused the occurrences of the acute urticaria G.C. experienced in the fall of 2013, all three records are consistent in noting that *after* G.C. received a flu vaccination, she experienced bruising, swelling and joint pain that continued after seeking treatment at the emergency room of Florida Hospital. *See* Pet. Ex. 2 at 4, 7; Pet. Ex. 9 at 3. Taken as a whole, the evidence indicates that G.C. did not simply experience a "rash alone," after she returned from Florida, as asserted by Dr. Schroeder, but instead G.C's rashes post-vaccination were accompanied with joint pain, bruising and swelling, all of which were absent in the fall of 2013. Additionally, post-vaccination, G.C. consistently had abnormal pr/cr ratio which was concerning to physicians to Johns Hopkins and was indicative of systemic involvement. *See* Pet. Ex. 2(a) at 12.

Following the theory proposed by Dr. Byers, an extensive review of the medical records and after hearing the compelling testimony of Mrs. Contino, I conclude that the petitioner has set forth a logical cause and effect relationship between the flu vaccination and G.C.'s urticarial vasculitis. G.C.'s symptoms post-vaccine are consistent with the medical literature describing symptoms of autoimmune vasculitis, and more importantly, those symptoms are distinct from the symptoms that G.C. experienced in the fall of 2013.

C. *Althen* Prong Three

1. Legal Standard

Althen prong three requires establishing a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen* at 1281. That term has been equated to the phrase "medically-acceptable temporal relationship." *Id.* A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." *de Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is medically acceptable timeframe must also coincide with the theory of how the relevant vaccine can cause an injury (*Althen* prong one). *Id.* at 1352.

2. Discussion and Conclusion

Petitioner argued that there was an acceptable temporal relationship between G.C.'s flu vaccination on December 3, 2014 and the onset of the first symptoms of urticarial vasculitis five days later, on December 8, 2014.

With respect to the temporal relationship between the vaccine and onset of G.C.'s symptoms, Dr. Byers opined that the onset of three to twenty- one days is an appropriate medical onset of symptoms based upon the relevant medical literature. Pet. Ex. 6 at 8; Tr. 109-112.

As such, Dr. Byers contended that the temporal association of three to five days is also supported by medical literature. She cited to an article by Felicetti et al.[36] to support the proposition that vasculitides have been reported as an adverse event following vaccination, with more frequent reports in association with influenza vaccines than with any other vaccine in three international vaccine reporting databases, including VAERS. Pet. Ex. 16(d) at 3. This article also notes that across the three databases, vasculitides appear to be more frequently reported in the pediatric population, among females and with a time to onset within 10 days from the vaccination. *Id.* at 6. Dr. Byers also referred to a case report by Cao and Sun[37] where an elderly gentleman presented to an emergency room five days after receiving the flu vaccine with extensive rash, fever and joint pain in his hips, knees and ankles. Pet. Ex. 16(b) at 2. He was diagnosed with leucocytoclastic vasculitis. *Id.* Another case report by Liu et al.[38] indicated the onset of painful erythematous eruptions on the patient's trunk, arms and thighs three days after receiving an H1N1 flu vaccination. Pet. Ex. 16(o).

Further, Dr. Byers asserted that five days is particularly medically appropriate because this was the third flu vaccine G.C. had received. Tr. 87. The Agmon-Levin article states that a

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[36] Patrizia Felicetti et al., *Spontaneous reports of vasculitis as an adverse event following immunization: A descriptive analysis across three international databases*, 34 Vaccine 6634-6640 (2016) [Pet. Ex. 16(d)].

[37] Sissi Cao and Dongemi Dongemi, *Leucocytoclastic vasculitis following influenza vaccination*, BMJ Case Rept. (2017), doi: 10.1136/bcr-2016-217755 [Pet. Ex. 16(b)].

[38] Po-Yu Liu et al., *Cutaneous Vasculitis Following Influenza Vaccination*, 49 Inter. Med. 2187-2188 (2010) [Pet. Ex. 16(o)].

second exposure to the same antigen might elicit a response within a shorter period. Pet. Ex. 8(b) at 2.

Additionally, this court has previously awarded entitlement where the petitioner's onset of symptoms of urticarial vasculitis began only a few days after the flu vaccination. *McElroy v. Sec'y of Health & Human Servs.,* No. 11-679, 2012 WL 1739873 at *4 (Fed. Cl. Spec. Mstr. Apr. 13, 2012). In that case, the petitioner received the flu vaccine on October 25, 2008 and on November 6, 2008, complained of a travelling urticaric rash on her trunk and extremities for *two weeks*, putting onset almost immediately after the vaccination. *Id* (emphasis added).

Respondent's expert, Dr. Schroeder, opined that the hives G.C. experienced in the fall of 2013 was the beginning stages of chronic urticaria. Resp. Ex. A at 10; Tr. 224. He testified that in the fall of 2013, G.C's hives could not be classified as "chronic urticaria" because the hives had not yet presented for six weeks. Tr. 225. He also asserted that the urticarial symptoms that predated the vaccination were no different in presentation than the symptoms G.C. experienced after the vaccination, aside for the "severe episode of skin manifestations," that occurred in Florida. Resp. Ex. A at 8. However, as discussed in greater detail above, the hives G.C. experienced in the fall appeared to be different in both symptomology and mechanism of activation. The post-vaccination skin manifestations were accompanied by bruises, swelling, joint pain and kidney issues that were not present during the late summer and early fall episodes. The August/September episodes appeared to be an allergic reaction, responsive to Benadryl and the post-vaccination condition being autoimmune, requiring immunomodification drugs and ongoing steroid treatment.

The post-vaccination condition appears to be autoimmune as opposed to allergic and five days is frequently period for onset for autoimmune conditions. There appears to be a preponderance of the evidence that G.C. experienced the initial presentation of her urticarial vasculitis within a medically appropriate timeframe following the flu vaccine on December 3, 2013.

VI. CONCLUSION

After a review of the entire record, I conclude that petitioner has established a reliable theory that the flu vaccination G.C. received on December 3, 2013 was the cause-in-fact of her urticarial vasculitis. Accordingly, petitioner is entitled to compensation. A separate damages order will be issued.

IT IS SO ORDERED.

s/Thomas L. Gowen
Thomas L. Gowen
Special Master